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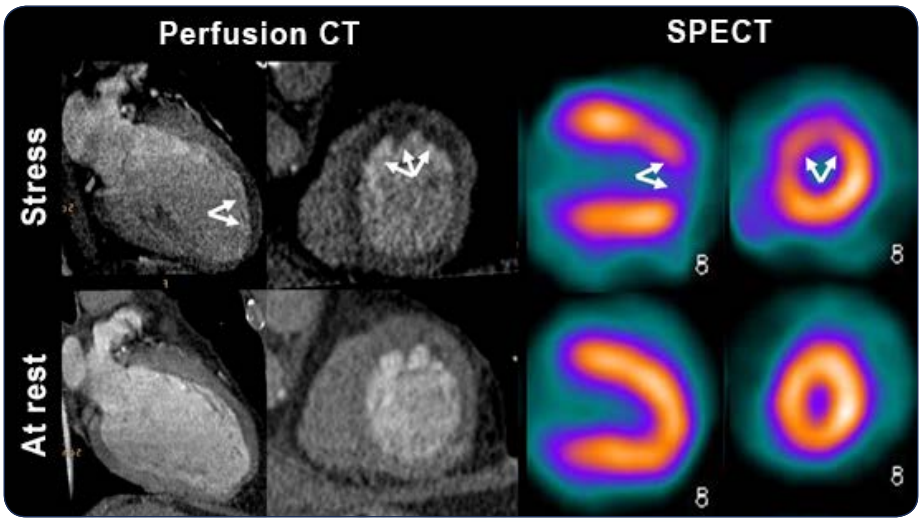

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Evidence-Based Alternative Therapies that "Touch the Heart"

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Introduction

Subcutaneous implantable defibrillator, bioabsorbable polymer stents, transcatheter aortic valve implant for certain patients with severe aortic stenosis, as well as the use of novel anticoagulants, are tangible examples of therapeutic advances in Cardiology in the end of this second decade of the 21st century. In parallel, despite their infinitely lower financial support and prominence in scientific journals and Cardiology Congresses, the non-pharmacological interventions defined as "alternative" have also been tested with the purpose of improving important outcomes in these patients. In Cardiology, studies also use Meditation, Tai Chi (TC), Yoga and even Laughter Therapy as forms of treatment. In this context, this clinical updating has two objectives: 1) To provide the reader of the Arquivos Brasileiros de Cardiologia (ABC cardiol) with access to information on the alternative therapies aforementioned; 2) To enable them, if they are interested, to use these therapies in their everyday professional life; 3) To show that Brazilian researchers have been publishing articles involving some of these alternative therapies in journals like the Arquivos Brasileiros de Cardiologia, as well as in international high impact journals.

Preamble - Meditation, TC and Yoga

These are ancient oriental practices which, over the last decades, have become more popular and have spread throughout the West. All of them share the fact that they can be found in ancient texts and scriptures, with their foundations often representing an intersection of "sacred" and science. These activities share the integration between body and mind, aiming, in addition to physical and physiological benefits, at changing the perspective of the world in search for greater happiness, quality of life and inner peace. There has been a marked increase in the number of publications on this issue over the last decades, but there are still few well-designed observational studies and randomized clinical trials (RCTs), with no potential bias or conflict of interest, contemplating these three practices. Some of them are detailed below.

Meditation

It is a practice whose origins reach back to more than 5,000 years and, in spite of being often associated with Buddhism and Hinduism, is present in most religious doctrines, including the three great monotheistic religions (Christianity, Judaism and Islam). The word meditation includes several practices with similar principles like techniques based on Buddhism (*zazen*, *shamatha and vipassana*), Yoga (Raja Yoga meditation), transcendental meditation, mindfulness and even compassion meditation (Tibetan Buddhism). An adequate definition of the technique and the procedures is very important to replicate results and, its absence, is a major methodology problem of several trials that used meditation and have already been published.

Studies report a modest effect of meditation on blood pressure (BP) decrease, in response to stress, anxiety and smoking cessation.[1] The effect on BP is small, with a meta-analysis of 19 studies, showing a reduction of 4 to 5 mmHg in systolic pressure and 2 to 4 mmHg in diastolic pressure.[2] Numerous studies in health and ill populations have explored the effects of meditation in psychological and psychosocial results. It is worth to highlight that most of them report some improvement in perceived stress levels, humor, anxiety, depression, quality of sleep or overall well-being.[3]

An analysis carried out by the Health Research and Quality Agency, restricted to RCTs and with active control groups, concluded, with low level of evidence, that meditation and mindfulness programs showed modest improvements in stress, anxiety and negative affect.[4] On the other hand, a group of researchers from the Clinics Hospital of Sao Paulo assessed, through an RCT, the practice of meditation compared with a control group in patients with heart failure (HF).[5] A decrease in sympathetic activation was observed in these individuals, as well as improvements in quality of life and increased respiratory efficacy measured by the VE/VCO_2 slope ratio.

Based on the data aforementioned, it is possible to note some benefits of meditation for patients at high risk or with already established cardiovascular disease. Nevertheless, several gaps still need to be fulfilled, such as the potential effect of meditation on the endothelial function, on heart rate variability (HRV), as well as on primary and secondary prevention of cardiovascular diseases.

Tai Chi

It is a Chinese martial art with its origins in Chinese traditional medicine and in Taoism. The slow and rhythmic movements aim at interconnecting the movements of the upper and lower limbs synchronously, moving smoothly, continuously and with no breaks and searching for stillness inside the movement. Although the movements of TC are slow and seem to be easy to perform, they work, for many patients, as a type of structured physical exercise.

Studies have demonstrated the beneficial effects of its practice, both in terms of physical and mental aspects,

Keywords

Cardiovascular Diseases; Meditation; Relaxation; Yoga; Tai Chi; Sense of Humor; Laughter Therapy.

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particularly: stress, depression and anxiety reduction; increased functional capacity; BP reduction and improvement of lipid profile.[6,7] Furthermore, studies in elderly patients have shown a significant improvement in balance, reduced risk of falling, decreased muscle and joint pain, improvement in osteoporosis and even improved or maintained cognitive performance.[6]

Due to a scientific gap in assessing the impact of TC practice on patients with coronary artery disease - CAD,[8] the Exercise Cardiology Research Group of the Hospital de Clínicas de Porto Alegre studied the effect of this practice on 61 post-AMI patients.[9] They were randomized for practicing TC for 60 minutes, three times a week or for stretching exercises (control group). After 12 weeks of training, the group who practiced TC showed significant improvement in peak oxygen consumption (14% = 3.1 $mL.kg^{-1}.min^{-1}$), whereas the stretching group did not show any improvements. Similar effects were found in some studies with HF patients, showing that this practice can impact positively on functional capacity increment.

Yoga

The last of the three oriental practices mentioned is the one which has the largest body of evidence in favor of potential benefits, be it due to a greater volume of studies or to the fact that the practice is more widespread in the West. This practice dates back to 1,500 years B.C. and is present in all Hindu holy books (Vedas, Bhagavad Gita and Upanishads). The word Yoga derives from Sanskrit and means union, and its practice is divided into three components, namely: the *asanas*, which are the different yogic postures; the *pranayamas*, which are breathing exercises and the *dhyanas*, which are basically meditative practices. Different studies have shown the physiological benefits of its practice, among which are metabolic (BP reduction, improvement in lipid and glycemic profile), anti-inflammatory (decrease in C-reactive protein and cytokines), immunological (enhanced CD4 T lymphocytes and telomerase activity), neuroendocrine (decreased cortisol, adrenaline and aldosterone) and autonomic (increased HRV and improved baroreflex sensitivity) effects.[10,11]

The evidences also indicate an increase in oxygen consumption and strength in patients with HF, decreased angina and increased functional capacity in individuals with CAD, as well as reduction of atrial fibrillation symptoms.[10] A systematic review and meta-analysis assessed the effects of Yoga on some cardiovascular risk factors, and found a mean reduction of 5 mmHg in systolic and diastolic pressures, body mass and body mass index reduction, LDL and triglycerides reduction, as well as increased HDL cholesterol levels.[11] More recently, a group of researchers from different institutions of Rio Grande do Sul carried out an RCT enrolling patients with HF and preserved ejection fraction. The authors compared the effects of Yoga combined with breathing techniques with a control group, in accordance with a recently published protocol.[12] Positive effects were found on inspiratory muscle force and autonomic modulation assessed by HRV in the group exposed to the intervention (non-published data).

Laughter therapy

Laughter is more than a visual and vocal behavior, it is always accompanied by a series of physiological changes, including spasmodic contractions of skeletal muscles, increased heart rate due to catecholamine release and hyperventilation with increased residual air exchange, leading to increased oxygen saturation.[13] The study of the effect of laughter and humor and its psychological and physiological impacts on the human body is called Gelotology. The first experiments in this area were carried out in the 30s, and assessed the effect of laughter on muscle tone and the respiratory mechanism in laughter. The increase in the number of studies in this area is based on the assumption that, if bad humor is harmful for the cardiovascular system, good humor (laughter therapy) and its physical changes might be beneficial.

One of the few studies that have used Laughter Therapy in unhealthy individuals was performed by Tan et al.[14] In this experiment, 48 diabetic patients with recent AMI were divided into two groups. The 24 patients in the experimental group were assigned to view a humor video for 30 minutes daily, as an adjunct to standard therapy. After a 1-year follow-up, the authors observed a significant reduction in BP compared with the patients from the control group. Furthermore, patients exposed to comedy had fewer episodes of arrhythmias, less use of nitroglycerin for angina and lower incidence of recurrent MI (only two vs. ten cases in the control group).

Finally, an RCT is in progress which aims at assessing hemodynamic biochemical responses of patients with stable CAD undergoing Laughter Therapy.[15] In this trial, patients of both sexes, aged ≥ 18 years, monitored regularly in a university hospital in the South region of Brazil, are being allocated to an intervention group (who will watch a 30-minute comedy film) or to a control group (who will watch a 30-minute neutral documentary). It is expected that some results will already be available by 2020.

Conclusion

We live at a time when Cardiology accelerates towards new technology, when, for instance, artificial intelligence emerges as a true "partner" of physicians. At the same time, ancient traditions such as Meditation, TC and Yoga, in addition to something as delightful as laughter, have been tested and may be used in the management of patients with different cardiomyopathies. Even though these therapies do not present a very robust body of evidence and are usually supported by small efficacy studies, they are simple, safe and low-cost therapeutic alternatives which, in addition to improving quality of life, can positively influence the physiological and biochemical parameters of these individuals. Finally, there is a perspective that, as the number of adherents of these practices increases, larger and better-designed studies will be carried out, which may establish the real role of these practices, whether in prevention or treatment of cardiovascular diseases.

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Pregnancy in Women with Complex Congenital Heart Disease. A Constant Challenge

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Abstract

Background: **The improvement in surgical techniques has contributed to an increasing number of childbearing women with complex congenital heart disease (CCC). However, adequate counseling about pregnancy in this situation is uncertain, due to a wide variety of residual cardiac lesions.**

Objectives: **To evaluate fetal and maternal outcomes in pregnant women with CCC and to analyze the predictive variables of prognosis.**

Methods: **During 10 years we followed 435 consecutive pregnancies in patients (pts) with congenital heart disease. Among of them, we selected 42 pregnancies in 40 (mean age of 25.5 ± 4.5 years) pts with CCC, who had been advised against pregnancy. The distribution of underlying cardiac lesions were: D-Transposition of the great arteries, pulmonary atresia, tricuspid atresia, single ventricle, double-outlet ventricle and truncus arteriosus. The surgical procedures performed before gestation were: Fontan, Jatene, Rastelli, Senning, Mustard and other surgical techniques, including Blalock, Taussing, and Glenn. Eight (20,0%) pts did not have previous surgery. Nineteen 19 (47.5%) pts had hypoxemia. The clinical follow-up protocol included oxygen saturation recording, hemoglobin and hematocrit values; medication adjustment to pregnancy, anticoagulation use, when necessary, and hospitalization from 28 weeks, in severe cases. The statistical significance level considered was $p < 0.05$.**

Results: **Only seventeen (40.5%) pregnancies had maternal and fetal uneventful courses. There were 13 (30.9%) maternal complications, two (4.7%) maternal deaths due to hemorrhage pos-partum and severe pre-eclampsia, both of them in women with hypoxemia. There were 7 (16.6%) stillbirths and 17 (40.5%) premature babies. Congenital heart disease was identified in two (4.1%) infants. Maternal and fetal complications were higher ($p < 0.05$) in women with hypoxemia.**

Conclusions: **Pregnancy in women with CCC was associated to high maternal and offspring risks. Hypoxemia was a predictive variable of poor maternal and fetal outcomes. Women with CCC should be advised against pregnancy, even when treated in specialized care centers. (Arq Bras Cardiol. 2019; 113(6):1062-1069)**

Keywords: **Pregnancy, Heart Defects, Congenital/complications Maternal Mortality, Fetal Mortality, Maternal and Fetal Outcomes.**

Introduction

In the last decade, the continuous and progressive improvement in the surgical and late postoperative treatment has allowed an increased number of children with complex congenital heart disease (CCC) to reach childbearing age.

The registry of 1000 cases of pregnant women followed at the Heart Institute of São Paulo (InCor)[1] between 1989 and 1999 showed that during that 10-year period, congenital heart diseases corresponded to 19.2% of the cases, which represented the second most frequent structural cardiac lesion. Among them, less than 1% were congenital complex lesions.

However, over the last 50 years, there has been a significant tendency in our country to an increase in the percentage of CCC during pregnancy, as observed throughout the world, as shown by the European Registry for Cardiac Diseases in Pregnancy (ROPAC), in which 20% of 66% of pts with congenital heart disease had complex heart defects.[2] This setting required a risk stratification scheme to predict adverse outcomes in pregnant women with congenital heart diseases seeking guidance to conceive. The modified World Health Organization (WHO)[3-4] classification is the most well-accepted risk stratification model for pregnancy in congenital heart disease patients, and it considers CCC as risk III, which means medical advice against pregnancy.

Despite this advice, both desired and unplanned pregnancy rates have been gradually rising, thus increasing the number of pregnant women with CCC. The scarcity of publications on pregnancy evolution in these women motivated this study.

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Objectives

Evaluate the evolution of complex congenital heart disease patients during pregnancy and identify variables related to poor maternal and fetal outcomes.

Method

This is an observational and retrospective study of 435 pregnant women with congenital heart disease, consecutively included in the InCor-Registry of Pregnancy and Cardiac Disease during a period of 10 years (2007 to 2017). Among of them, 42 pregnancies in 40 congenital heart disease patients, classified as complex by Bethesda conference[5,6] (Table 1) and included in risk category III by WHO[3,4] (Table 2) were selected for this study.

During the first prenatal appointment, all the patients had anatomical and functional diagnosis defined by the InCor-Congenital Heart Disease Team and began periodic follow-up every two weeks until the second trimester of pregnancy. Subsequently, this follow-up was altered to a consultation every week, during the third trimester, with the same cardiologists and obstetric teams according to the protocol established by the InCor- Pregnancy and Heart Disease Team. The protocol included:

- Advice on general measures (rest, restricted physical activities, control of anemia and eventual infections, dose adjustment or substitution of drugs to adapt to the current pregnancy status);
- Periodic evaluation of the oxygen saturation, maternal hematocrit and hemoglobin;
- Assessment by congenital heart diseases specialists (including new echocardiographic study);
- Follow-up with obstetrical team;
- Elective hospitalization of high-risk patients after 28 weeks (hypoxemia, pulmonary hypertension, serious obstructive lesions and important ventricular dysfunction) and
- Delivery according to obstetrical indications;
- Infective endocarditis prophylaxis during delivery with intravenous Ampicillin 2.0 g associated to gentamicin 1.5 gr/kg/intramuscular, applied one hour before delivery;
- Postpartum appointment for clinical check-up and collection of information on the delivery, based on the clinical summary of the hospital discharge, as well as on the maternal and newborn complications.

The following maternal variables were considered for this study: age, baseline heart disease; prior heart surgery; hypoxemia (oxygen saturation< 92% at rest, measured by digital oximeter and/or clinical signs of peripheral cyanosis); maternal hematocrit and hemoglobin; ventricular dysfunction (ventricular ejection fraction (EF) ≤ 50%); occurrence of heart complications, obstetric complications and maternal death.

Regarding the newborn, the variables considered were: gestational age at the delivery, fetal loss classified as: miscarriage (< 20 weeks), stillbirth (between 20 and 36 weeks) and neonatal death (up to 30 days after delivery) and malformations related to the maternal heart disease.

The conditions: hypoxemia, prior heart surgery and univentricular anatomy were studied as predictive variables of maternal and fetal outcomes.

Statistical analysis

The categorical variables were considered in the tables containing absolute (n) and relative (%) frequencies. The association of the categorical data was evaluated using the chi-square method and, when necessary, Fisher´s exact test. The distribution of the quantitative variables regarding normality was evaluated with the Kolmogorov-Smirnov test. The variables with normal distribution were presented as mean and standard deviation and compared using Student's *t*-test for independent samples. The non-parametric variables were

Table 1 – Types of Adult Patients with Congenital Heart Disease of Great Complexity

Conduits, valved or nonvalved
Cyanotic congenital heart disease (all forms)
Double-outlet ventricle
Eisenmenger´s syndrome
Fontan procedure
Mitral atresia; Tricuspid atresia; Pulmonary atresia
Single ventricle (also called double inlet or outlet, common or primitive)
Pulmonary vascular obstructive diseases
Transposition of the great arteries
Truncus arteriosus/hemitruncus
Other abnormalities of atrioventricular or ventriculoarterial connection, not included above(crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

Warnes AC et al. J AM Coll Cardiol 2001, 37:1161

Tabela 2 – Modified World Health Organization (WHO) classification of maternal risk during pregnancy in congenital heart disease

WHO I	Risk no higher of maternal mortality and very low morbidity: uncomplicated, small or mild (pulmonary stenosis; ventricular septal defect; patent ductus); successfully repaired simple lesions (atrial or ventricular septal defect; patent ductus arteriosus; anomalous pulmonary venous drainage).
WHO II	Small increased risk of maternal mortality and morbidity: unoperated atrial or ventricular septal, repaired tetralogy of Fallot, repaired coarctation, atrioventricular septal defect.
WHO III	Significant increased risk of maternal mortality and morbidity: systemic right ventricle (e.g. congenitally corrected transposition, simple transposition after Mustard or Senning repair); Fontan circulation ; cyanotic heart disease; other complex congenital heart disease
WHO IV	Very higher risk of maternal mortality and morbidity or severe morbidity Pulmonary arterial hypertension of any cause; severe systemic ventricular dysfunction; heart failure and LVEF <30%; severe left heart obstruction, severe (re)coarctation; Fontan with any complication.

WHO: modified World Health Organization; LVEF: left ventricular ejection fraction

presented as median and interquartile interval and compared using the Mann-Whitney test. The values of $p < 0.5$ were considered significant. The *SPSS* software version 18.0 was used for the statistic calculations.

This research was approved by the Institutional Review Board of Hospital das Clínicas of the School of Medicine of the University of São Paulo - SDC protocol 4563/17/063.

Results

The baseline clinical characteristics of 40 patients at the beginning of pregnancy and the types of structural cardiac lesions and previous surgical repairs, obstetric and fetal outcomes of the 42 pregnancies are shown in tables 3 and 4, respectively.

The analysis of the structural or functional cardiac lesion recorded at the beginning of the pregnancy (table 4) showed: hypoplastic right ventricle in cases 2, 16, 20, 23 and 26; left ventricular dysfunction (EF < 50%) in cases 11 and 20; valvular, infundibular or supravalvular stenosis, with gradient > 50 mmHg in cases 14, 20, 24, 25, 26, 30, 31, 35 and 37; important valvular regurgitation in cases 17, 19, 27, 28 and 32. Eight (20.0%) patients were unoperated. The anatomical and functional analysis showed that 16 (40%) patients were considered as univentricular hearts.

Maternal and fetal outcomes (Figure 1)

Maternal and fetal success was considered in 17 (40.5%) cases, when the mother and healthy newborn were discharged from the hospital after delivery without complications. Figure 1 shows the maternal-fetal evolution and complications. Heart failure occurred in cases 5, 6, 15, 24 and 41 (Table 4) and was treated with hospitalization, strict hygiene-dietetic measures, furosemide, carvedilol or metoprolol associated or not to digitalis, when indicated. Electrical cardioversion was needed for atrial flutter treatment in case 21 (Table 4). The hospitalization duration for the treatment of complications or for childbirth planning varied between 21 and 68 days (average of 45 days). There were two maternal deaths (4.7%) related to obstetric complications: hemorrhage after delivery and preeclampsia, cases 34 and 38, respectively (Table 4).

Table 3 – Baseline characteristics of 40 pregnant women

Clinical status	
Age (years), mean ± dp	16 to 41 (mean 24.5 ± 3.4)
Oxygen saturation (%)	76 – 99 (mean 88.5)
Hemoglobin (mg/dL)	10,5 – 22,0 (mean 14.8)
Hematocrit (%)	32 – 69 (mean 47)
Functional Class (NYHA) (%)	I and II: 35 (79%) pts
	III: 9 (21%) pts
	IV: 0 (0%) pts
Previous surgical repair	34 (77.3%) pts
No previous surgical repair	8 (20%) pts
Hypoxemia (Sat% < 92%)	19 (47.5%) pts

Dp: standard deviation; NYHA: New York Heart Association; Sat %: oxygen saturation (measured by digital oximeter); Pt: patient.

The obstetric complications are shown in Figure 1. The fetal losses correspond to miscarriages in cases 12, 17 and 37, stillbirth in case 34 and neonatal death in cases 14, 16 (premature babies) and 35 (Table 4). The delivery occurred on average at 37 weeks of gestation; 24 (54.5%) were Caesarian section due to obstetric raisons or progressive maternal clinical worsening. Among the live newborns, there were two (4.7%) cases of congenital heart disease: one with recurrence of maternal heart disease (case 25) and the other with tetralogy of Fallot (case 32); neither of the cases were preterm babies.

Among of the predictive variables of maternal and fetal outcomes, hypoxemia showed a significant correlation with worse pregnancy prognosis, while prior surgery (whether the mother had been submitted to previous surgery or not) and univentricular function showed no correlation with the maternal and fetal outcomes (Table 5).

Discussion

This study included one substancial series of pregnant CCC patients, submitted to the multidisciplinary protocol at the Heart Disease and Pregnancy tertiary care center. This studied group represented 9.6% of 435 pregnancies in women with congenital heart diseases included in the InCor-Registry during the last decade. It is undeniable that higher post-operative survival of these patients will result in an increasing number of pregnancies in women with CCC in the near future.

The CCC considered in this study were included in the WHO risk category III,[3,4] which means pregnancy is discouraged, justified by the rates of 25.5% of maternal complications and 70% of poor fetal outcome. These considerations are according to the results of this study, which recorded only 40% of successful pregnancies, i.e., healthy mothers and newborns without complications. The high rates of maternal events (36%) and fetal events (43%) are the bases for the WHO guideline that advises against pregnancy in this group of patients.

However, the global experience in this clinical situation is increasing and it represents a major challenge for clinicians. Occasionally, women become pregnant without prior counselling or sometimes they desire a pregnancy despite the advice against it.[7] The diversity of the anatomical and functional conditions of the heart defects in CCC restrict the creation of management protocols for eventual complications during pregnancy, delivery and postpartum.[7]

However, knowledge of the most common complications that occur in the late postoperative period of CCC helps in the management of pregnancy in these patients. In this regard, a study about the causes of death in patients with CCC showed that heart failure, sudden death, ischemic heart disease and infective endocarditis were the most common ones. In addition, the most significant anatomical lesions (except for Eisenmenger's syndrome) were the transposition of the great arteries and the Fontan circulation.[8]

A study of 120 necropsies of congenital heart disease patients[9] confirmed heart failure as the main cause of death, since the ventricular remodeling in response to volumetric and pressure overload during life favors fibrosis, hypertrophy and a reduced number of myocardial interstitial capillaries. Thromboembolism, which is the second cause of

Table 4 – The baseline of cardiac defects, types of previous surgical repair, obstetrical and fetal outcomes: 42 pregnancies

Case	Age (Years)	Specific Cardiac Defects	Surgical repair technique	Sat %	Hb/Ht	Delivery/ Gestational Age/ Newborn Weight/gr
1	18	d-TGA	Senning	99%	13.5/ 39	Vd/ 37/2150
2	20	AP + VSD	Fontan	80%	19.7/ 62	Cs/29/1950
3	21	AP + VSD + APC	no repair	80%	15.0 / 44	Vd/27/1750
4	18	Truncus arteriosus	Rastelli	99%	12.5/38	Cs/40/3360
5	20	AP + VSD + PDA	Rastelli	98%	11.6/ 35	Cs/33/1860
6	19	d-TGA	Jatene	96%	11.2/ 33	Vd/37/2230
7	33	DVSVD + PS	Conduit LV- Ao + RV – PT	98%	12.8/35	Cs/38/2850
8	27	DVEVE + AAVC	no repair	93%	15.9/47	Vd/37/2630
9	18	d-TGA + VSD + PS	Jatene	98%	12.1/ 36	Vd/38/3886
10	32	d-TGA + PS + VSD	BT + Rastelli	98%	10.5/ 32	Vd/38/3210
11	24	DVSVD+dTGA+ PS+VSD	Conduit VE-AO + Rastelli	99%	11.5 / 36	Vd/37/2250
12	19	dTGA+ASD+VSD+ PS	no repair	80%	17.0/54	Miscarriage
13	32	PA	BT + Glenn	76%	17.5/50	Cs/36/1980
14	23	dTGA + VSD	Jatene	87%	12.5/40	Cs/34/2130
15	21	Single Ventricle	Glenn+ Fontan	92%	13.5/42	Cs/31/1400
16	29	DVSVD	BT + Glenn	78%	13.8/49	Cs/29/1250
17	38	Single ventricle	Fontan	82%	16.8/50	Miscarriage
18	27	Single ventricle	Fontan	83%	16.9/50	Cs/28/850g
19	19	TA + VSD + PS	BT + Glenn +Fontan	87%	15.0/47	Vd/37/2030
20	29	PA + VSD	Rastelli + Conduit RV-PT	90%	13.0/42	Cs/37/2350
21	32	AT+ASD+ VSD + PS	Fontan	94%	10.4/32	Cs/35/1800
22	34	Single ventricle	no repair	89%	22.0/69	Abortion
23	29	d-TGA	Senning	93%	11.9/40	Vd/ 39/ 2720
24	30	DVEVE + VSD	Pulmonary truncus banding	89%	17.0/49	Cs/35/1750
25	16	d-TGA	Jatene	96%	12.5/40	Cs/38/3420
26	22	AT	no repair	85%	13.7/40	Cs/32/1150
27	29	d-TGA	Jatene	93%	12.2/39	Cs/38/2460
28	32	DVSVD+d-TGA+PS	Mustard	93%	12.5/45	Cs/36/2240
29	40	d-TGA	Jatene	95%	12.3/42	Cs/37/2570
30	17	DVEV único-E+ ASD+ VSD+PS	no repair	93%	15.9/47	Vd/ 39/ 2720
31	22	DVEV único -E	no repair	94%	12.8/45	Vd/37/2630
32	24	Truncus arteriosus	Conduit valved	93%	12.5/42	Cs/38/3270
33	32	dTGA+ ASD +VSD+ PS	Fontan	91%	13.0/43	Vd/33/1510
34	26	AP + VSD	no repair	87%	21.0/67	Vd/30/1120
35	18	dTGA+ASD+VSD+PS.	Senning	90%	11.8/42	Vd/38/2770
36	19	d-TGA + VSD+ASD+ PS	Conduit LV + Reconstruction atrioventricular	93%	11.8/42	Cs/37/2410
37	20	d-TGA	Jatene	95%	11.9/40	Cs/38/3220
38	41	AP + VSD+PDA	BT + Collateral arterial repair	87%	15.4/45	Cs/28/500
39	31	DVSVD + VSD	Rastelli + Conduit LV-AO	96%	13.4/40	Vd/36/2480
40	1	d-TGA +VSD+PS	Rastelli+ Conduit LV-Ao	90%	11.5/40	Vd/38/3500
41	27	AT + VSD + PS	BT+ Glenn + Fontan	93%	13.8/40	Cs/34/1750
42	24	Truncus arteriosus	Ao + VSD repair + pulmonary graft	94%	11.5/40	Cs/37/2168

TA: tricuspid atresia; ASD: interatrial communication; VSD: interventricular septal defect; AP: pulmonary atresia; D- TGA: complete transposition of the great arteries; DVEVE: double inlet left ventricle; DVSVD: double outlet right ventricle; AAVC: abnormalities of atrioventricular or ventriculoarterial connection; PS: pulmonary stenosis (infundibular,valvar or supravalvar); AP: pulmonary atresia; APC: aortopulmonary collateral arteries; PDA: patent ductus arteriosus; Truncus: Persistent truncus arteriosus; LV: left ventricle; Ao: aorta; RV: Right ventricle; PT: pulmonary truncus; BT: Blalock Taussing procedure; Sat %: oxygen saturation; HT: hematocrit % ; HB: hemoglobin mg/dl; Vd: vaginal delivery; Cs: cesarean section.

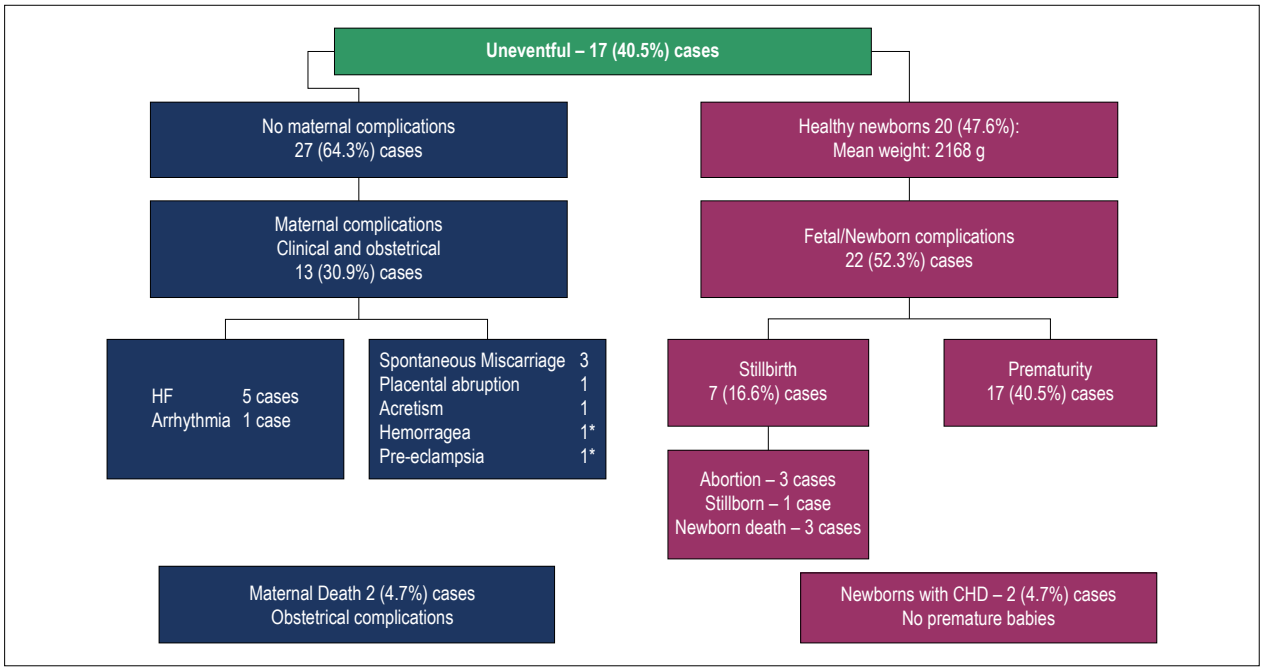

Figure 1 – *Maternal and fetal outcomes: 42 pregnancies. HF: heart failure; Acretism: placental acretism; CHD: congenital heart disease.*

Table 5 – Comparative analysis of presumptive variables of maternal and fetal outcomes

Variables No cases	Hypoxemia n = 19	No hipoxemia n = 23	p value	Univentricular n = 16	Bi-ventricular (n = 26)	p value	Operated n = 34	Unoperated n = 8	p value
Unventfull evolution n = 17	3 (15.7%)	14 (60.8%)	< 0.05	4 (25%)	13 (50%)	0.0	14 (41.2%)	3 (37.5%)	1.0
Maternal complications n = 13	9 (47.4%)	4 (17.4%)	< 0.05	7 (43.7%)	6 (23.1%)	0.18	10 (29.4%)	3 (37.5%)	0.68
Maternal death n = 2	2 (10.5%)	0	0.19	0	2 (7.7%)	0.51	1 (2.9%)	1 (12.5%)	0.34
Fetal complications n = 23	18 (94.7%)	5 (21.7%)	< 0.05	12 (75%)	11 (42.3%)	0.06	18 (52.9%)	5 (62.5%)	0.70
Stillbirths n = 7	7 (36.8%)	0	< 0.05	4 (25%)	3 (11.5%)	0.39	3 (8.8%)	4 (50%)	< 0.05
Premature babies n = 17	12 (63.1%)	5 (21.7%)	< 0.0.5	10 (62.5%)	7 (26.9%)	< 0.05	14 (41.2%)	3 (37.5%)	1.0
Mean weight newborns (g)	± 600	± 527	< 0.05	1841 ± 454	2531 ± 496	< 0,05	2246 ± 660	2296 ± 749	0.76

death, was significantly associated with histological signs of pulmonary hypertension, also detected in chronic hypoxemia. The third cause of death recorded was infective endocarditis, which reinforced the recommendation of antibiotic prophylaxis during delivery in our protocol.

The routine elective hospitalization as of the 28th week of pregnancy for patients at likely higher risk situation, regardless of the functional condition, was based on the fact that the third trimester is critical for the mother, due to the hemodynamic overload and higher prothrombotic activity, as well as for the fetus, due to the high incidence of prematurity and intrauterine growth restriction, which are characteristics of CCC.

Furthermore, elective hospitalization improved maternal and fetal monitoring, allowed intermittent oxygen therapy to be applied, individualized anticoagulation, and optimized therapy for possible complications and delivery planning.

Our results showed similar rates of cardiac (14.2%) and obstetric complications (16.6%). In both cases, maternal deaths were associated with obstetric causes (pre-eclampsia and postpartum hemorrhage). This result allows a reassessment of the severe cardiac reserve limitation in these patients, who do not tolerate the events inherent to pregnancy and postpartum, regardless of the baseline functional condition.

Pre-eclampsia, one of the causes of death in this study, is responsible for 15% of maternal deaths in Brazil, with an incidence of around 10% in the pregnant population.[10] Early diagnosis and an effective prenatal care, although they do not prevent the disease, can improve maternal mortality in healthy women. However, in patients with complex heart disease, the prognosis of pre-eclampsia is much worse, due to both systemic endothelial dysfunction, inherent to the disease and the circulatory overload caused by arterial hypertension.

Postpartum hemorrhage, the reason for the second death in our study, is considered an important obstetric cause of maternal death in women with heart disease, especially in hypoxemic patients. This fact was documented in a study of 366 primiparous women with congenital heart diseases, which recorded 21% of postpartum hemorrhage. That study identified early Caesarean section, general anesthesia and use of low-molecular-weight heparin at both prophylactic and therapeutic doses, as variables of higher correlation with postpartum bleeding. Furthermore, women with Fontan circulation had the highest blood loss and the difference remained significant after correcting for the other variables.[11]

In our study, the association of hypoxemia and postpartum hemorrhage associated with Caesarian delivery resulted in the second maternal death. Actually, the highest maternal and fetal morbidities associated with premature Caesarean delivery is due to maternal clinical instability and intrauterine growth restriction, common in complex heart situations.

A brief emphasis should be placed on the most common heart disease in this cohort, such as the transposition of the great arteries and the Fontan circulation. The promising evolution after the correction of the transposition of the great arteries through atrial inversion (Senning's procedure or Mustard's technique) or arterial inversion (Jatene's technique) has allowed the development of pregnancy.[12,13] However, there are expected events in the late postoperative period that may be unfavorable to the success of pregnancy. Supraventricular arrhythmias and ventricular dysfunction in adulthood may occur in about 40% of patients after surgical correction using Mustard's technique or Senning's procedure. On the other hand, neo-aortic valve regurgitation, present in 1-2% and coronary complications observed in 3-11% of cases, may both occur in the long term after Jatene's technique. Regarding Rastelli's surgery, the late evolution depends on the type of tissue used, which can determine different degrees of calcification and progressive occlusion of the graft.[14]

Based on these considerations, during pregnancy, one must be prepared for the treatment of heart failure and arrhythmias when there is right ventricular dysfunction and tricuspid regurgitation after Mustard's and Senning's techniques; heart failure and low output due to calcified conduits after the Rastelli procedure, of valve dysfunctions and/or coronary complications, when Jatene's technique had been used.[14]

This study showed that, with the exception of one patient who was not operated whose pregnancy ended in miscarriage (case 12), the other pregnant women with transposition of the great vessels of the base showed favorable maternal and fetal evolutions, regardless of the type of surgical correction. It is worth emphasizing that the expected complications were controlled with hospitalization and constant monitoring of the mother and fetus.

Fontan circulation has allowed the survival of 70% of the patients with univentricular heart disease up to childbearing age.[15] However, in the late postoperative period, complications such as atrial tachycardia, thromboembolism (related to hepatic and venous system stasis), heart failure, liver failure and, protein-losing enteropathy. The abnormal connection - vena cava and pulmonary circulation – despite the improvement in cyanosis, ventricular overload reserve and pulmonary circulation capacity, may be *threatened* by the variations in the central venous pressure and by the negative intrathoracic pressure induced by hyperventilation and changes in cardiac output during pregnancy.

The inability of patients with Fontan circulation to adapt to physiology of the pregnancy and postpartum period was documented in our study that showed worsening of the functional class in all the patients. Heart failure occurs because the abnormal anatomical and functional ventricle is unable to adjust to the increased cardiac output. However, there was no maternal death due to a good responses were obtained to the clinical treatment with the use of diuretic and beta-blocker in patients who developed heart failure (cases 15 and 41), and to electric cardioversion in case of atrial flutter (case 21).

On the other hand, the evolution unfavorable to the fetus was documented in six Fontan cases, resulting in a miscarriage and five premature deliveries. Review of the literature that included six studies with 255 pregnancies and 133 women showed 137 (69%) fetal loss, and 68 (59%) of the 115 live newborns were premature and six (5,2%) evolved to neonatal death. The causes of prematurity were not detailed, particularly in those induced by the anticipation of the delivery due to maternal reasons. However, the premature rupture of the amniotic membranes and placental premature detachment occurred in 6.2% and 10.9%, respectively.[16]

The poor fetal prognosis was confirmed by the multicenter study of the United Kingdom that included 50 women, 124 pregnancies, showed an incidence of 68 (54.8%) miscarriages and, among the 56 (45.2%) live newborns, four died due to extreme prematurity (delivery with gestational age below 32 weeks). On the other hand, the maternal complications (heart failure in 13.5%, arrhythmias in 11.3% and pulmonary thromboembolism in 1.19% of the cases) do not result in maternal death.[17]

The full anticoagulation routine in patients with Fontan circulation should be considered by reasons of the high risk of thromboembolism peculiar to this setting and the hypercoagulable state of the pregnancy and postpartum. This present study showed three cases of maternal thromboembolism, two of which were in a non-anticoagulated patient.

Patients with Fontan circulation should advise against pregnancy specially in patients with depressed ventricular function, cyanosis, important mitral valve insufficiency or protein-losing enteropathy.[15-17]

This study showed that hypoxemia was the presumable variables of the worst maternal-fetal prognosis, as previous report.[18] The unusual result of the previous surgical correction did not show any difference in the evolution of the pregnancy, possibly was related to a small number of the cases and some cases had cardiac lesion with an anatomy favorable to survival during childbearing age. Therefore, another study that analyzed 102 necropsies of congenital heart failure patients verified that the average age of cases not operated was higher than those operated and presented also less serious anatomical defects.[9]

Another highlight of our study is the record of two newborns (5%) with of congenital heart disease which equivalent to six times more than the 0.8% estimated for the general

population. This rate is still above the value by Oliveira et al. reporter which identifies 3 (3.2%) of cardiac malformations in children from 100 pregnant women with congenital heart diseases followed at InCor.[19] The recurrence of heart disease in the babies of mothers with congenital heart diseases should be considered in counselling before pregnancy in response to the questions about hereditary as well as indication of routine fetal echocardiography study.

Study limitations

Both the small number of patients and the wide heterogeneity of the anatomical defects contribute to a limitation of the accurate statistical analysis. However, it should be considered that this sample of patients was exclusively from the high risk group, in which pregnancy is not advised and constitutes a great guidance dilemma regarding family planning provided to women with CCC. The character of the study (retrospective and observational, restricted to a single center) can also influence the appropriate conclusions.

Final comments

Congenital heart diseases affect approximately 0.8% of all live newborns and the survival rate of 86% are highlighted in international records. It is estimated that there are currently more adults with congenital heart diseases than children, which naturally provides a considerable number of women at childbearing age.

The qualification of the multidisciplinary team is fundamental in the counselling of young women with heart disease regarding pregnancy, including advice such as alternatives to a safe and effective childbirth. Despite the stratification of the WHO risk III that allows the advice against pregnancy, the provision contained in the Brazilian Legislation should be considered:

> *Furthermore, article 226 should be considered: Based on the principles of human dignity and responsible parenthood, family planning is a free decision made by the couple, and it is the State's responsibility to provide educational and scientific resources to exercise this right, prohibiting any enforcement by official or private institutions" (our emphasis). This standard applies to other institutes: a) human dignity (article 1, III) and b) right to freedom (article 5, caput)*[20]

Conclusions

The strict care protocol during pregnancy, delivery, and puerperium did not prevent maternal deaths, prematurity or miscarriage in patients with CCC. Hypoxemia was a poor prognostic factor and maternal evolution was unsatisfactory, but the fetal outcome was worse.. Although the autonomy of intention to conceive should be respected, women with CCC should still be advised against getting pregnant.

Author contributions

Conception and design of the research: Avila WS, Rossi EG, Rossi EG, Miura N; Acquisition of data: Avila WS, Ribeiro VM, Testa C; Analysis and interpretation of the data: Avila WS, Ribeiro VM, Rossi EG, Binotto MA; Statistical analysis: Rossi EG; Writing of the manuscript: Avila WS; Critical revision of the manuscript for intellectual content: Avila WS, Rossi EG, Binotto MA, Bortolotto MR, Testa C, Hajjar LA, Miura N.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto do Coração under the protocol number XXX. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Complex Congenital Heart Diseases and Pregnancy: Maternal and Fetal Risks

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Short Editorial related to the article: Pregnancy in Women with Complex Congenital Heart Disease. A Constant Challenge

The diagnosis and treatment of congenital heart disease has made remarkable progress in recent decades and the success of this approach is evidenced by the increasing number of adults with congenital heart disease. Many of these patients have residual injuries or have undergone palliative surgery and face additional challenges in adulthood, requiring integrated care to reach a full life potential.[1]

Consequently, the number of women of childbearing age with congenital disease submitted to surgical repair, palliative procedure or the natural evolution of the disease is increasing, with a higher maternal and fetal risk in the presence of heart disease. Reproductive counseling is essential, by informing the consequences and possible complications and advising against pregnancy in the presence of more complex defects.[2]

There are several classification models and risk predictors applied to maternal cardiovascular involvement that help in the counseling and clinical management of these patients.[3] Pijuan-Domenech et al.[4] demonstrated that the modified version of the classification devised by the World Health Organization (WHO) is the best predictor of cardiac complications in pregnancy compared to other risk prediction models and it is the best accepted model for pregnancy in women with congenital heart disease.[4]

Pregnancy brings profound hemodynamic alterations and these physiological adaptations occur to allow an adequate adjustment of the metabolic needs of the mother and fetus, providing an adequate placental perfusion. Heart rate rises by 15 to 30%, peaking at the end of the second or the start of the third trimester. There is an increase in preload due to an increase in plasma volume and cardiac output increases by 30 to 50%. Additionally, there is an increase in the endothelial production of prostacyclin and nitric oxide, promoting a reduction in total vascular resistance.

Such cardiovascular adjustments are easily supported by women with normal cardiac reserve. However, these alterations may not be well tolerated in pregnant women with congenital heart disease, especially those with complex heart disease and limited capacity to adapt to significant hemodynamic alterations, which may lead to decompensation and increased risk of adverse maternal-fetal outcomes.[5]

Keywords

Pregnancy/complications; Heart Defects,Congenital/complications; Heart Defects,Congenital/trends; Maternal Mortality; Fetal Mortality; Maternal and Fetal Procedure Outcomes.

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Patients with complex structural alterations are associated with a higher chance of arrhythmias, decompensated heart failure and thromboembolic events. The volume overload that occurs in pregnancy, associated with increased excitability of adrenergic receptors caused by hormonal factors may facilitate the development of arrhythmias in patients with structural or residual cardiac defects after repair. The formation of scar tissue on the site of surgical manipulation may be involved with one of the pathophysiological factors of arrhythmias.[6] The heterogeneity and complexity of these malformations require specific management strategies and a multidisciplinary approach.[7]

The fetal and neonatal outcomes are also closely related to the complexity and severity of the maternal congenital heart disease. Early gestational losses and intrauterine growth restriction have been reported in these pregnancies.[8]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Avila et al.,[9] evaluated the evolution of pregnancy in patients with complex congenital heart disease, in an attempt to identify variables that could lead to a higher risk of unfavorable maternal-fetal outcome. A retrospective and observational study covering the last ten years, carried out in a single Cardiology and Obstetrics center, included 42 pregnancies in 40 patients with complex congenital heart disease classified as risk category III by the WHO, which means the woman is advised to avoid pregnancy.

The study results are in accordance with the worldwide literature, which shows a high rate of maternal and fetal problems. The main complications were heart failure and arrhythmia, and there were two maternal deaths due to obstetric causes. Among the most frequent structural defects were the transposition of the great arteries (with repair at the atrial or arterial level) and univentricular heart (Fontan procedure).

In the study, most patients with transposition of the great arteries had favorable maternal and fetal evolution. It is known that in patients with transposition of the great arteries, the risks associated with pregnancy are mainly related to patients submitted to repair at atrial level (Senning and Mustard procedure). There is a higher risk of developing arrhythmias and ventricular dysfunction of the systemic ventricle. Regarding patients submitted to arterial exchange (Jatene procedure), although the risk seems to be lower, greater attention should be paid to cases of dilated neoaorta or other residual complications.[10]

As for the univentricular group, in late postoperative period after Fontan surgery, an incapability to adapt to the pregnant condition was observed, with decompensation and functional worsening in all patients. It should be noted that in the hypoxemic scenario, the risk of poor maternal and fetal evolution is considerably present.

This issue is very relevant, since complex congenital heart disease has a very heterogeneous spectrum and few studies have evaluated whether maternal and fetal outcomes differ between the subtypes of this subgroup. More targeted studies may provide more accurate information for the counseling and better management of these patients.

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Influences on the Functional Behavior of Great Arteries during Orthostasis

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Abstract

Background: **Arterial compliance reduction has been associated with aging and hypertension in supine position. However, the dynamic effects of orthostatism on aortic distensibility has not been defined.**

Objective: **We sought to determine the orthostatic influence and the interference of age, blood pressure (BP) and heart rate (HR) on the great arteries during gravitational stress.**

Methods: **Ninety-three healthy volunteers (age 42 ± 16 years). Carotid-femoral pulse wave velocity (PWV) assumed as aortic stiffness was assessed in supine position (basal phase), during tilt test (TT) (orthostatic phase) and after return to supine position (recovery phase). Simultaneously with PWV acquisition, measures of BP and HR rate were recorded.**

Results: **PWV during TT increased significantly compared to the basal and recovery phases (11.7 ± 2.5 m/s vs. 10.1 ± 2.3 m/s and 9.5 ± 2.0 m/s). Systolic BP (r = 0.55, r = 0.46 and r = 0.39) and age (r = 0.59, r = 0.63 and r = 0.39) correlated with PWV in all phases. The significance level for all tests was established as $\alpha = 0.05$.**

Conclusion: **We conclude that there is a permanent increase in PWV during orthostatic position that was returned to basal level at the recovery phase. This dynamic pattern of PWV response, during postural changes, can be explained by an increase in hydrostatic pressure at the level of abdominal aorta which with smaller radius and an increased elastic modulus, propagates the pulse in a faster way. Considering that it could increase central pulse reflection during the orthostatic position, we speculate that this mechanism may play a role in the overall adaptation of humans to gravitational stress. (Arq Bras Cardiol. 2019; 113(6):1072-1081)**

Keywords: **Switch Arterial; Hypertension; Aging; Standing Position; Pulse Wave Analysis; Gravitation.**

Introduction

Great arteries are not only seen as mere passive conductors of blood, functioning only in its transportation and distribution, but rather playing a fundamental and complex role in the maintenance of circulatory homeostasis and in the genesis of cardiovascular disease.[1-2] The great arteries may be considered a functional organ with several roles, such as endocrine and paracrine activity, in addition to the capacity for muffling the pulsatile blood flow.

The functional behavior of the great arteries in the supine position was assessed noninvasively by measuring the pulse wave velocity (PWV) in several arterial segments.[3-5] Epidemiological and longitudinal studies using that methodology have shown the clinical relevance of this approach for predicting morbid cardiovascular events.[1,6–7]

However, due to methodological limitations, the functional response of the great arteries has not been investigated in the orthostatic position.[8]

The tilt test has long been used for assessing the influence of gravitational stress on the behavior of hemodynamic parameters.[9–10] Although this technique allows adequate reproducibility of the gravitational action upon individuals in active orthostatic position, only from the end of the 1980s that small studies have been carried out with primates, aiming at assessing the influence of postural changes on the behavior of aortic pulse wave and PWV.[8,11–13] Studying the function of the great arteries in the orthostatic position by noninvasively measuring carotid-femoral PWV may be important for understanding the vascular mechanisms of adaptation to gravity and their implications on cardiocirculatory homeostasis, development or progression of cardiovascular disease and occurrence of unadaptable postural events.

This study is the first to assess the effects of orthostatic position on the function of the great arteries in humans, by measuring the carotid-femoral PWV in healthy individuals

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and in individuals with untreated mild-to-moderate arterial hypertension. We tested the hypothesis that orthostatism could lead to increased PWV compared to the supine positions and considering the influence of blood pressure, age and heart rate.

Methods

Patient characteristics

To define the sample size, we used studies that evaluated PWV in supine position.[4-7]

The study included 93 individuals, 74 males and 19 females whose ages ranged from 18 to 75 years (42 ± 16 years). Twenty-nine (31.1%) individuals had systolic blood pressure levels ≥ 140 and/or diastolic blood pressure levels > 90 mm Hg. These individuals either had undiagnosed arterial hypertension or had voluntarily interrupted the antihypertensive treatment for more than 30 days. Their anthropometric and hemodynamic characteristics are shown in Table 1.

The exclusion criteria were as follows: clinical history or evidence of any type of cardiac structural disease; overweight or obesity; diabetes mellitus; smoking; dyslipidemia; peripheral vascular disease; chronic renal failure; clinical data suggestive of dysautonomia; and orthostatic intolerance or previous vasovagal events. Patients with arterial hypertension on antihypertensive treatment and patients on any medication that could interfere with the results of the parameters assessed or that could account for the occurrence of orthostatic hypotension during the tilt test were also excluded from the study.

Automatic measurement of carotid-femoral PWV

Carotid-femoral PWV index, a measure of aortic stiffness, was assessed with an automatic device (Complior, Colson, France) that measures the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and femoral arteries by using 2 pressure transducers (TY-306 type; Fukuda Deshi Co., Tokyo, Japan). PWV was calculated as the ratio between the distance and the foot-to-foot time delay and was expressed in meters per second. (6). All PWV measurements in the supine position were taken and assessed by a single observer. Obtainment of PWV during the tilt test required 2 researchers, who were acquainted with the technique in the supine position and were trained for PWV measurement in the orthostatic position.

Protocol of the tilt test associated with PWV measurement

All individuals were assessed in the morning. They were instructed to fast for 12 hours. Prior to the examination, anthropometric measurements of weight, height, and waist and hip perimeters were taken. Then, the individuals were placed in the supine position on a mechanical table of tilt test.

After a 20-minute rest, during which the individuals were instructed about the dynamic sequence of the protocol, the following baseline measurements were taken: PWV, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and pulse pressure (PP). After that, the patients were tilted at an angle of 70º. The tilt test lasted 20 minutes. The measurements of parameters monitored during tilt testing were performed at 2-minute intervals and 2 minutes after returning to the supine position. Electrocardiographic monitoring was continuously performed. Blood pressure was noninvasively measured at 2-minute intervals using the Omega 1400 monitor (Invivo Research Laboratories, USA) while PWV measurements were being taken or when the patient reported any symptom or had clinical signs or electrocardiographic abnormalities suggestive of that diagnosis.

Statistical analysis

Anthropometric, biological and hemodynamic characteristics were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used to compare hemodynamic parameters obtained at baseline condition,

Table 1 – Anthropomorphic and hemodynamic characteristics of the participants

Characteristics	Participants (n = 93)		
Sex	Male (n = 74)		Female (n = 19)
	Mean ± Standard deviation		
Age, years	42	±	16
Weight, kg	71	±	12
Height, cm	1,7	±	0,1
BMI, kg/m^2	24,7	±	3,1
SBP, mmHg	130	±	18
DBP, mmHg	82	±	13
MBP, mmHg	99	±	15
HR, bpm	66	±	11
PP, mmHg	47	±	13

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: medium blood pressure; PP: pulse pressure; HR: heart rate. The continuous values are expressed as mean ± SD.

during the tilt test at 70° (0–2 min, 10 min and 20 min), and in the recovery phase (0–2 min). The correlation between PWV obtained during the protocol and all parameters was determined using Pearson's correlation coefficient in the entire sample. Then, multiple linear regression was used to assess the influence of the different hemodynamic parameters on the PWV during the tree phase. All assumptions required for regression analysis were verified.

The partial linear correlation coefficients between PWV and age controlled for the blood pressure effect were calculated for each phase of the protocol. Similarly, the influence of age on the correlation of PWV and blood pressure was determined. Then, multivariate analysis of variance (MANOVA) and analysis of covariance (ANCOVA) were performed to assess the independent effects of age and SBP on PWV in the different phases of the protocol. Considering that the 2 major modulating factors of PWV level are age and SBP, the clinical results were assessed after adjustment for these 2 variables. Aiming at assessing the variables that interfere with heart rate behavior in orthostatic position, multiple linear regression was performed. A normality assessment of the data was performed for all variables.

The significance level for all tests was established as $\alpha = 0.05$. The statistical analyses were performed using the SPSS for Windows software (version 18.0, SPSS Inc., 2010).

Results

Effects of the tilt test at 70 on the hemodynamic characteristics of the participants

Figure 1 shows the dynamic behavior of the hemodynamic variables during the protocol.

Table 2 shows the mean values of the variables studied at baseline, during the tilt test, and in the recovery phase.

Based on the analysis of these data, the response of the individuals to postural changes was associated with a 6% increase in DBP, which was maintained during the entire phase of orthostatic position. The same was observed for the MBP value in orthostatic position. On the other hand, PP in orthostatic position decreased by 10.6%. An 11.5%-increase in PWV in orthostatic position (PWVp) was observed as compared with the baseline PWV value.

Association between PWV in the supine position and anthropometric and hemodynamic characteristics of the participants

The results of the linear correlation analysis between carotid-femoral PWV in the supine position and the anthropometric and hemodynamic parameters are shown in Table 3.

Multiple linear regression showed that age ($p < 0.001$) and SBP ($p < 0.001$) were the only independent predictive variables of baseline PWV. These 2 factors accounted for approximately 50% of the variability observed in baseline PWV ($r^2 = 0.505$, $p < 0.001$).

Association between mean PWV during the tilt test at 70° and the anthropometric and hemodynamic characteristics of the participants

Analysis of the correlation between PWV measurements taken in the supine position (baseline PWV) and PWV during the tilt test (PWVp) showed a significant influence of baseline PWV on the response obtained in orthostatic position (Figure 2A).

Results of the linear correlation analysis between carotid-femoral PWVp obtained during the tilt test and the anthropometric and hemodynamic parameters of the study participants are shown in Table 4.

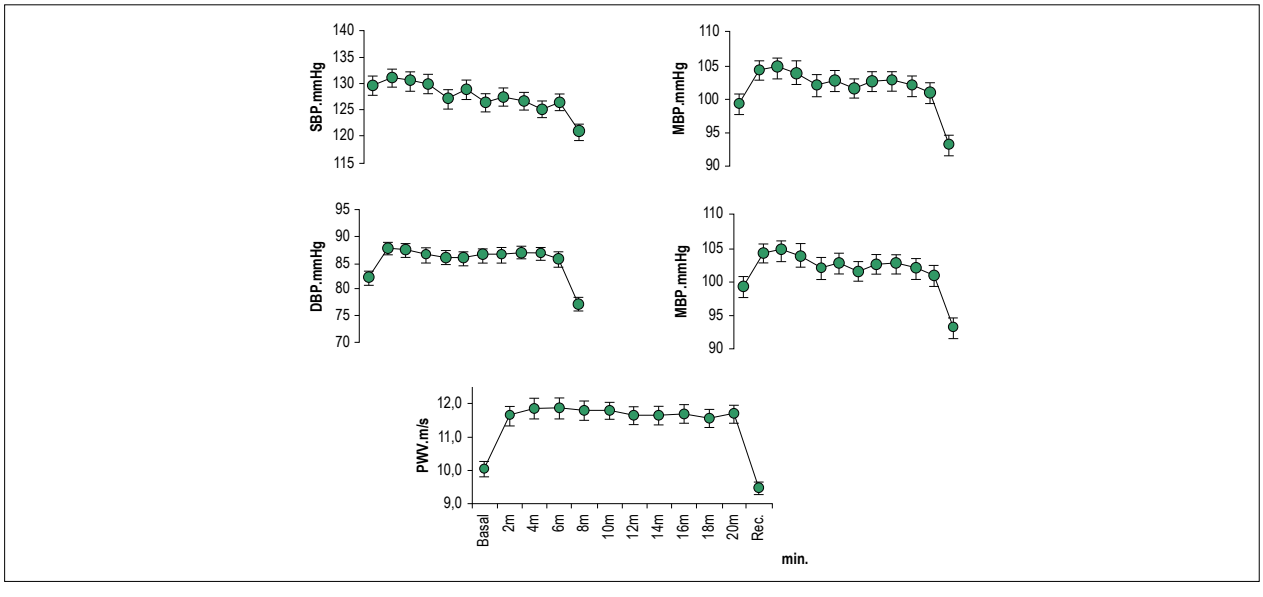

Figure 1 – *Chart showing the dynamic behavior of hemodynamic parameters monitored during the protocol. 151x155 mm (96 x 96 DPI)*

Table 2 – Effects of the tilt test at 70°/20 min. (mean in standing position) on the participants' hemodynamic parameters and PWV

Variable	Basal	Tilt test (mean in standing position)	Recovery
	Mean ± SD	Mean ± SD	Mean ± SD
SBP, mmHg	130 ± 1811	128 ± 15	121 ± 16†††
DBP, mmHg	082 ± 13***	087 ± 11	077 ± 13†††
MBP, mmHg	099 ± 15***	103 ± 11	093 ± 14†††
PP, mmHg	047 ± 13***	042 ± 8	044 ± 11†††
HR, bpm	066 ± 11***	079 ± 14	068 ± 13†††
PWV, m/s	010 ± 2.3***	011 ± 2.5	009 ± 2,0†††

*** *p < 0.001 vs. tilt test;* ††† *p < 0.001 vs. tilt test. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: medium blood pressure; PP: pulse pressure; HR: heart rate; PWV: pulse wave velocity.*

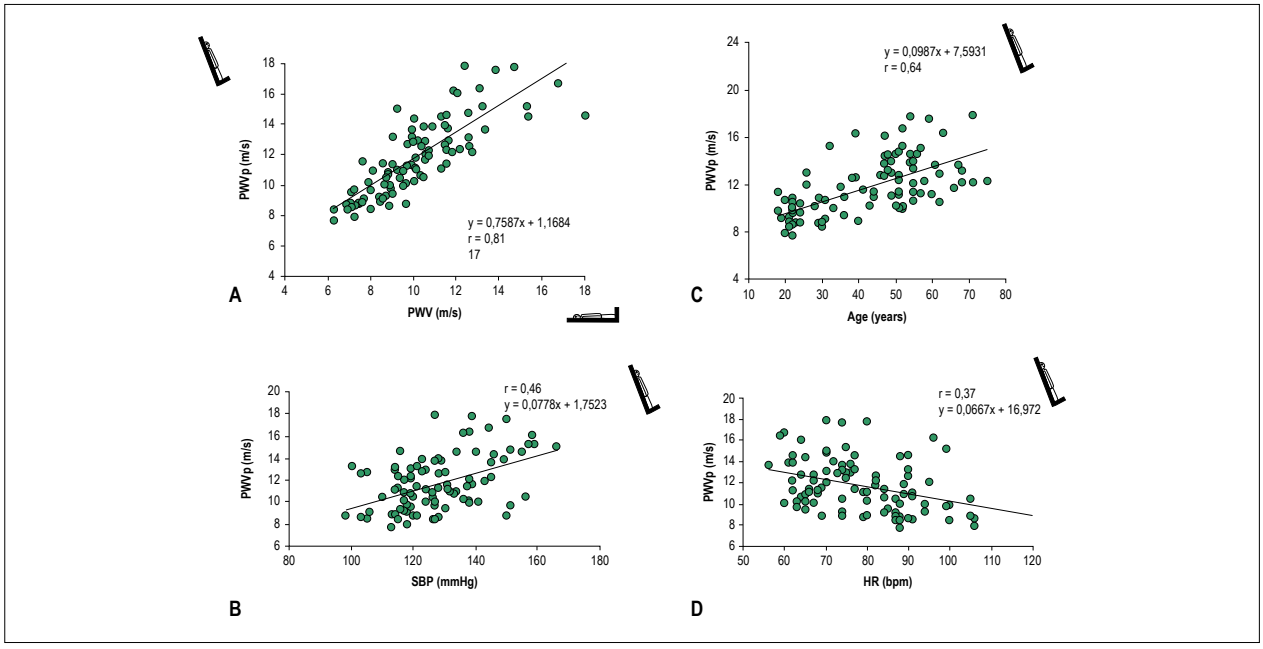

Figure 2 – *Chart of dispersion between carotid-femoral pulse wave velocity in the standing position (PWVp) and: A – basal carotid-femoral pulse wave velocity (basal PWV), p < 0.01; B – systolic blood pressure (SBP), p < 0.001; C – age, in 93 participants, p < 0.001; D – heart rate (HR) in 93 participants, p < 0.001.*

Table 3 – Correlation between carotid-femoral pulse wave velocity in the supine position and anthropomorphic and hemodynamic parameters

Parameters	Correlation coefficient	p value
Age, years	0.593	< 0.001
Weight, kg	0.063	NS
Height, cm	–0.125	NS
BMI, Kg/m²	0.194	NS
SBP, mmHg	0.547	< 0.001
DBP, mmHg	0.528	< 0.001
MBP, mmHg	0.560	< 0.001
HR, mmHg	0.063	NS
PP, mmHg	0.216	< 0.05

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: medium blood pressure; HR: heart rate; PP: pulse pressure; NS: no significance.

Table 4 – Correlation between mean carotid-femoral PWV during the tilt test at 70°/20 min with anthropomorphic and hemodynamic parameters

Parameters	Correlation coefficient	p value
Age, years	0.638	< 0.001
Weight, kg	0.220	< 0.05
Height, cm	–0.020	NS
BMI, kg/m²	0.323	< 0.01
SBPp, mmHg	0.464	< 0.001
DBPp, mmHg	0.363	< 0.001
MBPp, mmHg	0.358	< 0.001
HRp, mmHg	–0.366	< 0.001
PPp, mmHg	0.307	< 0.01

BMI: body mass index; SBPp: mean systolic blood pressure during the tilt test; DBPp: mean diastolic blood pressure during the tilt test; MBPp: mean medium blood pressure during the tilt test; HRp: mean heart rate during the tilt test; PPp: mean pulse pressure during the tilt test; NS: no significance.

Once again, multiple linear regression defined age and SBP as the major independent predictive factors of PWV obtained during the tilt test, accounting together for 49% of the variations in PWV during that test ($r^2 = 0.490$).

Association between PWV during the recovery phase and the anthropometric and hemodynamic characteristics of the participants

The correlation of variables obtained when the individuals returned to the supine position 20 minutes after the tilt test (recovery phase) was assessed. This final phase of the study represents an immediate response (0–2 min) of the hemodynamic parameters and their correlation with PWV during the recovery phase (PWVrec). A significant correlation was observed between PWVrec and most variables assessed in this phase of the protocol. Once again, the variable age had the greatest positive correlation ($r = 0.533$, $p < 0.001$) with PWVrec. A positive correlation was also observed between PWVrec and the following parameters: BMI ($r = 0.26$, $p < 0.05$); SBP ($r = 0.39$, $p < 0.001$); DBP ($r = 0.49$, $p < 0.001$); and MBP ($r = 0.457$, $p < 0.001$). In the recovery phase, a negative correlation between HR ($r = 0.055$, NS) and PWVrec was no longer observed. As occurred in the 2 preceding phases, multiple linear regression in the recovery phase showed that SBP ($p < 0.001$) and age ($p < 0.001$) were independent predictors of variations in PWVrec. Together, these variables accounted for approximately 40% of the variations in PWVrec.

Analysis of the effects of distensibility pressure on aortic stiffness in the baseline supine position, orthostatic position and after the tilt test

Variation in the carotid-femoral PWV, as an index of aortic stiffness, was assessed with regard to the SBP values, aiming at comparing the effects of distensibility pressure on the mechanical properties of the great arteries in the population (Figure 2B).

The analysis of SBP in the passive orthostatic position showed that SBP accounted for approximately 21% ($r^2 = 0.214$, $p < 0001$) of the variations observed in PWV. After adjusting SBP for age, SBP proved to play an even more significant role in the PWVp behavior pattern ($r^2 = 0.38$, $p < 0.001$).

Finally, in the statistical analysis performed in the recovery phase, SBP continued to play a significant role in the PWVrec variations ($r^2 = 0.15$, $p < 0.001$). The same was observed for SBP adjusted for age ($r^2 = 0.23$, $p < 0.001$).

Analysis of the effect of aging on aortic stiffness in the baseline supine position, orthostatic position and after the tilt test

To assess the effects of aging on arterial stiffness, the correlation curve (Figure 2C) was performed with regard to age. In all phases of the protocol, PWV significantly increased with age ($r^2 = 0.351$, $p < 0.001$; $r^2 = 0.4066$, $p < 0.001$; $r^2 = 0.283$, $p < 0.001$).

Assessment of the effect of heart rate on PWV measured in the different phases of the protocol

The influence of heart rate behavior on arterial distensibility was assessed. As previously reported, no correlation was observed between HR and PWV assessed in the baseline and recovery phases.

On the other hand, during the tilt test, a negative correlation was observed between PWVp and HR (Figura 2D).

Heart rate accounted for approximately 13% of the variation in PWV during the tilt test ($r^2 = 0.136$, $p < 0.001$), and this influence continued to be observed even after PWV was adjusted for age ($r^2 = 0.154$, $p < 0.001$). The heart rate decrease in orthostatic position was significantly conditioned to age increase in the participants ($r^2 = 0.27$, $p < 0.001$).

Finally, the correlation between the HR behavior in orthostatic position and the hemodynamic parameters at baseline was assessed. A negative correlation with baseline PWV measurement was observed ($r = -0.30$, $p < 0.01$).

Discussion

The main new finding of this study was the instant and significant increase in PWV in orthostatic position (Table 3). This pattern of vascular functional behavior was present in all individuals studied regardless of age, resulting in PWV levels in young individuals during the tilt test similar to those of elderly individuals in the supine position.

As observed in this study, although SBP is one of the most important variables accounting for a direct increase in PWV, both at baseline and in orthostatic position (Table 4), no additional increase in SBP was detected during the tilt test compared with its baseline levels (baseline SBP: 130 ± 18 mmHg, SBPp: 128 ± 15 mmHg, NS). Indeed, a decreasing trend was observed in orthostatic position. This finding is in accordance with literature data, which also evidenced lack of a statistically significant increase or even a decreasing trend in SBP in orthostatic position.[14]

Another important aspect is that although this study did not directly assess vasomotor activity, the fact that it found an increase in MAP (baseline MBP: 99 ± 15, MBPp: 103 ± 11, $p < 0.05$) means that there was probably an increase in peripheral vascular resistance due to reflex sympathetic activation induced by the fall in pulse pressure while standing. Thus, although a variable PWV may be strongly influenced by the MBP, the increased PWV can be attributed to both secondary circulatory disorders due to gravitational stress and increased peripheral vascular resistance, rather than to the effect of high MBP.

Transmission of pulse wave is known to be primarily dependent on arterial elasticity or stiffness coefficient. However, several other factors should be considered. Some of these factors are related to cardiovascular physiology, while others result from specific pathophysiological conditions.[15] Analyzing the correlation between baseline PWV and PWVp, a direct influence of the baseline pattern of arterial compliance was observed on the response of the great arteries to orthostatic position (Figura 2).

Because no significant increase in SBP was observed in orthostatic position, the increase in PWV may have resulted from circulatory dynamics disorders resulting from gravitational force, in association with structural and geometric characteristics of the aorta. This hypothesis is based on the Moens-Korteweg formula and on the knowledge that PWV depends on vascular radius and thickness, as well as on the vascular elastic module.

Measurement of PWV during the tilt test exposes the arterial segments to gravitational stress in a distinguished form, imitating, to a certain extent, what occurs during active orthostatic position.

In fact, the immediate consequence of orthostasis is that gravity favors a progressive increase in blood pressure in the segments below the cardiac level in orthostatic position.[8,16–18]

The hydrostatic pressure generated by the gravitational force changes the indifferent hydrostatic point, defined as the axial reference in which the venous blood column pressure is not altered by postural reorientation. Such point is located at the right atrial level in supine position and in the infradiaphragmatic aortic territory in orthostatic position. Because of this, an increase in blood flow to the arterial segments with greater elastic module and smaller radius occurs, evidencing the increase in the measured carotid-femoral PWV.[11,16] This increase in PWV accounts for the early return of the reflected waves from the peripheral sites to the ascending aorta. This wave, reflected earlier (during the ventricular ejection period), adds to the incident wave generated by left ventricular ejection and influences the contour of the pressure and flow waves.[10] In other words, the earlier return of the reflected component, occurring during the systolic component of the pulse wave, leads to an increase in pulse pressure (pulse summation).[19–20] This increase, provided by the reflected wave in the initial portion of the arterial pulse wave, may result from a complex, evolutionary, functional, anatomical-humoral adaptation of the vascular system, to maintain an effective cerebral blood flow in response to bipedalism (Figure 3).[21]

The observed increase in PWVp can also be attributed to the emergence of new sites of reflection of the pulse in the peripheral circulation due to a possible increase in peripheral vascular resistance in response to standing.

A phasic response of the central hemodynamics to gravitational stress has been reported in experimental studies with baboons. A later systolic peak resulting from the reflected component of the pulse wave does not occur immediately after taking orthostatic position in these animals. Therefore, the reflected wave appears later in diastole, suggesting a decrease in PWV. Then, the so-called compensatory phase occurs during response to baroreflex.[12,22]

The role played by wave reflection in the circulatory homeostasis in orthostatic position is reinforced by the observation that nitroglycerin, used sublingually for tilt test sensitization, causes peripheral vasodilation, leading to a delay in the reflected component of the pulse wave and consequent reduction in the proximal systolic pressure, culminating in symptoms of low cerebral blood flow in patients with neuromediated syncope.[23-24]

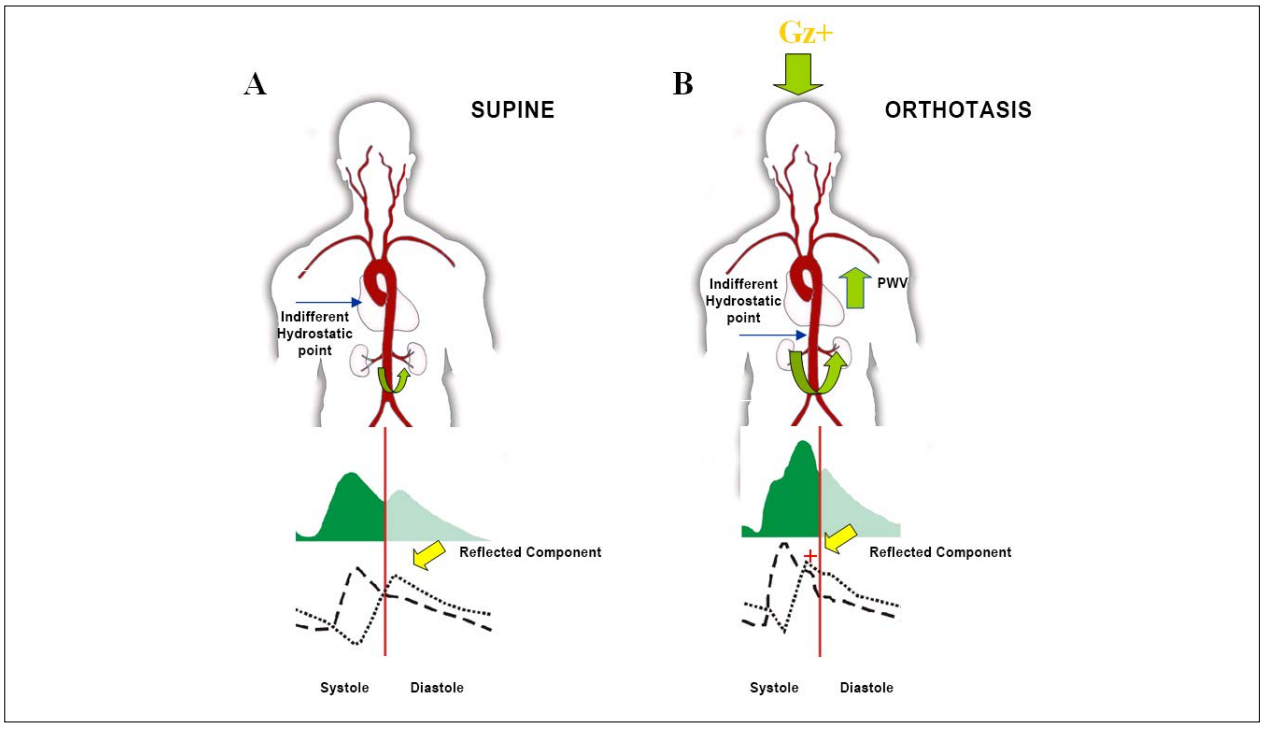

Figure 3 – *Sketch of the mechanism proposed for pulse wave velocity behavior in a healthy young individual. A – In the supine position, the reflected component occurs during the diastole due to a smaller PWV. B – In orthostatic position, due to the gravitational force, the indifferent hydrostatic point moves to the subdiaphragmatic aorta, which has a smaller radius and a greater elastic module; therefore, PWV increases, leading to an earlier return of the reflected component of the pulse wave, which then occurs with a systolic "pulse summation". Thus, pulse wave morphology is altered. 321x263 mm (72 x 72 DPI)*

In reality, although a decrease in the coefficient of reflection is observed using nitroglycerin, an increase in aortic stiffness is paradoxically observed. This secondary aortic stiffness was attributed to a possible reflex activation of the sympathetic nervous system.[25]

Analysis of PWV behavior in this series of patients also showed that the increase in PWV was positively correlated with age, showing that, even in the elderly, who have higher baseline PWV levels, an additional increase occurred by taking orthostatic position ($r^2 = 0.357$, $p < 0.001$ in the supine position and $r^2 = 0.406$, $p < 0.001$ in orthostatic position). In reality, this additional increase in PWV in the elderly results from the addition of structural findings with the dynamic postural component.

Another intriguing aspect of this study was the discovery of a negative correlation between HR and PWV in orthostatic position ($r = –0.36$, $p < 0.001$). Age was the major variable responsible for HR behavior in orthostatic position ($r^2 = 0.27$, $p < 0.001$).

Aiming at better understanding that finding, the correlation between HR measured during orthostatic stress and baseline PWV was also assessed. A negative correlation between HR and baseline PWV ($r = –0.29$, $p < 0.01$) was observed. This result shows a clear association of the baseline pattern of arterial compliance with the level of HR response to orthostatic position.

Initial experimental studies and studies in human beings in the supine position reported a positive correlation between increased HR and increased aortic stiffness.[1,7,26–27] However, Wilkinson et al.,[14] in a study assessing PWV behavior and the invasive augmentation index in healthy individuals undergoing atrial stimulation, reported no significant alterations in aortic distensibility due to an increase in HR.[14]

Further to the lack of consensus on the effects of heart rate on PWV, the possible mechanisms contributing to PWV changes with heart rate have yet to be fully elucidated, although many investigators have attributed heart-rate related changes in arterial stiffness to the viscoelasticity of the arterial wall. With high heart rate being an independent prognostic factor of cardiovascular disease and its association with hypertension, the interaction between heart rate and PWV continues to be relevant in assessing cardiovascular risk.[28]

Although a first analysis of these data point to a potential disagreement with our findings, they should be considered as complementary to each other and analyzed within a dynamic context, because they were obtained in very distinct physiological conditions.

Cross-sectional studies have reported that baseline HR does not differ between young and elderly individuals in the supine position.[29–30] However, HR assessment of healthy individuals in the sitting position has shown that HR decreases with age in both sexes. On the other hand, studies using the tilt test to assess cardiovascular adaptation to orthostatic stress have also reported a significantly lower response of HR in elderly individuals.[16]

The decrease in HR variability due to postural change observed in elderly patients compared with that in young individuals has been attributed to a decrease in the recruitment of the activity of baroreceptors in orthostatic position.[16,29–30]

Considering the dynamic behavior of aortic compliance due to postural change, a greater decrease in systolic volume (SV) in young individuals could lead to a decrease in pulsatile aortic strain, with a subsequent decrease in baroreceptor stimulation and an increase in HR.[31]

Maintenance of systolic volume in elderly individuals has been attributed to lower venous compliance in this group, allowing preservation of cardiac filling volume, and, consequently, of systolic volume.[11] However, a lower HR associated with age, such as that observed in this study, could also mean an adaptive mechanism of man to bipedalism.

Heart rate is known to affect preload via its effect on diastolic filling time and to modulate the myocardial contractility status, altering the myocardial concentration of Ca^{2+} and Na^{+}. As a consequence of increase in myocardial contractility, HR also modulates end-systolic volume, systolic volume and ejection fraction.[11] Thus, a lower HR could initially allow better cardiac performance in the presence of a stiffer arterial system.

Considering all that has been presented so far, the following hypothesis was formulated: the return of the reflected component of the pulse wave is fundamental to the immediate adaptation to orthostatic position, as well as to the adequate adaptation of baroreceptors. Based on data from this study, it is not possible to determine whether this increase is not only due to the dynamic circulatory changes secondary to gravity, but also to sympathetic activation in response to decreased stroke volume and pulse pressure. If the above hypothesis is correct, one may consider the role played by our findings in some very common clinical conditions associated with orthostatic position (Figure 4).[9,32–34]

Study limitations

This study has some limitations. Assessment of sympathetic response was not performed during the tilt test through venous measurement of catecholamines or recording of neural sympathetic activity through electroneuromyography.[35] However, although the present study did not directly assess vasomotor activity, an increase in mean arterial pressure (supine: 099 ± 15 mmHg vs. orthostasis: 103 ± 11 mmHg, $p < 0.01$) allowed us to infer that there has been an increase in peripheral vascular resistance due to the reflex sympathetic activation induced by the drop of pulse pressure in orthostasis.

Another limiting factor was the lack of study of the baroreflex response to orthostatic stress caused by the tilt test, which resulted in lack of data referring to its dysfunction and to the specific location of alterations in its reflex arch. Change in HR was the only response observed, with no other baroreflex measurements, particularly those of systolic volume, although they have been shown to be closely related.[36]

Another possible source of error in PWV measurement lies in determining the arterial segment. Its superficial and noninvasive measurement allows only an estimation of the distance traveled by the pulse wave.

Obtainment of carotid-femoral PWV comprises the analysis of a relatively long arterial segment, which may be extremely tortuous from the three-dimensional point of view. Another factor is that the vessel may be distorted by the direct application of

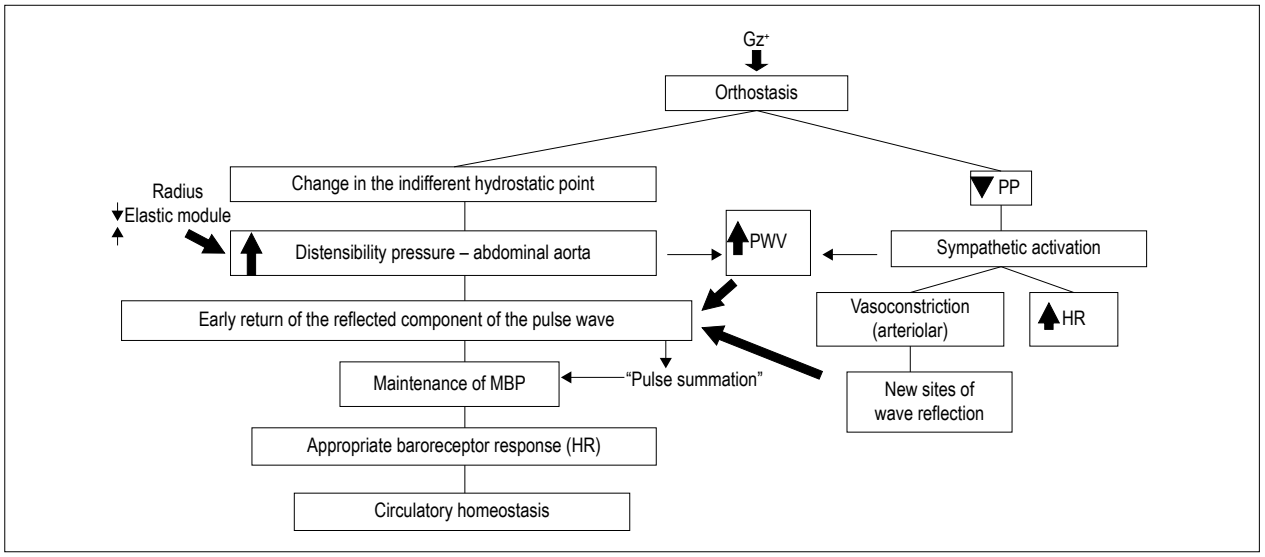

Figure 4 – *Hypothesis proposed for the role played by the increase in carotid-femoral pulse wave velocity in the maintenance of circulatory homeostasis in response to orthostatic stress. 309x165 mm (72 x 72 DPI). PP: pulse pressure; PWV: pulse wave velocity; MBP: medium blood pressure; HR: heart rate.*

the pressure transducer. This aspect is more evident in deeper vessels.[37] These observations become potentially more significant when carotid-femoral PWV measurement is considered during the tilt test. The change from supine decubitus to orthostatic position may increase the difficulty in recording femoral pulse, mainly in obese individuals. In some cases, recording femoral pulse is impossible. In this study, we tried to reduce these sources of error by using observers who were very well-trained in measuring PWV in the supine and orthostatic positions.

Although this study does not allow comparison of the influence of sex on arterial behavior in orthostatic position, the inclusion of female individuals in this study may not have interfered with the response of PWV increase to postural stress. Considering the greater arterial distensibility in young females,[38] a relatively smaller increase could occur in PWV due to postural stress caused by the tilt test. However, this hypothesis cannot be statistically confirmed with the data from this study.[39]

Conclusion

In conclusion, our study of healthy individuals and in individuals with untreated mild-to-moderate arterial hypertension demonstrates a rapid increase in PWV during the tilt test and its return to baseline levels when resuming to supine position. We found strong indications that these results may enable a better comprehension of the response of the great arteries to gravitational stress. These results may also elucidate this behavior in the long run, in the presence of inherent degenerative disorders, such as arterial hypertension and aging, and predetermined genetic markers.

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Author contributions

Conception and design of the research: Neto JE, Ferreira A; Acquisition of data: Neto JE, Ferreira A, Futuro G, Santos LC, Gomes F, Heringer Filho N; Analysis and interpretation of the data: Neto JE, Ferreira A; Statistical analysis and Obtaining financing: Neto JE; Writing of the manuscript: Neto JE, Mill JG; Critical revision of the manuscript for intellectual content: Neto JE, Ferreira A, Mill JG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Postural Changes and their Influence on Functional Behavior of the Great Arteries

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Short Editorial related to the article: Influences on the Functional Behavior of Great Arteries during Orthostasis

The large arteries, especially the aorta, are known to play a major role in the circulation of blood flow both during ventricular ejection and during diastole, thus providing the blood supply required by the organs. Additionally, the damping function exercised by the aorta plays a fundamental role in central hemodynamics, providing adequate ventricular-arterial coupling during the cardiac cycle.[1]The loss of this function due to increased arterial stiffness plays a role in the development of hypertension and left ventricular hypertrophy and has been associated with the development of atherosclerosis and myocardial ischemia.[2] Noninvasive methods for assessing the function of large arteries, such as pulse wave velocity (PWV) measurement, have provided a better understanding of the correlations of arterial stiffness with cardiovascular disease, and have been used as prognostic markers in different populations.[3]However, due to methodological limitations, all studies have been performed in the supine position, and the impact of postural changes, especially orthostasis, has not been evaluated on these vascular properties. Thus, the study by Elias Neto et al.[4] published in this issue, as the first to evaluate the effect of orthostasis on the aortic functional properties in normotensive and hypertensive individuals not treated by the aortic PWV measurement in humans, provides important information to understand the role of these properties in the physiological adaptation of central hemodynamics in relation to the gravity effects. The authors evaluated nearly 100 individuals with no evident cardiovascular disease by measuring carotid-femoral PWV performed in the supine and standing positions after the 70° tilt test and demonstrated a significant and sustained increase in PWV throughout the tilt test, in both young and older individuals. Interestingly, although there was a direct and significant association between baseline and post-orthostasis PWV values and systolic blood pressure (SBP), SBP remained unaltered or showed a slight decrease during the tilt test and, therefore, the increase in PWV during inclination occurred by other mechanisms of circulatory adaptation, including an increase in peripheral arterial resistance (indirectly suggested by the observed increase in mean BP) and changes in circulatory dynamics promoted by the gravitational force, which are related to the differential structural and geometric characteristics of the aorta throughout its trajectory. In a study with a smaller number of individuals and another methodology for PWV assessment, the authors also found an increase in PWV with the tilt test and attributed this increase to increased hydrostatic pressure and greater sympathetic activity.[5]

Due to gravitational effect, blood flow increases in the more distal arterial segments, which have smaller diameter and less elasticity, causing an increase in PWV and also in BP in the infradiaphragmatic territories.[6] The consequence of this increase in carotid-femoral PWV would be the early return of the retrograde wave to the heart, increasing pulse pressure at the aortic root, which could contribute to maintaining a more adequate cerebral blood flow with the biped position assumed by humans. It is noteworthy that this same mechanism of early wave reflection in the aortic root is one of the main factors responsible for SBP increase in the elderly, as a consequence of the increase in arterial stiffness observed with aging.[7] Evaluating the results of the study by Elias Neto et al., the PWV of young individuals after orthostasis showed values similar to those found in the elderly in the dorsal position, corroborating the role of increased PWV with increased retrograde wave in the individual's adaptation to the orthostatic position.

However, it is still necessary to recognize the role of this adaptive circulatory phenomenon to the orthostatic position in the development of cardiovascular pathologies, such as arterial hypertension and atherosclerosis. One could speculate, for instance, whether an exacerbated response of this adaptive mechanism, with an exaggerated increase in PWV due to orthostasis, could participate in the mechanism of arterial hypertension in some situations, such as isolated spurious systolic hypertension of young individuals, partially explained by the increase in the pulse wave amplification phenomenon between the aorta and the brachial artery.[8]

Recently, some studies have evaluated the influence of gravity on arterial stiffness and the role of these changes in orthostatic adaptation to the absence of gravity.[9,10] In one of these studies, the authors demonstrated that astronauts who showed more tolerance to orthostatism after a prolonged period in space showed an increase in arterial stiffness manifested by increased pulse velocity, while intolerant individuals showed increased arterial distensibility.[9] These data reinforce the participation of increased PWV in the process of adaptation to gravity.

As mentioned by the authors, the study has some limitations, making some hypotheses just speculative ones, such as the participation of greater sympathetic activity in this process,

Keywords

Aorta/physiopathology; Hypertension; Hypertrophy,Left Ventricular; Blood Flow; Pulse Wave Analysis; Stending Position; Gravitation; Aging.

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since it has not been directly evaluated. Another limitation not mentioned by the authors, but which may show differences in result interpretation, is the predominance of males in the studied population. It is well known that women have higher measures of arterial stiffness, especially earlier reflection waves, probably associated with smaller aortic diameter.[11] These changes could interfere with the response of PWV to orthostasis in different genders, as seen in a small study with astronauts who remained 6 months without gravity, with women showing greater degrees of carotid stiffness than men after returning to the effect of gravity.[10]

Nevertheless, these findings provide important parameters for discussing the participation of large-vessel buffering properties in physiological adaptations to postural changes, which may provide new therapeutic strategies for clinical conditions where these adaptations are inadequate.

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Risk of Obstructive Sleep Apnea and Echocardiographic Parameters

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Abstract

Background: Obstructive sleep apnea (OSA) is a chronic progressive disorder with high mortality and morbidity rate, associated with cardiovascular diseases (CVD), especially heart failure (HF). The pathophysiological changes related to OSA can directly affect the diastolic function of the left ventricle.

Objectives: To assess the association of the risk of OSA, evaluated by the Berlin Questionnaire (BQ), and echocardiographic (ECHO) parameters related to diastolic dysfunction in individuals without HF assisted in primary care.

Methods: A cross-sectional study that included 354 individuals (51% women) aged 45 years or older. All individuals selected were submitted to an evaluation that included the following procedures: consultation, filling out the BQ, clinical examination, laboratory examination and transthoracic Doppler echocardiography (TDE). Continuous data are presented as medians and interquartile intervals, and categoric variables in absolute and relative frequencies. The variables associated with risk of OSA and at the 0.05 level integrated the gamma regression models with a log link function. A value of $p < 0.05$ was considered an indicator of statistical significance. Exclusion criteria were presence of HF, to fill out the BQ and patients with hypertension and obesity not classified as high risk for OSA by other criteria. All individuals were evaluated on a single day with the following procedures: medical appointment, BQ, laboratory tests and ECHO.

Results: Of the 354 individuals assessed, 63% were classified as having high risk for OSA. The patients with high risk for OSA present significantly abnormal diastolic function parameters. High risk for OSA confirmed positive and statistically significant association, after adjustments, with indicators of diastolic function, such as indexed left atrium volume LAV-i ($p = 0.02$); E'/A' ($p < 0.01$), A ($p = 0.02$), E/A ($p < 0.01$).

Conclusion: Our data show that patients at high risk for OSA present worsened diastolic function parameters measured by TDE. (Arq Bras Cardiol. 2019; 113(6):1084-1089)

Keywords: Cardiovascular Diseases; Sleep Apnea, Obstruction; Indicators, Morbimortality; Heart Failure; Ecocardiography/methods; Polysonography/methods.

Introduction

Obstructive sleep apnea (OSA) is a chronic progressive disorder with high mortality and morbidity rate and is associated with cardiovascular diseases (CVD), including heart failure (HF).[1] The physiopathological interaction between OSA and cardiovascular disease is complex and involves sympathetic activation, oxidative stress and inflammation, endothelial disfunction and disfunction of the Circadian clock gene.[2-4]

Besides polysomnography, considered the gold standard for the diagnosis of OSA, there are different scales which do not diagnose the disease, but indicate the people at risk, among which is the Berlin Questionnaire (BQ).[5] A meta-analysis published in 2017 estimated that the sensitivity of the Questionnaire to detect OSA was 76%, 77% and 84% and its specificity was 59%, 44% and 38% for patients with mild, moderate and severe OSA, respectively. It is necessary to point out the adequate sensitivity which enables the BQ as a tracking too, making early diagnosis of OSA possible.[6]

The prevalence of diastolic disfunction in patients with OSA ranges from 23% to 56% and there is a dose-response relation between the severity of diastolic disfunction and the severity of strong physiopathological basis demonstrated for a continuum of diastolic disfunction and heart failure in their two phenotypes, which means a greater risk for these patients to develop HF. The association of OSA with diastolic disfunction was observed even in its initial stages.[7]

We have not yet found studies of the association of characteristic echocardiographic parameters of diastolic disfunction and the presence of the risk of OSA in patients with no signs or symptoms of heart failure.

The purpose of this study was to assess the association of the risk of OSA and echocardiographic parameters related to diastolic disfunction in patients without HF assisted by "*Programa Médico de Família*" (PMF – Family Doctor Program) in the city of Niterói.

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Methods

A cross-sectional study that integrates the DIGITALIS STUDY and included 633 individuals (51% females) between 45 to 99 years of age enrolled in the PMF, Niterói, RJ. The data were obtained from July 2011 to December 2012. The methodology applied was previously described.[8]

All individuals selected for the study were evaluated on a single day. The evaluation included the following procedures: filling out the questionnaire, consultation and clinical examination, laboratory tests and transthoracic Doppler echocardiography (TDE).

Of the 633 participants examined by the DIGITALIS STUDY, 64 were excluded for having been diagnosed with HF or for not having answered the BQ completely, and 214 for having hypertension or being obese and not having been classified as having risk of OSA by other criteria. For the present analysis, 354 individuals were included (figure 1).

The TDE scans were performed by two echocardiographers who had no previous knowledge of the results of the other tests, using two pieces of equipment (Cypress 20 Acuson/ Siemens EUA/AU-3 Partner, Esaote — Italy). The tests were performed according to the recommendations for quantification of chambers of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE). Systolic function was evaluated by measuring the left ventricular ejection fraction (LVEF) by the Simpson's method.[9]

The participants were categorized into positive or negative for the risk of OSA based on their answers to the individual items of the QB and their total score in the categories of symptoms.[5]

Statistical analysis

This was performed with the SPSS v 21.0 (Chicago, Illinois, USA). Continuous data are presented as medians and interquartile ranges and categorical variables as relative and absolute frequencies. The differences between groups with and without risk of OSA were tested by the non-parametric Mann-Whitney test and the categorical variables by the qui-square test with correction of continuity and Fisher's exact test, when necessary. The variables that presented an association with the risk of OSA at a 0.05 level integrated the gamma regression models with a log link function. As echocardiographic parameters are very correlated among each other, it was chosen to adjust a model for each parameter (outcome) associated with the presence or absence of risk of OSA in the preliminary analysis at a level of 0.05. Exposed and non-exposed coefficient exponentials are interpreted as the result of the arithmetic means of the outcome. A value of $p < 0.05$ was considered an indicator of statistical significance.

Ethical considerations

This study was conducted according to the principles established in the Declaration of Helsinki, revised in 2000 (Scotland, 2000). The protocol for the study was approved by the Institution's Research Ethics Committee under code number CAAE:0077.0.258.000-10.

Results

Of the 354 individuals analyzed, 63% were classified as having a risk of OSA. Table 1 presents the clinical characteristics according to the presence of the risk of OSA. Individuals with risk were mostly women, older, with higher BMI, glucose, uric acid and triglyceride levels, urine albumin-to-creatinine ratio and blood pressure. The patients with risk of OSA, compared to the ones with no risk, presented greater abnormalities of the diastolic function parameters: LAV-i (+), DT (+), E(-), E'/A' (+), E/E' (-), A(+), E/A (+), PPEI (+) and VIS (+), which may indicate a less effective diastolic function. Such differences were statistically significant (Table 2).

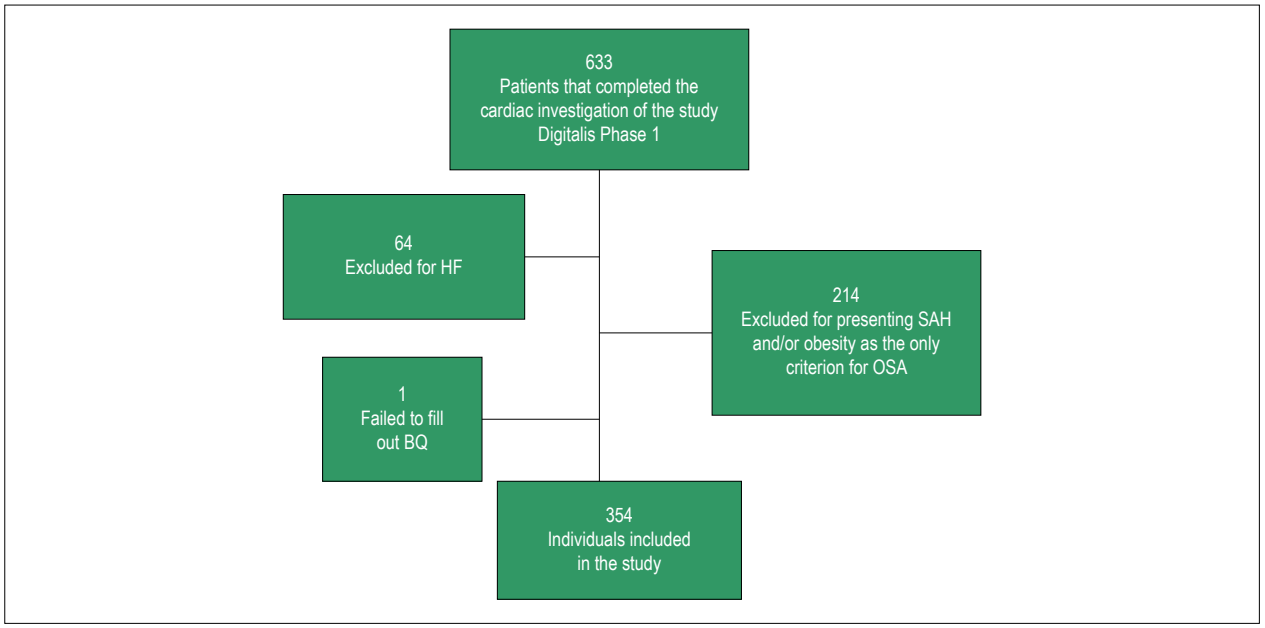

Figure 1 – *Flowchart of sample selection. BQ: Berlin Questionnaire; HF: heart failure; HBP: high blood pressure or arterial hypertension; OSA.*

Table 1 – Median with interquartile* range or absolute and relative frequency ** of clinical characteristics according to the presence of high risk for OSA modified***

	High risk of OSA modified*		Value
	Yes n = 223	No n = 131	
Gender			**0.01**
Male	79 (35.4)	66 (50.4)	
Female	114 (64.6)	65 (49.6)	
Age (in years)	57.0 (51.0–63)	54.0 (49.0–61.0)	0.01
BMI kg/m^2	29.4 (26.1–33.0)	24.6 (22.4–27.3)	< 0.01
Glucose (mg/dL)	102.5 (92.0–117.2)	97.0 (88.0–108.0)	< 0.02
Urea (mg/dL)	31.0 (26.0–37.0)	31.0 (25.2–36.0)	0.69
Creatinine (mg/dL)	0.82 (0.71–0.99)	0.85 (0.74–0.96)	0.56
Uric acid (mg/dL)	5.6 (4.4–6.6)	4.7 (3.9–5.6)	< 0.01
Cholesterol (mg/dL)	219.0 (193.0–250.0)	213.0 (187.0–239.0)	0.17
LDL-cholesterol(mg/dL)	135.8 (117.7–163.5)	134.1 (107.3–159.1)	0.19
HDL-cholesterol (mg/dL)	41.0 (51.5 (63.0)	55.0 (44.0–63.0)	0.23
Triglycerides (mg/dL)	126.5 (96.0 (183.7)	106.0 (73.0–153.0)	< 0.01
Urine albumin-to-creatinine ratio	9.9 (5.7–22.3)	7.7 (4.7–13.6)	< 0.01
Mean heart rate (bpm)	71.0 (63.0–80.0)	69.0 (62.5–76.5)	0.19
Systolic arterial pressure I (mmHg)	137.33 (122.5–152.0)	122.0 (113.3–129.5)	< 0.01
Diastolic arterial pressure (mmHg)	84.0 (76.3–92.67)	75.5 (70.3–80.7)	< 0.01
Myocardial infarction			
Yes	9 (4.0)	4 (3.1)	0.86
No	214 (96.4)	127 (96.9)	
Stroke			
Yes	11 (4.9)	1 (0.8)	0.07
No	212 (95.1)	130 (99.2)	

*OSA: obstructive sleep apnea; BMI: body mass index; bpm: beats per minute. *Differences tested by the Mann-Whitney test; ** Differences tested by Pearson's qui-square test with continuity correction or Fisher's exact test when necessary; *** Individuals who were classified as at risk only in category 3 were excluded (Adapted from Netzer et al., 1999).*[5]

The exponentials of the coefficients for each gamma regression model are presented in table 3. In all cases, the exponentials of the coefficients were adjusted for gender, age, BMI, fasting glucose, triglycerides, uric acid, urine albumin-to-creatinine ratio and systolic and diastolic blood pressure in their continuous forms. Association of the high risk of OSA with less effective diastolic function was confirmed for: LAV-i (+), E/A (+), E'/A'(+), A (+) association with DT (+) E' (+), which reached a significance of 0.10 (Table 3).

Discussion

The present study evaluated the presence of abnormalities on TDE, associated with diastolic disfunction, in individuals without signs or symptoms of HF, according to the presence of risk of OSA. The BQ was used as a tool and the individuals with obesity and high blood pressure who did not present other criteria for OSA were excluded. In primary care, selective methods for OSA are more easily applied than standard polysomnography, being useful in the stratification of risk, as they have lower costs and are easily accessible.[7] Using the BQ in the population assisted in primary care programs, such as the "*Médico de Família*" program, would help to select patients at risk for OSA, who should then be referred for TDE and polysomnography investigation.

OSA is related to different physiopathological mechanisms triggered by hypoxia and sleep fragmentation, involving sympathetic hyperactivity, inflammation, endothelial disfunction and oxidative stress, among other factors leading to arterial hypertension, atrial fibrillation, stroke and HF outcomes.[10]

Various studies have demonstrated alterations of different markers of diastolic function of the LV in patients with OSA as an indexed increase in left atrial size (LAV-i),[11,12,13] altered E/A ratio,[14,15] early diastolic mitral annular velocity (E')[16,17] and increase in E/E ratio.[14,18] Our data show alterations in some of these markers: LAV-i, E'/A' ratio, A wave, E' and E/A ratio in patients at risk for OSA.

Table 2 – Median with interquartile* range or absolute and relative frequency ** of echocardiographic parameters according to the presence of high risk of OSA modified

	High risk of OSA modified		p value
	Yes	No	
ILAD (cm/m^2)	1.9 (1.7–2.1)	1.9 (1.7–2.0)	0.37
ILAV-i (ml/m^2)	21.1 (17.7–24.9)	19.9 (16.8–22.7)	0.01
DT (ms)	228.0 (186.0–261.0)	200.0 (174.0–228.0)	< 0.01
E' (cm/s)	10.0 (8.0–12.0)	11.5 (9.0–13.0)	< 0.01
E'/A'	0.83 (0.64–1.20	1.14 (0.80–1.37)	< 0.01
E/E'	6.4 (5.4–7.8)	6.0 (5.0–7.0)	0.02
E (cm/s)	63.0 (53.0–76.0)	66.1 (54.0–75.0)	0.31
A (cm/s)	68.0 (56.0–81.9)	58.0 (48.0–68.0)	< 0.01
E/A	0.93 (0.7–1.2)	1.18 (0.9–1.4)	< 0.01
ILVM (g/m^2)	89.4 (77.3–103.6)	88.7 (74.4–102.0)	0.49
IFDV (ml/m^2)	62.08 (53.5–68.7)	63.8 (54.0–72.3)	0.15
RWT (mm)	0.3 (0.3–0.4)	0.3 (0.3–0.4)	0.28
IPWT (mm)	8.0 (7.0–9.0)	8.0 (7.0–8.0)	0.03
ILVDD (mm)	49.0 (46.0–51.0)	48.0 (45.0–51.0)	0.53
IVS (mm)	8.0 (7.0–9.0)	8.0 (7.0–9.0)	0.02

*ILAD: indexed left atrial diameter; LAV-i: indexed left atrial volume; WT:E' wave deceleration time; E: early diastolic mitral annular velocity; E'/A': early diastolic mitral flow velocity; A:atrial contraction; ILVM: indexed left ventricular mass; IFDV: indexed final diastolic volume; RWT: relative wall thickness; IPWT: indexed posterior wall thickness; ILVDD: indexed diastolic left ventricular diameter; IVS: intraventricular septum. *Differences tested by the Mann-Whitney test; ** Differences tested by Pearson's qui-square test with correction by Fisher's exact test when necessary.****** Individuals who were classified as at risk only in category 3 were excluded (Adapted from Netzer et al., 1999).[5]*

Table 3 – Exponentials of gamma regression adjusted coefficients* of the presence of high risk of OSA (yes/no)*****

	Exponential of the adjusted coefficient	p value
LAV-i (ml/m^2)	1.10 (1.02–1.18)	0.02
TD (ms)	1.05 (0.99–1.11)	0.10
E'	1.05 (0.99–1.11)	0.10
E'/A'	0.87 (0.72–0.96)	< 0.01
E/E'	1.01 (0.94–1.09)	0.81
A	1.10 (1.02–1.18)	0.02
E/A	0.86 (0.79–0.94)	< 0.01
IEPP (mm)	1.02 (0.98–1.06)	0.24
SIV (mm)	1.02 (0.98–1.06)	0.42

LAV-i: indexed left atrial volume; WT: E' wave deceleration time; E: early diastolic mitral annular velocity; E'/A': early diastolic mitral flow velocity; A: atrial contraction; IPWT: indexed posterior wall thickness; IVS: intraventricular septum. For each regression model whose outcome was an echocardiographic parameter, exponentials of the coefficients were adjusted for gender, age, BMI, fasting glucose, triglycerides, serum uric acid, urine albumin/creatinine ratio and systolic and diastolic arterial pressure in their continuous forms (mmHg), **Gamma regression with log link function; ***Berlin Questionnaire.*

We observed that LAV-i, a marker of diastolic disfunction, presents a strong association with the presence of high risk of OSA, identified by the BQ, regardless of the presence of hypertension or obesity, when not associated with an indicator of the risk of OSA. Wachter et al.[3] investigated if OSA affects diastolic function in a primary care cohort and observed that diastolic function is independently associated with OSA in patients with cardiovascular risk factors.[3] Gottlieb et al. observed that in patients without HF and coronary arterial disease, the presence of OSA was an independent HF predictor in men and not in women.[19] In another study, Usui et al.[20] demonstrated that the severity of OSA may contribute directly to LV diastolic disfunction regardless of LV geometry, arterial stiffness, obesity and is associated with cardiovascular risk factors.[20]

In patients with controlled arterial hypertension, Lisi et al.[21] observed that mild to moderate OSA, diagnosed by polysomnography, is associated with diastolic disfunction, regardless of age, gender and mean arterial blood pressure levels and in the absence of concentric left ventricular hypertrophy or increased left atrium. The authors suggest that nocturnal hypoxemia could be the key factor for the development of diastolic disfunction.[21]

Hypertension is the main cause of diastolic disfunction and is also one of the biggest consequences of OSA.[22] Two studies excluded obese individuals from the analysis[20,23] and at least one excluded obese and hypertensive individuals.[23] The two articles studied solely individuals with OSA and compared the moderate OSA group with the one with severe OSA. In both studies, the E/A association was statistically significant. In the study of Imai et al.,[23] LAV-i and E/E' ratio were significantly bigger in the severe OSA group. The data from these two studies show that the association of the OSA with abnormal diastolic function may occur in non-obese and non-hypertensive individuals. Due to the high prevalence of these two conditions, in the present study, it was not possible to exclude them from the analysis to confirm the independent association and the risk of OSA and the indicators of diastolic disfunction.

The present study evaluated the contribution of several echocardiographic parameters, which represent, with bigger reliability, the structural or cardiac function abnormalities that may be associated with the diagnosis of OSA. LAV-i. TD, E/A ratio, E'/A' ratio and A wave abnormalities in individuals with OSA indicated a less effective diastolic function in patients with sleep disorders, compatible to findings that defined OSA through polysomnography.

Limitations

The BQ does not confirm the OSA and only points out those patients at risk for the syndrome, with reduced sensitivity and specificity, questionable reproductivity, because the perception and documentation of what is informed may not be precisely estimated, since it involves limitations resulting from the level of literacy or pre-existing cerebral vascular conditions of the informant, making it difficult to understand the BQ, especially by the elderly. Due to the limitation of resources and because it is a tracking study, each patient was examined by only one echocardiographer, preventing inter or intra-observer concordance examination. Despite these limitations, the results according to the TDE parameters among the risk groups were in line with those of the literature.

Because it is a cross-sectional study, it was not possible to establish a causal link. Despite having excluded from the analysis hypertensive and obese individuals that who did not meet any other criterion for the risk of OSA according to the BQ, those at risk presented higher mean BMI, systolic and diastolic arterial pressure, which notwithstanding the control (inclusion in multiple models) still may have caused residual confounding.

Conclusions

Evaluation of the association of OSA and the presence of structural and functional cardiac abnormalities obtained by the TDE can contribute to a discussion about the adoption of the BQ in the community, to select individuals with cardiovascular risk that should undergo TDE, despite its limitations.

This strategy of fast execution may be easily incorporated into the routine of assessment of patients with risk factors for the development of HF, but it still needs a detailed analysis and long-term follow-up for its definitive prescription.

Author contributions

Conception and design of the research: Leite AR, Garcia-Rosa ML, Lagoeiro AJ; Acquisition of data: Leite AR, Macedo EA, Vasques Netto D, Santos CC, Martinez DM; Analysis and interpretation of the data: Garcia-Rosa ML, Lagoeiro AJ; Statistical analysis: Garcia-Rosa ML; Writing of the manuscript: Leite AR, Garcia-Rosa ML, Macedo EA, Lagoeiro AJ, Martins WA, Vasques Netto D, Santos CC, Martinez DM; Critical revision of the manuscript for intellectual content: Garcia-Rosa ML, Lagoeiro AJ, Martins WA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro under the protocol number 0077.0258.000-10. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Correlation between Obstructive Sleep Apnea and Left Ventricular Diastolic Function Assessed by Echocardiography

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Short Editorial related to the article: Risk of Obstructive Sleep Apnea and Echocardiographic Parameters

Obstructive sleep apnea (OSA) is a disease characterized by recurrent upper airway obstruction during sleep, resulting from the repetitive collapse of these pathways, resulting in hypoxia and sleep fragmentation.[1] It is a very common disorder, being more common in men, but it can also affect women and children.[1] Its prevalence has been estimated at approximately 14% among men and 5% among women and OSA has been defined in these studies as the presence of an apnea-hypopnea index > 5 events per hour of sleep, associated with 4% of oxygen desaturation.[2]

OSA is associated with a significant increase in sympathetic activity during sleep, influencing heart rate and blood pressure. The increase in the sympathetic activity is induced by a number of mechanisms, including chemoreflex stimulation by hypoxia and hypercapnia, baroreflex, endothelial dysfunction, and venous return and cardiac output alterations.[3]

The abnormal pattern of breathing during sleep, associated with repeated awakenings, results in hemodynamic, autonomic, inflammatory, and metabolic effects that may contribute to the pathogenesis of several cardiovascular diseases: systemic arterial hypertension, coronary disease, cardiac arrhythmias (atrial fibrillation, or sudden death due to arrhythmia), heart failure, left ventricular (LV) hypertrophy, cerebrovascular accident, and pulmonary hypertension.[4]

OSA should be suspected whenever a patient presents with excessive daytime drowsiness, snoring and asphyxiation during sleep, particularly in the presence of risk factors such as obesity, male gender and older age. However, OSA is not a clinical diagnosis and objective tests should be performed for the diagnosis.[5]

In this issue of the Brazilian Archives of Cardiology, Leite et al.[6] show the correlation between the risk of OSA and echocardiographic parameters related to LV diastolic dysfunction. A total of 354 individuals included in the study answered the Berlin Questionnaire (BQ), a tool used to estimate the risk of OSA, with 63% of them being classified as having a high risk for this disorder.

Keywords

Cardiovascular Diseases; Sleep Apnea,Obstructive; Hypertrophy,Left Ventricular; Indicators of Mortality and Morbidity; Heart Failure; Echocardiography/methods; Polysomngraphy/methods; Risk Factors.

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Most sleep disorder researchers do not recommend the routine use of assessment tools such as questionnaires or algorithms to select patients at higher risk for OSA, as these tools have not shown to be superior to the clinical history and physical examination in the clinical assessment of these patients.[7]

The American Academy of Sleep Medicine clinical guideline published in 2017 strongly recommends that questionnaires and clinical prediction algorithms should not be used to diagnose OSA in the absence of polysomnography.[7] These tools are considered to be of low diagnostic accuracy. Regarding the QB, used in the aforementioned study in this issue,[6] the literature discloses a large number of false negative results, thus limiting its usefulness as a tool for OSA diagnosis. A review of 19 studies that analyzed the performance of the BQ compared to polysomnography data showed an overall sensitivity of 0.76 (95% CI: 0.72 to 0.80), whereas the overall specificity was 0.45 (95% CI: 0.34 to 0.56). This result discloses a very high number of false negative results (209 of 1,000 patients), with compromised diagnostic accuracy.

Therefore, this is a limitation of the study under analysis, since we do not study a population of OSA patients, but individuals at high risk of OSA, using a diagnostic tool considered to be of low diagnostic accuracy.

It is understood that, in an environment without sleep disorder specialists, the assessment tools, such as questionnaires and clinical prediction algorithms, may be useful because they promote the uniformity of sleep assessment, and, when necessary, expand their use counting on other health team professionals to apply them. However, one should bear in mind that the application of these tests does not replace a good clinical evaluation, with anamnesis and physical examination, much less the polysomnography, which remains the gold standard for the diagnosis of OSA.[7]

The study by Leite et al.[6] aimed to evaluate the behavior of echocardiographic parameters in OSA. Restrictions are made to the characterization of the studied population (patients at risk of OSA according to the BQ), but the results obtained were consistent with the literature findings. Increased left atrial volume and the behavior of mitral flow indices characterize LV diastolic dysfunction.[6]

Left atrial enlargement in OSA was characterized in a recent study by Cetin et al.,[8] who analyzed 55 patients diagnosed with OSA through polysomnography. Left atrial volume and left atrial deformation parameters were assessed through speckle-tracking echocardiography (strain and strain rate). Exercise capacity was also assessed through exercise testing. It was concluded that LV diastolic dysfunction is more prevalent in patients with severe OSA and is associated with reduced exercise performance. Left atrial remodeling contributed to exercise capacity prediction in this subgroup of patients.[8]

Short Editorial

A meta-analysis of 17 studies on LV remodeling and dysfunction in OSA,[9] concluded that this syndrome leads to left atrial dilation, and LV hypertrophy, dilation, increased mass and systolic function reduction.[9] The treatment of OSA may be beneficial in preserving LV structure and function.[9]

An interesting review carried out in Romania by Sascau et al.,[10] demonstrates that the moderate and severe forms of OSA are associated with increased atrial volumes, altered LV diastolic function and then LV systolic function. The assessment of right ventricular ejection fraction may also be compromised, being better evaluated by three-dimensional echocardiography. Moreover, the contribution of two-dimensional speckle-tracking echocardiography has been very effective, differentiating between active and passive wall movements. Abnormal strain values, a subclinical marker of myocardial dysfunction, can be detected even in patients with normal ejection fraction and volumes. LV longitudinal strain is more affected by the presence of OSA.[10]

In conclusion, the work by Leite et al.[6] highlights the contribution of echocardiography in OSA evaluation, a frequent disorder with different facets of pathophysiological interaction with cardiovascular diseases. The technological development of echocardiography, particularly with three-dimensional and speckle tracking techniques, shows a continuing contribution to the study of OSA.

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Myocardial Perfusion by Coronary Computed Tomography in the Evaluation of Myocardial Ischemia: Simultaneous Stress Protocol with SPECT

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Abstract

Background: Functional assessment to rule out myocardial ischemia using coronary computed tomography angiography (CCTA) is extremely important and data on the Brazilian population are still limited.

Objective: To assess the diagnostic performance of myocardial perfusion by CCTA in the detection of severe obstructive coronary artery disease (CAD) compared with single-photon emission computerized tomography (SPECT). To analyze the importance of anatomical knowledge to understand the presence of myocardial perfusion defects on SPECT imaging that is not identified on computed tomography (CT) scan.

Method: A total of 35 patients were evaluated by a simultaneous pharmacologic stress protocol. Fisher's exact test was used to compare proportions. The patients were grouped according to the presence or absence of significant CAD. The area under the ROC curve was used to identify the diagnostic performance of CCTA and SPECT in perfusion assessment. P < 0.05 values were considered statistically significant.

Results: For detection of obstructive CAD, CT myocardial perfusion analysis yielded an area under the ROC curve of 0.84 [a 95% confidence interval (CI95%): 0.67-0.94, p < 0.001]. SPECT myocardial perfusion imaging, on the other hand, showed an AUC of 0.58 (95% CI 0.40 – 0.74, p < 0.001). In this study, false-positive results with SPECT are described.

Conclusion: Myocardial perfusion analysis by CTA displays satisfactory results compared to SPECT in the detection of obstructive CAD. CCTA can rule out false-positive results of SPECT. (Arq Bras Cardiol. 2019; 113(6):1092-1101)

Keywords: Coronary Artery Disease/physiopathology; Myocardial Ischemia; Tomography, Emission-Computed, Single-Photon/methods; Myocardial Perfusion Imaging; Cineangiography/methods.

Introduction

In order to adequately assess coronary artery disease (CAD), both anatomical and functional analysis using myocardial perfusion methods should be considered, since both have prognostic and diagnostic value. Multimodal assessment and the combination of these techniques provide safe information on the anatomical and functional diagnosis of obstructive CAD, enabling better clinical and therapeutic planning.[1,2]

In the last years, we have observed several coronary computed tomography angiography (CCTA) studies of patients with moderate stenosis. The patients were referred to perform complementary functional tests, such as pharmacologic stress cardiac magnetic resonance imaging and single photon emission computed tomography (SPECT) to verify the presence of perfusion defects. This approach allows for, with high sensitivity and specificity, the characterization of ischemia in patients with obstructive CAD.[1-3]

Myocardial perfusion by CCTA is still little explored. Stress computed tomography (CT) myocardial perfusion imaging is a technique which has shown consistent results in the diagnosis of obstructive CAD. In its turn, myocardial perfusion scintigraphy is a well-established method for detection of CAD. The possibility of integrating anatomy and function in a single exam can enhance stratification of obstructive CAD and ensure better patient management.[3-7]

The clinical benefits of CCTA are changing the perspectives of contemporary cardiology,[7] not only for grading stenosis, but also for characterizing the atherosclerotic load and the types of plaques. Recent data in the literature, on the evaluation of significant obstructive CAD (> 50%) by CCTA, have revealed good accuracy, with high sensitivity (82-99%) and specificity (94-98%), when compared to invasive cinecoronariography.[1-6,8]

Multicentric studies, published in the last years, have demonstrated the high negative predictive value of CCTA

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(95-100%), emphasizing its excellent performance in excluding CAD. This fact should be increasingly exploited in clinical practice, avoiding invasive exams.[3-6,8-10]

SPECT assessment of myocardial perfusion can allow for better stratification of patients with intermediate stenosis and definition of therapeutic strategies, aiming at better prognosis.[11-18] On the other hand, the use of hybrid technology, which combines the anatomical information from CCTA and rubidium-82 (Rb-82) myocardial positron emission tomography (PET) perfusion imaging, presents high accuracy in CAD detection;[19-31] however, this approach is still expensive and difficult to implement clinically.

Thus, we observe that CCTA can aggregate perfusion imaging and, therefore, be increasingly used as the initial test for CAD, which remains one of the leading causes of mortality in Brazil and worldwide. Nevertheless, although several studies have demonstrated the diagnostic and prognostic value of myocardial perfusion by CCTA in patients with suspected CAD, these data are still limited in the Brazilian population. Besides, it is uncertain whether the use of CCTA analysis can replace other myocardial perfusion methods, such as SPECT, especially in places where this method may not be available. The implementation of myocardial perfusion assessment by CCTA is simple and less expensive compared to other methods.

Our purposes were: to evaluate the diagnostic performance of myocardial perfusion assessment by CCTA for significant obstructive CAD detection compared with SPECT; to analyze the importance of anatomical knowledge to understand the presence of myocardial perfusion defects by SPECT that cannot be identified by CCTA; and to describe SPECT false positives.

Method

This is an observational study that assessed patients clinically indicated to undergo myocardial scintigraphy for CAD stratification. All patients accepted and signed the informed consent form to participate in this research on myocardial perfusion assessment by CCTA. The study and the Free and Informed Term of Consent were approved by the Research Ethics Committee of Análise de Projetos de Pesquisa (CAPPessq), do Hospital Universitário Antônio Pedro (HUAP)/Universidade Federal Fluminense (UFF) number número 392.966.

Patient selection for this observational study included 38 patients from our institution [Antonio Pedro University Hospital – Federal Fluminense University (HUAP-UFF)], recruited in the Nuclear Medicine service (Figure 1).

The CCTA results (anatomy and perfusion) were considered as research data and were not reported to the patient's clinical

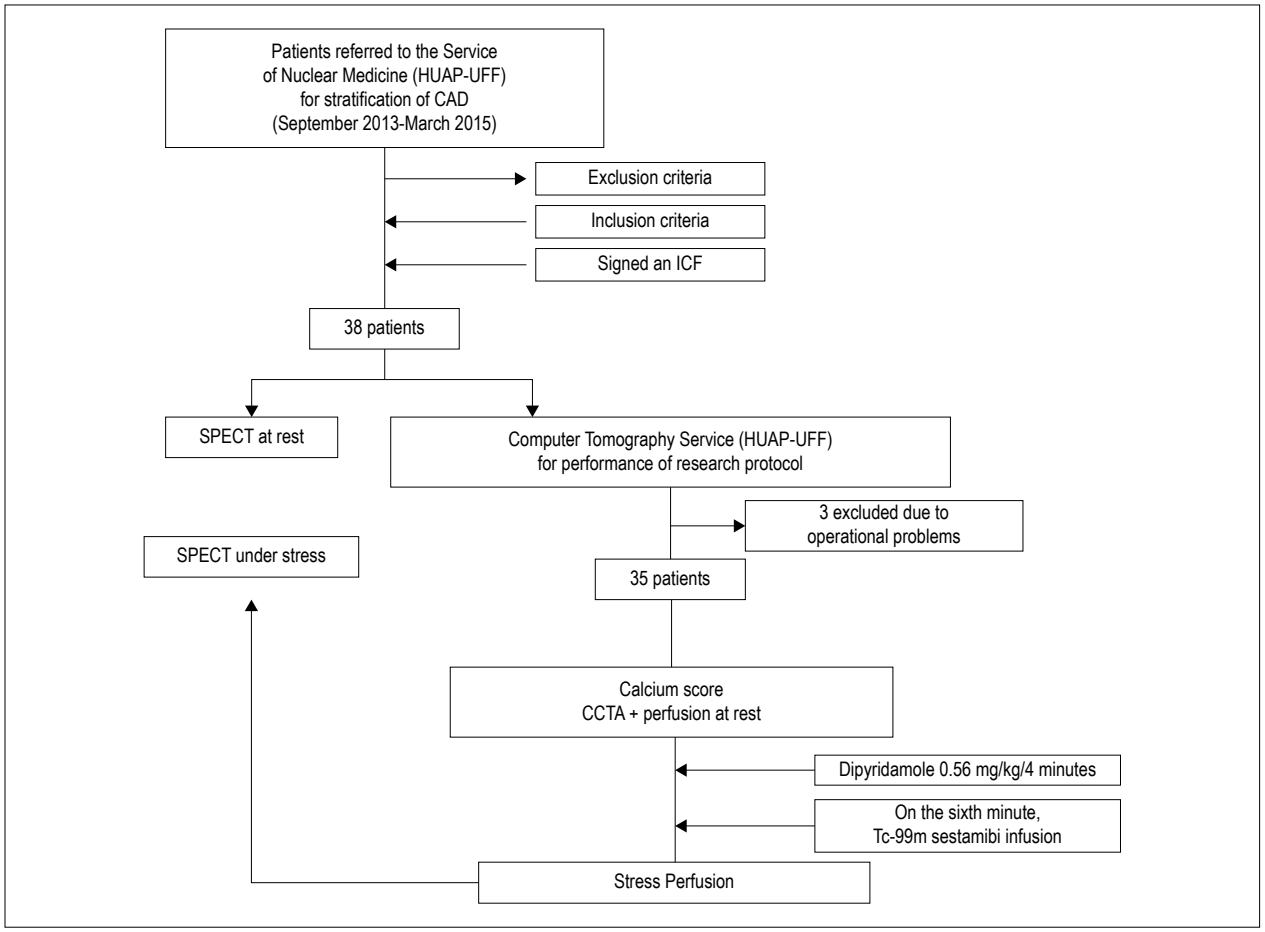

Figure 1 – *The selection of patients for this observational study included 38 patients from our institution [Antonio Pedro University Hospital – Federal Fluminense University (HUAP-UFF)], recruited in the Nuclear Medicine Service. CTA: computed angiotomography; CAD: coronary artery disease; SPECT: Single-photon emission computed tomography; ICF: Informed consent form.*

physician, except in case of identification of significant lesions in the trunk of the left coronary artery or in the LAD coronary artery detected by CCTA. The inclusion criteria were patients with medical request for stress/rest myocardial perfusion scintigraphy to assess CAD.

Patients with creatinine above 1.5 mg/dl, obstructive pulmonary chronic disease, asthmatic patients, patients who were allergic to iodinated contrast material or for whom dipyridamole or metoprolol was contraindicated and any other aspect that the researcher deemed limiting to the method were excluded.

The exams were performed with the following flow: first the patitent was selected at the Nuclear Medicine Service and, after signing the free and informed term of consent, the patient was referred to the service of radiology to undergo CCTA (perfusion at rest) followed by myocardial perfusion under pharmacological stress with dipyridamole. Before the infusion of iodinated contrast material, during stress-induced hyperemia, 2-methoxy-isobutyl-isonitrile-99mTc (sestamibi-^{99m}Tc) was infused at the computed tomography room.

The CCTA protocol included two imaging acquisitions: one for coronary anatomy assessment by CTA, which is also used to assess myocardial perfusion at rest; and a second myocardial perfusion under pharmacological stress performed shortly after the first acquisition. The mean acquisition time was 30 ± 5 minutes.

The first acquisition was volumetric and static, having been performed retrospectively using the following parameters: 120 KV, 240-400 mA and 512 × 512 matrix, 70 ml iodinated contrast media at a concentration of 350 mg/mL, infused at 5 ml/s. The second acquisition was performed following the same parameters and soon after 5 to 6 minutes from the beginning of dipyridamole infusion (Persantin®, Boehringer Ingelheim España S.A., España) (0.56 mg/kg/4 minutes). We chose to infuse it by hand, after images of the ascending aorta were blurred using iodinated contrast media, because it facilitates the correct selection of the beginning of acquisition, especially in the stress phase, which must occur a little earlier than usual for other coronary studies. During dipyridamole infusion, the patients' heart rate, blood pressure and symptoms were monitored every minute. Immediately after the conclusion of stress perfusion evaluation, 240 mg of aminophylline were administered (Minoton®, Teuto Brasileiro S.A., Brazil) to reverse the vasodilatation effect of the stress agent. This CT protocol was idealized in a 64-detector tomographic angiography (Brilliance CT 64-slice, Philips, Netherlands) and the mean dose of radiation was 12.1 ± 5.2 mSv.

Myocardial perfusion scintigraphy (SPECT) was performed with intravenous infusion of Tc-^{99m} sestamibi, using a single-day protocol (rest-stress). The patient was referred to the Radiology Sector, and the injection of the radiotracer was performed at the tomography room, in the Radiology Sector. Soon after CT was finished, the patient was referred to stress imaging acquisition (first-passage perfusion) with a maximum interval of 30 minutes. After this stage and an interval between 60 and 120 minutes, the rest phase was performed with a new injection of Tc-99m sestamibi. The mean dose administered in each stage was 925 MBq. The images were acquired 30 to 90 minutes after intravenous administration of the agent. A total of 64 projection images of the chest were acquired from an arc of 180 degrees, from the 45-degree right anterior oblique view to the 45-degree left posterior oblique view. In the rest phase, the acquisition time was 30 seconds per projection; in the stress phase, the acquisition time was 30 seconds per projection as well. In both the stress and rest phases, ECG-synchronized image acquisition was performed.

To analyze the correlation between the myocardial perfusion techniques, the following criterion was used to characterize myocardial ischemia: there should be perfusion defects on stress images with no correspondent perfusion defect on rest images of both CCTA and SPECT.

Myocardial perfusion and CCTA were assessed visually and semi-quantitatively by two blinded and independent observers, without any knowledge of clinical data or other exams. Disagreements were resolved by means of consensus. The degree of coronary stenosis was graded, according with visual and semi-quantitative assessment by CCTA, as non-significant (< 50% reduction in luminal diameter) and significant (> 50% reduction in luminal diameter).

Statistical Analysis

All continuous variables were expressed as mean ± standard deviation and the categorical variables as number and percentage. Fisher's exact test was used to compare between proportions. Based on CCTA fidings, the patients were grouped according with the presence or not of significant CAD. The criterion used to define significant CAD was existence of obstruction > 50% of the lumen of coronary arteries. Sensitivity and specificity were estimated and displayed as number and percentage. The analysis of the area under the ROC curve was used to identify the efficacy of CCTA (CT perfusion) and scintigraphy (SPECT) in the diagnosis of perfusion data in this study. The research was conducted on two groups: one with stenosis > 50% on anatomical assessment by CCTA, as the "true positive" surrogate marker in this population, compared with the group with stenosis < 50% in the same method as the "true negative" (AUC ≥ 0.5 to < 0.7 = poor fit; AUC ≥ 0.7 to < 0.9 = good fit; AUC ≥ 0.9 to 1.0 = excellent fit). Intra- and interobserver agreement was obtained by using intraclass correlation coefficient reliability analysis (CCI < 0.40: poor agreement; CCI = 0.40 to 0.59: fair agreement; CCI = 0.60 to 0.74: good agreement; CCI = 0.75 to 1.00: excellent agreement). About 43% of perfusions performed using CCTA techniques (15/35) were reassessed by the same observer; the analysis was performed by a second independent observer to characterize the variability between the analyses. A total of 1,440 segments were assessed using the 16-segment model of the American College of Cardiology (ACC) and the American Heart Association (AHA), with 240 LV segments being analyzed by observer 1 at rest and, subsequently, under pharmacological stress, totaling 480 segments. Observer 1 repeated this analysis after a 3-month period, blinded to the previous analysis. Observer 2 performed the independent analysis, blind and with no previous agreement with the first observer. Both observers have more than 10 years experience in performing CCTA.

Statistical analysis was performed using MedCalc® statistical software (Version 18.5 – 64-bit; MedCalc Software bvba, Ostend, Belgium). Two-tailed p values < 0.05 were considered statistically significant.

Results

Clinical and demographic characteristics of the sample

A total of 38 patients were selected; out of these, 35 were included in the study. Three patients were excluded: one patient due to long wait times to undergo the stress phase as a result of problems with schedule and other two due to technical problems in the Radiology Sector.

Out of the 35 patients studied, with a mean age of 52.5 ± 9 years, 18 were women (51%). Table 1 shows the main clinical and demographic characteristics of the population analysed.

Obstructive CAD assessment by CCTA

In this study, obstructive CAD (stenosis > 50%) was present in 43% (n = 15) of the patients; non-obstructive lesions were identified in 57% (n = 20) of the patients.

Table 1 – Clinical characteristics of the participants

Variables	Group
Age (years)	52.5 ± 9
Male sex, n (%)	17 (49)
SAH, n (%)	31 (88)
Diabetes Mellitus, n (%)	14 (40)
Smoking, n (%)	5 (14)
Dyslipidemia, n (%)	16 (45)
Previous AMI, n (%)	9 (26)
Typical chest pain, n (%)	10 (28)
Atypical chest pain, n (%)	8 (22)
Dyspnea, n (%)	11 (31)
Altered stress test, n (%)	1 (2)
Revascularization, n (%)	7 (20)
CAD family history, n (%)	10 (28)

SAH: Systemic arterial hypertension, AMI: Acute myocardial infarction; CAD: Coronary artery disease.

Perfusion defects on scintigraphy and CT

The distribution of perfusion defects on both methods are shown in Table 2. Based on the data from Table 2, it was possible to observe a difference between the distribution of perfusion defects on scintigraphy and CT. A total of 57.1% (n = 20) of the patients presented perfusion defects at myocardial scintigraphy, with only half of them (28.5%; n = 10) also presenting defects at CT. On the other hand, when perfusion defects were not detected on scintigraphy (n = 15), in the majority of the cases (60.0%; n = 9), CT showed no perfusion defects. These data showed that CT perfusion imaging sensitivity was 70%, and SPECT sensitivity was 66% for detection of perfusion defects (Figure 2).

Perfusion defects on scintigraphy in relation to obstructive CAD

Based on the data in Table 3, it was possible to demonstrate a significant association between normal scintigraphy and absence of obstructive coronary lesions.

Twenty patients had abnormal myocardial scintigraphy, and half of them (n = 10) also presented obstructive CAD at CCTA. Table 4 shows false-positive scintigraphy findings. In contrast, when scintigraphy was normal (n = 15), in most of the cases (66%), there was no presence of obstructive lesions on tomography; this association did not reach statistical significance (p = 0.49). According to these data, the sensitivity of scintigraphy for anatomical assessment by CTA was 66%, with a specificity of 50% (Figure 3).

Perfusion defects on myocardial perfusion CT in relation to obstructive CAD

Based on the data in Table 3, it is possible to show a significant association between abnormal CT and presence of obstructive coronary lesions. Out of all the patients, 54.2% (n = 19) presented abnormal CT, and most of them (73.6%; n = 14) also presented coronary obstructive lesions on CT. In contrast, when perfusion tomography was normal, which occurred in 45.7% (n = 16) of the patients, in almost all the cases (93.7%, n = 15), the tomography showed no obstructive lesions (p = 0.0001). According to these data, CT perfusion imaging sensitivity for the diagnosis of obstructive CAD was 93%, and specificity for detecting the absence of obstructive CAD on CCTA was 75% (Figure 3).

Analysis of the area under the curve for obstructive CAD detection

Myocardial perfusion with CT showed an AUC of 0.84 for the detection of obstructive CAD, with a confidence interval

Table 2 – Perfusion defects on scintigraphy (SPECT) and myocardial perfusion CT (n = 35)

Perfusion defects	Positive myocardial perfusion scintigraphy	Negative myocardial perfusion scintigraphy
Positive CT myocardial perfusion	10	6
Negative CT myocardial perfusion	10	9

P = 0.73 (two-sided Fisher's exact test). SPECT: Single-photon emission computed tomography; CT: computed tomography.

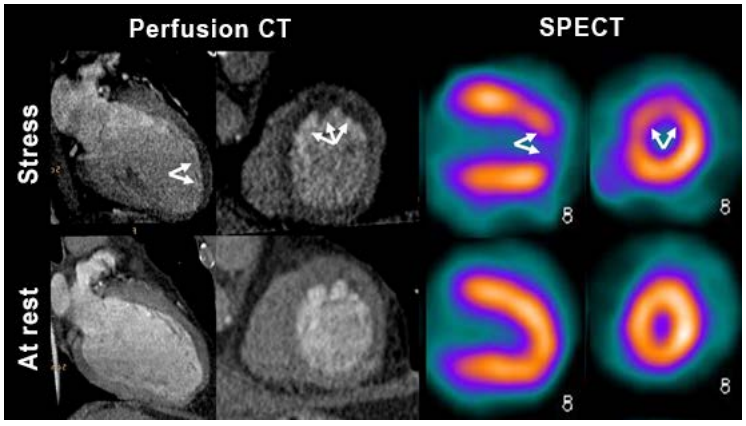

Figure 2 – *Comparison between myocardial perfusion images with stress perfusion defects on computed tomography (CT) and on single-photon emission computed tomography (SPECT). Concordant example of a same patient with significant obstructive anterior descending (LAD) coronary artery disease.*

Table 3 – Perfusion defects on scintigraphy (SPECT) and myocardial perfusion CT in relation to obstructive CAD (n = 35)

Perfusion defects	Positive SPECT*	Negative SPECT*	Positive CT**	Negative CT**
Obstructive CAD	10	5	14	1
Non-obstructive CAD	10	10	5	15

*Two-sided Fisher's exact test for SPECT (*p = 0.49) and for CT (**p = 0.0001). CAD: coronary artery disease; SPECT: Single-photon emission computed tomography; CT: computed tomography.*

Table 4 – False-positives on myocardial scintigraphy

Cause of false-positive	Positive SPECT	Negative SPECT
Deep myocardial bridge	2	2
Anatomical variation (short anterior descending artery)	1	1
Low levels (tracer leakage)	1	1
Patient with a 40% LAD stenosis	1	1
Patient with coronary-cavitary microfistulas	1	1
Others (microcirculation disease?)	4	4

SPECT: Single-photon emission computed tomography; CT: computed tomography.

(CI) range of 0.67 – 0.94 ($p < 0.001$). On the other hand, SPECT myocardial perfusion had an AUC of 0.58, with a CI range of 0.40 – 0.74 ($p < 0.001$) (Figure 4).

Assessment of correlation between observers of computed tomography for perfusion imaging

Excellent intra- and inter observer correlation was reported in the assessment of stress perfusion, with an ICC of 0.90 (0.87-0.92) and 0.94 (0.93-0.96), respectively. The intraobserver correlation of perfusion at rest was also excellent, with an ICC of 0.96 (0.95-0.97). For interobserver correlation of perfusion at rest the result was good, with an ICC of 0.71 (0.63- 0.78).

Discussion

In this study, it was possible to assess the diagnostic performance of myocardial perfusion by CCTA for the detection of significant obstructive CAD in relation to SPECT. The perfusion findings of scintigraphy with ^{99m}Tc-sestamibi were compared with the findings of myocardial perfusion by 64-detector row computed tomography. As a strength of this study, we highlight the simultaneous use of the same pharmacological stress agent for CT perfusion image acquisition, and the administration of the radiotracer, which enables performance of CT and subsequent scintigraphy image acquisition, because it lacks significant redistribution. Another important data was the possibility for anatomical localization and correlation with the presence of myocardial perfusion defects by SPECT. In this study, it was also possible to understand why the defect was not detected by CCTA and to describe SPECT false positives.

If we assess myocardial perfusion alone, an intermediate correlation between CT and scintigraphy images will be found, especially because the sensitivity of CT perfusion sensitivity for perfusion defects detection on SPECT was 70%, with a

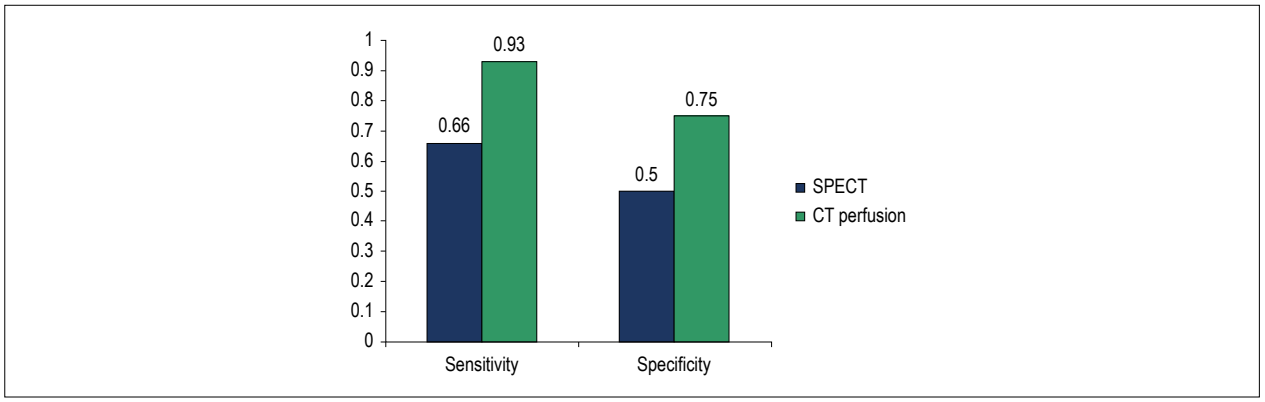

Figure 3 – *Comparison between myocardial perfusion methods sensitivity and specificity for detecting obstructive coronary artery disease. SPECT: Single-photon emission computed tomography; CT: computed tomography.*

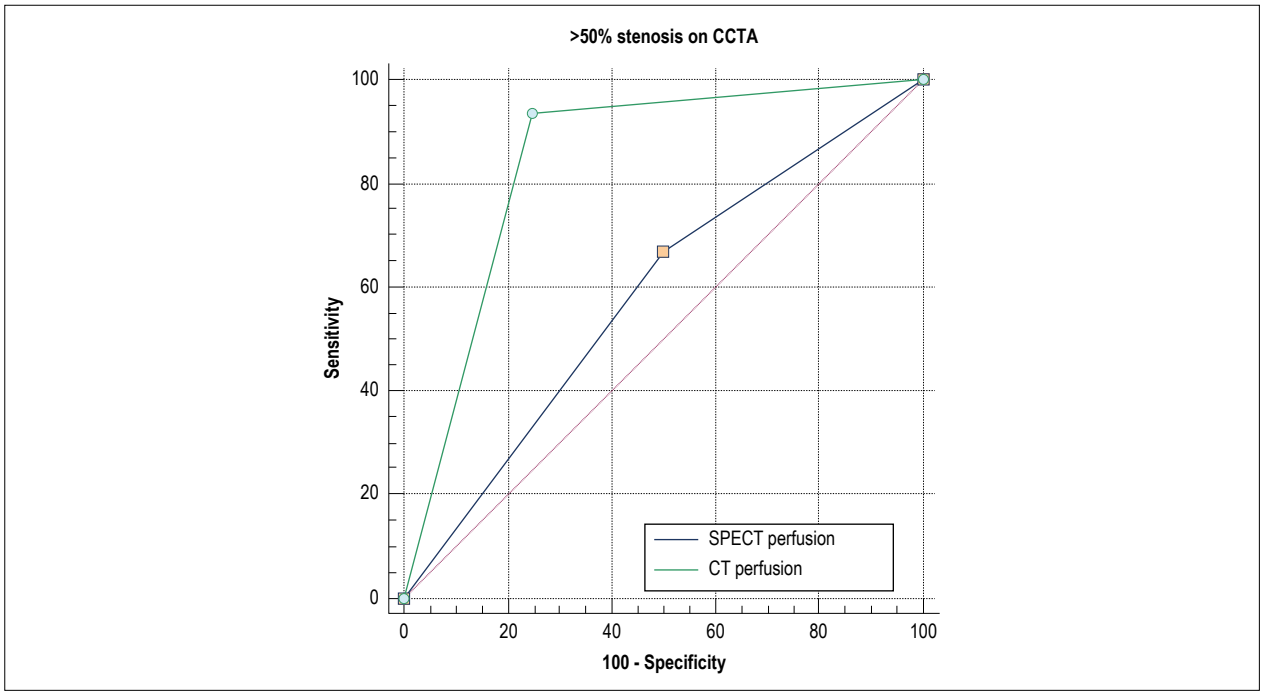

Figure 4 – *Analysis of the area under the ROC curve showing diagnostic perfusion performance of CT [0.84 (CI 95%: 0.67-0.94, p < 0.001)] and of scintigraphy (SPECT) [0.58 (CI 95%: 0.40-0.74, p < 0.001)], in this study.*

specificity of 66%, considering that scintigraphy is the standard method used to assess perfusion. Tanami *et al*.[32] clearly state that CCTA has better accuracy than SPECT for detecting significant obstructive CAD. Hence, it is necessary to explore this finding and understand that many patients with false-negative SPECT results are unnecessarily submitted to cardiac catheterization, due to lack of anatomical assessment.[32-35]

An interesting finding, in line with previous studies, is the comparison between the sensitivity and specificity of the two perfusion techniques in detecting obstructive coronary lesions, considering that coronary CT is the gold standard for the diagnosis of anatomic CAD.[35-37] In this study, we observed better ischemic catheterization by CT myocardial perfusion when compared with SPECT. It is important to highlight that catheterization was not used as the gold standard and, thus, these results may vary if other methods of reference are used, such as flow fractional reserve (FFR).[37-39] Rochitte et al.,[35] showed that combined CCTA and stress perfusion imaging accurately identifies patients with > 50% lesion in the catheterization and who presented perfusion defects at SPECT. Moreover, the rational use of these techniques and multimodality assessment are important in modern cardiology, since they are always associated with increased exposure to radiation.[36]

In the study carried out by Arbab-Zadeh et al.,[36] greater accuracy was observed for CT perfusion imaging when compared with SPECT (92%*versus* 62%, p < 0.001), but the

authors used another methodology with a higher slice CT system (320 detectors), as well as a slightly different protocol, which is not a problem, according with recommendations.[37] In contrast, other studies compared CCTA with SPECT and PET perfusion imaging with invasive catheterization with FFR, as a gold standard. Interestingly, perfusion PET was the exam that better correlated with the gold reference, whereas CCTA and SPECT performed similarly, showing that anatomic measures are not substitutes for functional assessment and that, even when the best method for anatomy assessment is used, functional assessment of coronary lesions is required.[36,38-40]

Another finding of the study that needs discussion is the presence of 10 patients (28%) with abnormal SPECT who did not present significant obstructive CAD on CCTA. Considering that CCTA is the anatomical method of reference in this study, we observed a high number of "false-positive" myocardial perfusion scintigraphy findings. We believe that a large part of these findings may be related with microcirculation disease (40%), since it was not possible to identify another cause that could explain them. The other findings (60%) were explained by anatomy assessment by CCTA. The best example is the case of a patient with myocardial bridge in which CT provided the anatomical substrate for the diagnosis of underlying myocardial ischemia detected by both SPECT and CT, already previously published by our research group.[41] With regard to scintigraphy, we observed that one of the studies presented low levels of the tracer, due to tracer leakage, that was not detected during the study and, therefore, was not excluded from the analysis. We believe that further studies need to be conducted in order to better clarify these findings, because they will affect clinical decision-making.

There are several factors that can be potentially responsible for disagreements between the tests. Some of them are obvious, such as differences in spatial resolution between the techniques (CT has submillimeter resolution, whereas SPECT has a resolution of 6 mm) and the distinct contrast properties used: the ^{99m}Tc-sestamibi exhibits a roll-off phenomenon, in which there is a limitation of its regional distribution when the flow is increased above certain threshold, while the same does not occur with iodinated contrast.[9,42-52]

In the Brazilian context, in spite of the absence of nuclear medicine services, combined CCTA and myocardial perfusion imaging is available, thus we consider this method as a simple and enforceable strategy. Some aspects should be considered, such as the use of beta-blockers to reduce heart rate for CCTA imaging, which can have a relative influence on the ischemic area detectable by SPECT, especially in cases of microcirculation disease. Another aspect is obesity, because in these patients the quality of the images is worsened, which can cause disagreement between the techniques. Another point is that, in order to perform CT perfusion, the patient needs to be inside the equipment in the stress phase, which makes the use of pharmacological stress mandatory. If physical stress could be used, perhaps the results would have been different from what we found.[35,42,44]

For CCTA, undoubtedly, the greatest limitation is exposure to radiation and iodinated contrast media, which are agents with potential adverse events. This protocol optimization, with new equipment, may be capable of reducing the levels of exposure; however, even so, the protocol shall only be adopted in selected patients, where information can be complemented. Studies using 320 detectors have shown that the combination of CT perfusion and CCTA can promote lower radiation exposure compared to the conventional protocol for myocardial perfusion imaging (9 mSv and 13 mSv, respectively).[35,36]

Standardization of CT analysis is still a limitation, and the use of automatic analysis software is one of the priorities for technology development, since there are no polar maps yet, as in nuclear medicine, to display ischemic and normal patients for quantification of the level of ischemia, with validated and widely available software.

Among other limitations of our study, as we detailed throughout the discussion, is the small number of individuals recruited. We believe that this is a partial limitation and should encourage further studies in different populations. We also took into account the false-positive scintigraphy results that might have influenced its performance, because we believe that the majority of cases can be explained by anatomy. Last but not least, one could imagine that the use of CCTA as an anatomical test would be limiting. In this case, numerous studies have compared CTA and catheterization with excellent results, which validates this approach.

Conclusion

Myocardial perfusion assessment by CCTA, after dipyridamole stress, is feasible and simple, with satisfactory results, when compared with SPECT, for obstructive CAD detection. Combined assessment of anatomy and stress perfusion by CCTA shows good capacity for detecting significant obstructive CAD, while ruling out SPECT false-positive findings.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Ker WS, Mesquita CT, Nacif MS; Acquisition of data: Ker WS, Neves DG, Mesquita CT, Nacif MS; Critical revision of the manuscript for intellectual content: Ker WS, Magalhães TA, Santos AASMD, Mesquita CT, Nacif MS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Programa de Pós-graduação Ciências Cardiovasculares under the protocol number 392,966. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Myocardial Computed Tomography Perfusion: One More Piece on The Board

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Short Editorial related to the article: Myocardial Perfusion by Coronary Computed Tomography in the Evaluation of Myocardial Ischemia Simultaneous Stress Protocol with SPECT

The most appropriate way to evaluate patients with stable coronary artery disease (CAD) and the subsequent definition of the therapeutic approach has been the subject of debate in recent years. For several years the anatomical evaluation was considered sufficient to indicate myocardial revascularization. The emergence of several methods of non-invasive functional evaluation in clinical practice as well as data from observational studies demonstrating that there is a level of ischemia above which a revascularization strategy might result in benefit regarding cardiovascular events raised doubts whether an strategy based in coronary anatomic findings was the best option.[1,2] This questioning changed the paradigm of CAD evaluation. Although randomized clinical trials have failed to demonstrate that the extent of ischemia can determine which patients would benefit from a revascularization strategy,[3-5] the fact that the presence of moderate to severe ischemia is undeniably a marker of cardiovascular risk has lead functional evaluation to become a fundamental part in the management of patients with stable CAD.

In this context, Ker et al.[6] in this edition of the *Arquivos Brasileiros de Cardiologia* evaluated 35 patients undergoing a simultaneous pharmacologic stress protocol of myocardial perfusion evaluation by computed tomography angiography (angio-CT) and single-photon emission computed tomography (SPECT) and compared the sensitivity of the methods using the presence of obstructive lesion evidenced by angio-CT greater than 50% as the gold standard for the presence of significant CAD.[6]

For the detection of obstructive CAD, the evaluation of myocardial perfusion by angio-CT had an area under the curve of 0.84 [confidence interval of 95% (95%CI): 0.67 to 0.94, $p < 0.001$]. SPECT had an area under the curve of 0.58 (95%CI: 0.40 to 0.74, $p < 0.001$). The sensitivity of SPECT to detect stenosis greater than 50% determined by angio-CT was 66%, with specificity of 50%. The sensitivity of perfusion angio-CT for detection of obstructive CAD was 93%, with specificity of 75% for the detection of absence of obstructive CAD by coronary angiography. In this study, false positives were considered when ischemia was present in a SPECT study with absence of obstructive CAD demonstrated by angio-CT. The authors concluded that the evaluation of myocardial perfusion by angio-CT presents satisfactory results in comparison with SPECT and that angio-CT can exclude false-positives of SPECT studies.

Although it is noteworthy the importance of developing new techniques to improve the evaluation of patients with CAD, it is fundamental to analyze which gold standard is used to test the accuracy of new diagnostic modalities. It is recognized that one of the limitations of the CT angiography is a specificity and positive predictive values suboptimal and a tendency to overestimate coronary lesions, being its sensitivity and negative predictive value excellent, providing necessary reassurance to exclude significant CAD,[7] This limitation hinders a more adequate analysis of the diagnostic accuracy of the methods in this study, because the method used as a reference has its main limitation in predicting the presence of ischemia. In addition, anatomy evaluated by CT served as the gold standard for assessing the sensitivity and specificity of CT perfusion, that is, the tested method served as its own gold standard. In the CORE 320 study, cardiac catheterization was used as a reference for the diagnosis of CAD.[8] In the CORE 320 study, the sensitivity of the angio-CT was 88% and the specificity was 55%, and SPECT presented sensitivity and specificity of 62% and 67%, respectively. Recently, catheterization associated with the measurement of fractional flow reserve (FFR) has been considered the method of choice for testing the diagnostic accuracy of other functional methods.

On the other hand, the presence of perfusion abnormalities in a functional test in the absence of obstructive CAD cannot always be categorized as "false-positive" results. It is increasingly recognized the role of coronary microcirculation dysfunction as a cause of ischemia and symptoms, generating the term microvascular angina.[9] In this sense, methods that quantify the absolute coronary flow, such as positron emission tomography (PET), allow the quantification of myocardial flow and coronary flow reserve and can detect microvascular dysfunction. Unfortunately, cardiac PET is not a reality in Brazil.

Several publications in the literature do not demonstrate similar sensitivity and specificity of SPECT in comparison of what was determined by Ker et al.[6] In a meta-analysis comparing SPECT, magnetic resonance and PET, using coronary catheterization without FFR as a gold standard, Jaarsma et al.[10] reported a sensitivity of 84% and specificity of 61% for SPECT.[10] In a recent meta-analysis that used coronary catheterization with FFR as a gold standard, the sensitivity and specificity of SPECT was 74% and 79%, respectively.[11]

Keywords

Coronary Artery Disease/physiopathology; Myocardial Ischemia; Tomography, Emission Computed/methods; Cineangiography/methods; Myocardial Perfusion, Imaging; Cardíac Catheterization; Exercise.

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Short Editorial

SPECT is an excellent non-invasive method for evaluating stable CAD, predominantly in patients with intermediate risk, or even in high-risk patients to help in the planning of the therapeutic approach. In addition, it is possible to use exercise as the stress protocol in patients who have the adequate functional capacity and good clinical condition. It is well known that an exercise stress protocol is the method of choice to evaluate patients with suspected or established CAD.

In conclusion, to assess the accuracy of a diagnostic method, it is critical to choose the right gold standard. The use of anatomic criteria based on the angio-CT findings does not invalidate the study of Ker et al.,[6] which opens a perspective for a new non-invasive technique that can assist in the proper management of patients with stable CAD, as well as creates the perspective of new research in this area. In the future, myocardial perfusion by angio-TC may be aggregated to the existing diagnostic armamentarium for the evaluation of patients with stable CAD, always taking into account the characteristic of the patient, and especially the functional capacity and possibility of exercise. In this context, non-invasive diagnostic methods that allow to perform exercise stress protocols should be the first choice.

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Impact of Transcatheter Aortic Valve Implantation on Kidney Function

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Abstract

Background: **Chronic kidney disease (CKD) is frequently present in patients with aortic valve disease. Decreased kidney perfusion as a consequence of reduced cardiac output may contribute to renal dysfunction in this setting.**

Objective: **Given the potential reversibility of kidney hypoperfusion after valve repair, this study aimed to analyze the impact of percutaneous transcatheter aortic valve implantation (TAVI) on kidney function.**

Methods: **We performed a retrospective analysis of 233 consecutive patients who underwent TAVI in a single center between November 2008 and May 2016. We assessed three groups according to their baseline estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²): Group 1 with eGFR ≥ 60; Group 2 with 30 ≤ eGFR < 60; and Group 3 with eGFR < 30. We analyzed the eGFR one month and one year after TAVI in these three groups, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate it.**

Results: **Patients from Group 1 had a progressive decline in eGFR one year after the TAVI procedure (p < 0.001 vs. pre-TAVI). In Group 2 patients, the mean eGFR increased one month after TAVI and continued to grow after one year (p = 0.001 vs. pre-TAVI). The same occurred in Group 3, with the mean eGFR increasing from 24.4 ± 5.1 mL/min/1.73 m² before TAVI to 38.4 ± 18.8 mL/min/1.73 m² one year after TAVI (p = 0.012).**

Conclusions: **For patients with moderate-to-severe CKD, kidney function improved one year after the TAVI procedure. This outcome is probably due to better kidney perfusion post-procedure. We believe that when evaluating patients that might need TAVI, this 'reversibility of CKD effect' should be considered. (Arq Bras Cardiol. 2019; 113(6):1104-1111)**

Keywords: **Aortic Valve Stenosis/complications;renal Insufficiency,Chronic; Calcinosis; Renal Dialysis; Diabetes Mellitus; Cardyomyopathies; Hypertension.**

Introduction

Since Bright[1] first described the association between chronic kidney disease (CKD) and heart disease in 1836, many epidemiological studies have confirmed and extended this finding.

With higher life expectancy, the prevalence of valvular heart disease, such as aortic valve disease, is increasing, and patients needing intervention are older and display multiple comorbidities.[2] Surgical intervention is the most effective therapeutic option, but transcatheter aortic valve implantation (TAVI) has become an important treatment choice for inoperable or high-risk patients.[2-4]

Many studies show poor short- and long-term outcomes in patients with CKD submitted to TAVI.[5,6] Other studies on this field focus on acute kidney injury (AKI) after TAVI, showing that AKI is not merely an independent predictor of adverse outcome but also predisposes to the development of CKD. Cases of AKI requiring dialysis have a poor prognosis (50% in-hospital mortality), and a significant proportion of patients progress to end-stage kidney disease.[7–9]

Aortic valve disease is frequently seen in CKD patients[10] due to progressive and accelerated leaflet calcification, a well-known complication of kidney failure. The key modulators in this field have not been totally identified, but might include calcification inhibitors (e.g., fetuin-A and matrix Gla protein), calcification promotors (e.g., hyperphosphatemia, calcium-phosphate product, parathyroid hormone), and leptin. On the other hand, long-standing aortic stenosis may contribute to CKD by impairing forward blood flow from the heart, causing chronic hypoperfusion and resulting in organ damage, and by increased renal venous pressure associated with right-sided heart failure.[11,12] Hypothetically, these pathological CKD mechanisms can be reversed after correction of aortic valve stenosis.

Little is known about the reversibility of CKD after aortic valve replacement. The dynamic changes in kidney function after TAVI have not been described and are not fully understood.

Given the potential reversibility of the pathological CKD mechanism after the correction of aortic valve disease, this study aimed at analyzing the variations in kidney function after TAVI.

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Methods

We performed a retrospective analysis of patients submitted to TAVI at the Hospital de Santa Cruz – Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, between November 2008 and May 2016. We excluded patients under dialysis prior to the procedure and those with a follow-up of less than one month in our center (Figure 1).

Demographic and clinical data were collected from patient chart review. All patients met standard indications for aortic valve replacement.

TAVI was performed mainly by a transfemoral approach. Transapical, subclavian, and transaortic accesses were used in case the former approach was not adequate due to calcification, tortuosity, or caliper. Delivery catheters between 14 F and 20 F sizes were used for valve delivery after previous aortic valve stenosis crossing with a guidewire. Preparation by valvuloplasty with an undersized aortic valve balloon was left to the discretion of the operators, as well as post-dilation valvuloplasty. Several types of valves were selected according to anatomic, valvular, and clinical characteristics based on computed tomography angiography and/or transesophageal echocardiogram (TEE): self-expandable, balloon, and mechanically expandable devices were implanted (respectively Corevalve®/Corevalve Evolut®/Portico®, Edwards®, and Lotus®) in the cath lab by a team including an experienced interventional cardiologist and cardiac surgeons, under fluoroscopic guidance and discretionary intraprocedural TEE. The protocol of the center determined the type (Iomeron® or Visipaque®) and volume (mL) of the iodine contrast selected.

Patient baseline characteristics included demographic data and comorbidities, such as diabetes, coronary artery disease, peripheral vascular disease, hypertension, chronic heart failure, and obesity (Body Mass Index ≥ 30 kg/m^2). Comorbidities found in patient charts were classified in accordance with the International Classification of Diseases, Ninth Revision (ICD-9). Kidney function was assessed by estimated glomerular filtration rate (eGFR), which was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[13] using the closest serum creatinine (sCreat) within 5 days prior to the procedure and after 1 and 12 months (1 year). Based on pre-TAVI eGFR, we evaluated three groups according to the categories suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines:[13] Group 1 with eGFR ≥ 60 mL/min/1.73 m^2 (patients without CKD or CKD G1-2); Group 2 with 30 ≤ eGFR < 60 mL/min/1.73 m^2 (CKD G3a-b); and Group 3 with eGFR<30 (CKD G4-5). Start of renal replacement therapy (RRT) and mortality during follow-up were also considered.

Categorical variables were expressed as frequency distributions and percentages, and continuous variables as mean ± standard deviation. Continuous variables as median values were tested using the paired Student's t-test, and categorical variables were compared with the chi-square test. Differences in eGFR among the three groups over time were analyzed using repeated measures ANOVA. Sphericity was determined by the Mauchly's test when the p-value > 0.05. When the Mauchly's test did not identify sphericity, we used repeated measures ANOVA with Greenhouse-Geisser correction. Multivariate logistic regression was generated for analyses predictors of eGFR improvement.

All statistical tests used the software SPSS version 22.0 (IBM Corp., Armonk, NY, USA). We considered p < 0.05 statistically significant.

Results

We analyzed data from 233 consecutive patients submitted to TAVI in a single center in Lisbon, Portugal, from November 2008 to May 2016.

Table 1 summarizes the baseline characteristics of the patients. The mean age of the patients was 81.8 ± 7.5 years (47 to 94 years), and 56.7% were females. Among all patients, 30.5% had diabetes; 40.3%, coronary artery disease; 22.3%, peripheral vascular disease; 69.5%, hypertension; 35.2%, chronic heart failure; and 17.2% were obese. The mean sCreat was 1.2 ± 0.49 mg/dL, and the mean eGFR was 55.2 ± 19.9 mL/min/1.73 m^2. During the follow-up period, 26.6% of patients died.

Before the TAVI procedure, 100 patients were in Group 1, 101 in Group 2, and 32 in Group 3. The three groups did not present differences regarding gender, incidence of comorbidities, and mortality (Table 1).

Mean eGFR in Group 1, Group 2, and Group 3 before TAVI was 74.6 ± 9.5 mL/min/1.73 m^2, 45.3 ± 8.4 mL/min/1.73 m^2, and 25.0 ± 4.5 mL/min/1.73 m^2, respectively (p < 0.001).

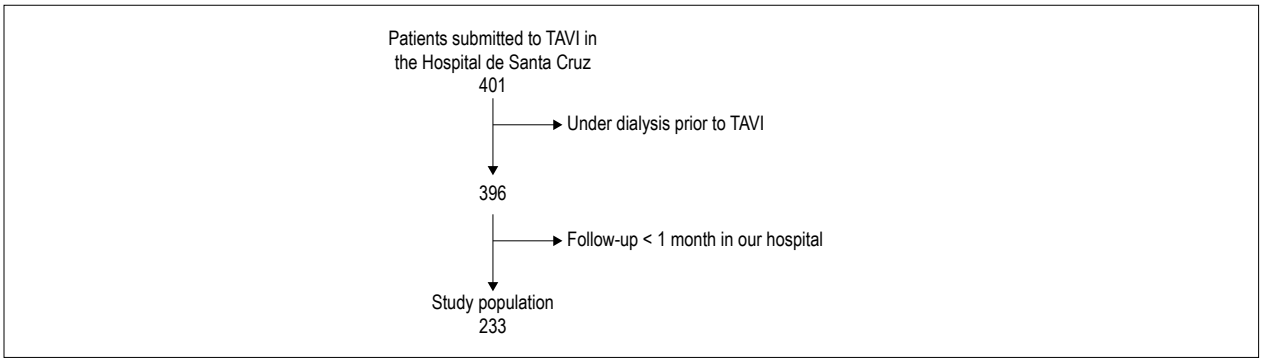

Figure 1 – *Flowchart of the patient population. TAVI: transcatheter aortic valve implantation.*

Table 1 – Baseline characteristics

	All patients (n = 233)	Group 1 (n = 100)	Group 2 (n = 101)	Group 3 (n = 32)	P-value
Females, n (%)	132 (56.7)	49 (49)	66 (64.7)	17 (54.8)	0.078
Age (years, mean ± SD)	81.8 ± 7.5	80.0 ± 9.2	83.5 ± 5.6	81.7 ± 4.9	0.003
Diabetes, n (%)	71 (30.5)	27 (27)	31 (30.4)	13 (41.9)	0.30
Coronary artery disease, n (%)	94 (40.3)	36 (36)	45 (44.1)	13 (41.9)	0.46
Peripheral vascular disease, n (%)	52 (22.3)	18 (18)	28 (27.5)	6 (19.4)	0.23
Hypertension, n (%)	162 (69.5)	73 (73)	70 (68.6)	19 (61.3)	0.46
Chronic heart disease, n (%)	82 (35.2)	30 (30)	37 (36.7)	15 (48.4)	0.16
Obesity, n (%)	29 (17.2)	14 (14)	14 (13.7)	1 (5.9)	0.43
sCreat	1.2 ± 0.49	0.85 ± 0.16	1.26 ± 0.26	2.13 ± 0.45	< 0.001
eGFR	55.2 ± 19.9	74.6 ± 9.5	45.3 ± 8.4	25.0 ± 4.5	< 0.001
Iodine contrast volume (mL)	144.8 ± 82.8	152.7 ± 101.2	139.9 ± 65.1	134.5 ± 64.7	0.434
Dead n (%)	62 (26.6)	29 (29)	21 (20.6)	12 (38.7)	0.11

sCreat: serum creatinine; eGFR: estimated glomerular filtration rate.

The mean volume of iodine contrast was 144.8 ± 82.8 mL, with no differences in the three groups (p = 0.434). Out of all patients, 54.5% received Iomeron®, and 45.5% received Visipaque®. In Group 1, 65.0% of patients received Iomeron®, and 35.0% received Visipaque® (p = 0.004). In Group 2 and Group 3 patients, there was no difference between the iodine contrast used (p = 0.092 and p = 0.151, respectively) (Table 2).

The TAVI procedure had a significant effect on kidney function in the three groups. Sphericity was assumed by Mauchly's test in Group 1 and Group 3 [χ^2 (2) = 4.34, p = 0.144, χ^2 (2) = 0.54, p = 0.763[. Greenhouse-Geisser correction was used in Group 3 [χ^2 (2)=6.93, p = 0.031].

Patients from Group 1 showed a progressive decrease in eGFR after TAVI [F (2-118) = 12.77, p < 0.001], reaching a value of 63.4 ± 19.2 mL/min/1.73 m^2 one year after the procedure (Table 3 and Table 4). The decline in kidney function was more significant in the first month after the TAVI procedure (Table 4 and Figure 2-A).

Patients from Group 2 presented an increase in eGFR [F (2-94) = 6.25, p = 0.003] one month and one year after TAVI (Table 5). The difference between eGFR means was higher one month after the procedure (Figure 2-B). Group 3 had the same results, that is, the mean eGFR increased over time after the procedure [F (2-32) = 5.91, p = 0.014], and the improvement in kidney function was greater in the first month (Table 6 and Figure 2-C).

A multivariate analysis adjusted for gender, age, and comorbidities did not change the variations in eGFR across the three groups.

In a logistic regression model for patients whose kidney function worsened after one month and one year, the contrast administered was a predictor of worsening. Administration of Iomeron® was a predictor of worsening in renal function after one year (HR 4.397, 95%CI 1.584–7.286, p = 0.002). On the other hand, the volume administrated was not a predictor of worsening in eGFR after one month (HR 0.997, 95%CI 0.994–1.001, p = 0.125) and one year (HR 0.999, 95%CI 0.995–1.002, p = 0.476).

The incidence of patients needing to initiate dialysis twelve months after the TAVI procedure was 2.4% (five patients). Before TAVI, one of these patients was in Group 1; two were in Group 2; and two were in Group 3. We did not find a statistically significant difference in mortality among the three groups (p=0.11). All of these patients had chronic heart failure, and four died.

Discussion

This analysis contains data from patients who underwent TAVI in a single center from November 2008 to May 2016. The present results suggest that kidney function might improve in patients with CKD G3-5 after the correction of aortic stenosis. However, in patients with no CKD or with CKD G1-2 (eGFR ≥ 60 mL/min/1.73 m^2), the eGFR decreased during the follow-up. This study also shows a low incidence of new dialysis – 2.4% (five patients).

Several studies address the prognosis and factors that influence mortality and other poor outcomes in patients with CKD undergoing aortic valve replacement, but little is known about the effect of the treatment of aortic valve disease on kidney function.

This study reveals that our patients with CKD G3-5 (eGFR < 60 mL/min/1.73 m^2) had an improvement in kidney function one month after aortic valve replacement, maintaining the improvement after one year of follow-up. Other studies have also indicated this potential reversibility of CKD, both early and after one year of follow-up.[2,14–16]

A study with 69 patients from a single center in Brazil[14] showed an acute kidney recovery after the TAVI procedure. After one year of follow-up, all patients who had an acute recovery remained with improved levels of sCreat. This work also suggests that kidney recovery is more frequent in patients who had more severe renal

Table 2 – Iodine contrast administered to the three groups

	Iomeron® (n; %)	Visipaque® (n; %)	p-value
Group 1	65; 65.0%	35;35.0%	0.004
Group 2	42; 41.2%	62; 58.8%	0.092
Group 3	20; 64.5%	11; 35.5%	0.151

Table 3 – Evolution of kidney function after TAVI

	N patients	eGFR pre-TAVI (mL/min/1.73 m²)	eGFR 1 month after TAVI (mL/min/1.73 m²)	eGFR 1 year after TAVI (mL/min/1.73 m²)	p-value
Group 1	60	74.9 ± 9.0	65.6 ± 20.0	63.4 ± 19.2	<0.001
Group 2	48	45.4 ± 8.5	50.1 ± 15.1	52.6 ± 16.4	0.001
Group 3	17	24.4 ± 5.1	34.9 ± 18.1	38.4 ± 18.8	0.012
All patients	125	56.7 ± 20.5	55.5 ± 20.9	55.8 ± 19.9	0.51

*eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation. *p-value between eGFR pre-TAVI and eGFR 1 year after TAVI.*

Table 4 – Repeated Measures ANOVA: pairwise comparisons (Group 1)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	9.276*	2.533	0.002	3.034	15.518
	eGFR 1 year after TAVI	11.521*	2.612	< 0.001	5.084	17.958
eGFR 1 month after TAVI	eGFR pre-TAVI	-9.276*	2.533	0.002	-15.518	-3.034
	eGFR 1 year after TAVI	2.245	2.072	0.849	-2.861	7.351
eGFR 1 year after TAVI	eGFR pre-TAVI	-11.521*	2.612	<0.001	-17.95	-5.084
	eGFR 1 month after TAVI	-2.245	2.072	0.849	-7.351	2.861

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

dysfunction before aortic valve replacement. Azarbal et al.[15] have found similar results. In their work, acute kidney recovery (defined as a positive change in eGFR of ≥ 25% 48 hours after TAVI) was strongly associated with baseline CKD: 8.9% in patients with eGFR > 60 mL/min/1.73 m² compared to 26.6% in patients with eGFR < 60 mL/min/1.73 m². Also, in a multivariate logistic regression model, lower baseline eGFR was highly predictive of acute kidney recovery (OR 3.27, 95%CI 1.84–5.82, p < 0.001).[15]

Najjar et al.[16] showed that patients with moderate and severe CKD (30 ≥ eGFR > 60 and eGFR < 30, respectively) had initial improvement in eGFR, peaking one week after the aortic valve replacement. The improvement was maintained after one year for patients with moderate CKD and after six months in patients with severe CKD compared with the pre-TAVI eGFR value. The group with severe CKD also presented a better short- and long-term survival in this study.

We believe that these results are due to an improvement in cardiac output and a reduction in venous congestion after aortic valve replacement, leading to better kidney perfusion, and therefore an improvement in kidney function. These data suggest that a better kidney function can be expected in patients with CKD G3-5, which may have important implications in the selection of individuals for the treatment of aortic valve diseases.

The short- and long-term prognosis of aortic valve replacement in patients with CKD prior to the procedure often calls into question the benefit of valve repair in these patients. Recently, some studies have shown that the poor prognosis associated with CKD is influenced by the stage of the disease.[5,6,15,16] Gibson and his work group[19] revealed that eGFR < 60 mL/min/1.73 m² is an important predictor of mortality post-TAVI (HR 5.0, 95%CI 1.87–13.4, p = 0.001) as well as in short-term follow-up (HR 2.98, 95%CI 1.85–4.80, p < 0.001). Other recent study[20] shows that for patients with eGFR < 60 mL/min/1.73 m², a variation as small as 5 mL/min/1.73 m² in eGFR could make a measurable difference in risk of death, RRT, or both at 30 days and 1 year of follow-up. Nguyen et al.[21] showed that a worsening in renal function was associated with increased in-hospital mortality, hospital length of stay, and intensive care unit length of stay in surgical aortic valve replacement patients, but not in TAVI patients. Our study contradicts these data. We found no difference in mortality among patients with CKD G3-5 compared to those who had CKD G1-2 or no CKD before TAVI.

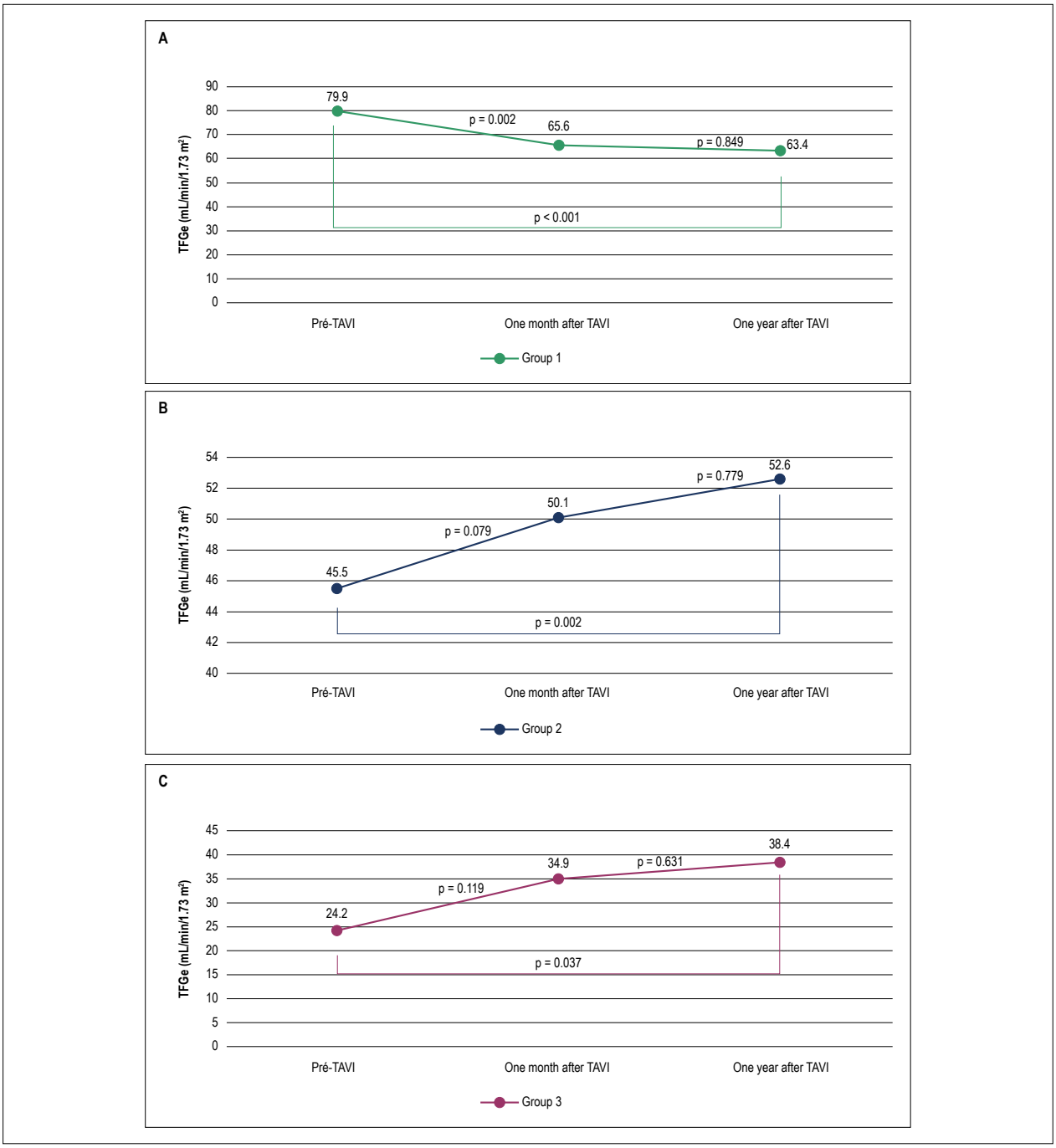

Figure 2 – *Comparison of eGFR between groups after the TAVI procedure. A: Group 1; B: Group 2; C: Group 3. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

Regarding the administration of contrast, the three groups showed no differences regarding the volume received; thus, volume was not a predictor of worsening in eGFR after one month and one year. The predictive value of contrast volume for kidney dysfunction after TAVI is controversial:[15,22,23] in a meta-analysis with over 3,800 patients post-TAVI, higher contrast use was not clearly associated with a greater risk of AKI.[24]

However, we found a difference in the type of contrast administered in Group 1: most patients with CKD G1-2 at baseline received Iomeron® and this iodine contrast was a predictor of worsening in eGFR. Iodine contrast is divided into three groups according to their osmolarity. Iomeron® is a low-osmolar contrast characterized by values within 300–900 mOsm/kg H_2O.[25] Visipaque® is iso-osmolar, having an osmolarity level similar to that of blood (290 mOsm/kg H_2O)

Table 5 – Repeated Measures ANOVA: pairwise comparisons (Group 2)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	-4.716	2.019	0.079	-9.728	0.295
	eGFR 1 year after TAVI	-7.201*	2.007	0.002	-12.184	-2.219
eGFR 1 month after TAVI	eGFR pre-TAVI	4.716	2.019	0.071	-0.295	9.728
	eGFR 1 year after TAVI	-2.485	2.178	0.779	-7.893	2.923
eGFR 1 year after TAVI	eGFR pre-TAVI	7.201*	2.007	0.002	2.219	12.184
	eGFR 1 month after TAVI	2.485	2.178	0.779	-2.923	7.893

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

Table 6 – Repeated Measures ANOVA: pairwise comparisons (Group 3)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	-10.453	4.670	0.119	-22.938	2.031
	eGFR 1 year after TAVI	-13.923*	4.944	0.037	-27.138	-0.708
eGFR 1 month after TAVI	eGFR pre-TAVI	10.453	4.670	0.119	-2.031	22.938
	eGFR 1 year after TAVI	-3.470	2.658	0.631	-10.576	3.636
eGFR 1 year after TAVI	eGFR pre-TAVI	13.923*	4.944	0.037	0.708	27.138
	eGFR 1 month after TAVI	3.470	2.658	0.631	-3.636	10.576

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

and dimeric structure opposed to monomeric low-osmolar contrast media.[25] Despite the many years of experience in the use of iodine contrast, the exact pathogenesis of contrast-induced nephropathy (CIN) remains unknown. The causes might include the osmotic effect of contrast media on the kidneys, the increased levels of vasoconstrictive factors, such as adenosine or endothelin, the reduced levels of vasodilators, such as nitric oxide or prostacyclin, and the toxic effect of contrast molecules on renal tubules.[25] According to the American College of Radiology guidelines, iso-osmolar iodixanol has no evident superiority over low-osmolar contrast with respect to the incidence of CIN.[26] Regardless, the difference in the contrast administrated may be one of the factors contributing to the poorer results in patients from Group 1, although there are not enough data to prove this supposition, namely whether these patients had AKI after the procedure. Another hypothesis that could explain the kidney function variation in patients with CKD G1-2 is that, prior to the aortic valve repair, they could not tolerate the angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor antagonists (ARA-II), and as such, the therapeutic could be optimized after the procedure, thus explaining the GFR variation.

We found an incidence of new dialyses of 2.4% (five patients) after a year of follow-up in all categories of CKD without statistical difference between them. A recent study in this field showed a difference in new-dialysis patients according to their CKD stage, with an incidence of 1.2%, 3.74%, 14.6%, and 60.1% in CKD 1-2, CKD 3, CKD 4, and CKD 5, respectively.[18] Given the low incidence of patients who started dialysis in the follow-up period after TAVI, drawing statistically relevant conclusions would not be accurate; nevertheless, we believe that some of these results stand out: (i) the mean age of these patients was 80 ± 5.96 years, similar to the mean age of all the analyzed population (81.8 ± 7.5 years); (ii) almost all patients died (4 out of 5); (iii) all patients had chronic heart failure, which probably contributed to the outcome.

The main limitations of this study concern its retrospective and observational nature. The use of patient charts for data collection is also a limitation, as some data might be missing or incorrectly coded. In addition, a significant number of patients were excluded, which could introduce a systematic bias toward the patients included in the study. Also, sCreat fluctuates often day-to-day, as it is influenced by numerous factors, such as hydration state, medication, or comorbidities. These variations in sCreat significantly affect the estimated kidney function. The present study also has some limitations regarding the patients' follow-up: short follow-up period (one year); the decline in kidney function with age may be a confounding factor for the true benefit of aortic valve

replacement in these patients; and other important covariates not included in this study (such as the severity of aortic stenosis, intra-procedure events, including hypotension, and AKI after the procedure).

Summarizing, the association between worse outcomes in CKD patients undergoing TAVI is well-established, while the potential reversibility of kidney function after aortic valve replacement has not been well-investigated. Despite the limitations, our study provides some significant evidence of reversibility of CKD after aortic valve replacement, probably due to improved renal perfusion post-procedure. Further randomized controlled studies involving more patients and longer follow-up periods are necessary to evaluate the reversibility of CKD after aortic valve replacement.

Conclusions

Our study suggests that the correction of aortic stenosis is associated with an improvement in kidney function in patients with moderate to severe CKD, showing some significant evidence of reversibility of CKD after aortic valve replacement. The confirmation of this 'reversibility of CKD' effect is clinically important insofar as it may help to improve the decision-making process, refining risk stratification in these challenging groups of patients, and perhaps become one of the indications for TAVI.

Author contributions

Conception and design of the research and Writing of the manuscript: Calça R; Acquisition of data: Calça R, Teles RC, Brito J, Nolasco T, Almeida MD; Analysis and interpretation of the data and Statistical analysis: Calça R, Teles RC, Branco P, Weigert A; Critical revision of the manuscript for intellectual content: Teles RC, Branco P, Gaspar A, Neves JP, Mendes M, Weigert A, Machado DS.

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No potential conflict of interest relevant to this article was reported.

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Impact of Transcatheter Aortic Valve Implantation on Kidney Function: the "Renovalvular" Interaction in Aortic Stenosis

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Short Editorial related to the article: Impact of Transcatheter Aortic Valve Implantation on Kidney Function

The advent of renal congestion in heart failure was first described by Frédéric Justin Collet (1870–1966), a French pathologist who found the notion of passive renal congestion related to heart dysfunction, creating the revealing term "*rein cardiaque*" in the early 1900s.[1] The term cardiorenal syndrome emerged from a 2004 National Heart, Lung, and Blood Institute Working Group conference evaluating the complex interactions between the heart and kidney.[2] The main pathophysiological mechanisms related to this condition are increased central venous and intra-abdominal pressures; reduced cardiac output and cardiac index; neurohormonal dysregulation; oxidative stress and inflammatory mediators.[3] Degenerative aortic stenosis (AS) represents one of the most prevalent valvular heart diseases and an important cause of heart failure, with a strong correlation with aging process. The combination of atherosclerosis, biomineralization and oxidative stress leads to calcium deposition within the valve leaflets.[4] The *"renovalvular"* interaction in AS may represent a two-way path, from a pathophysiological perspective. In one way, AS may impair kidney function by arterial hypoperfusion and systemic venous congestion. On the other way, chronic kidney disease (CKD) is also an important risk factor for AS, due to the massive and aggressive calcification of the leaflets, mainly imposed by imbalances in the calcium and phosphorus homeostasis.[5]

For patients with AS undergoing conventional surgical aortic valve replacement (AVR), there is an increase in complication rates such as major bleeding and reoperation when comparing patients with moderately reduced kidney function (estimated glomerular filtration rate [eGFR] between 30–60 ml/min/1.73 m^2) versus those without kidney disease.[6] Mortality after surgical AVR also increases with worsening GFR.[7]

The development of the transcatheter aortic valve replacement (TAVR) for the treatment of AS has brought hope for a group of patients without effective therapeutic perspective due to their clinical profile, characterized by the presence of clinical frailty and multiple comorbidities, making surgical AVR not feasible.[8] In this scenario, TAVR represents a potentially less invasive therapeutic alternative for patients with AS and CKD. Some previous studies evaluated the clinical impact of TAVR on patients with CKD. In the classical PARTNER trial, there was a 34.4% 1-year mortality for patients with severe CKD.[9] For patients undergoing dialysis treatment and TAVR, there was also a higher mortality rate and major bleeding.[10] Moreover, the occurrence of acute kidney injury in the peri-procedural TAVR period is also associated with poor outcomes.[11] On the other hand, some previous studies demonstrate a positive impact of TAVR on renal function, especially in patients with moderate to severe CKD, with a significant recovery of eGFR possible related to the improvement of cardiac output and reduction of systemic venous congestion.[12-14]

Promisingly, the present study conducted by Calça et al.,[15] provides additional data on the positive impact of TAVR on the kidney function. Through a retrospective and unicentric study, 233 patients with AS who underwent TAVR were stratified into 3 groups according to basal eGFR (ml/min/1.73 m^2): group 1 (eGFR > 60), group 2 (30 ≤ eGFR < 60) and group 3 (eGFR < 30). The renal function was re-accessed one month and one year after TAVR. The authors observed a significant improvement in eGFR in patients with moderate (group 2) to severe (group 3) CKD (around 15.6% in one year; around 58.6% in one year, respectively). Conversely, patients from group 1 had a progressive decline in eGFR one year after the TAVR procedure ($p < 0.001$ vs. pre-TAVR). Nevertheless, there was a low incidence of dialysis therapy in one year (2.4%). Possible reasons implicated by the authors in this worsening of eGFR in group 1 were higher use of iodinated contrast in this group (65% of patients) and the use of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors in the post-procedure period. Multivariate logistic regression analysis identified that the use of iodinated contrast was an independent predictor of worsening kidney function, unrelated to the volume of contrast used.

Despite its inherent limitations (single center, retrospective and observational study) the study by Calça et al.[15] brings a promising light on the impact of TAVR on kidney function in patients with moderate to severe CKD. This pre-procedure kidney dysfunction may not be an exclusion issue for the TAVR, given to the possibility of short- and medium-term improvement. Future randomized, multicenter studies, with a stricter contrast type control and longer, follow up, are required for a definitive conclusion.

Keywords

Heart Failure/complications; Renal Insufficiency/complications; Aortic Valve Stenosis/complications; Transcatheter Aortic Valve Replacement/trends; Risk Assessment.

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Coronary Artery Dilation in Children with Febrile Exanthematous Illness without Criteria for Kawasaki Disease

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Abstract

Background: Coronary dilatation is the most important complication of Kawasaki disease (KD) and, in addition to some clinical characteristics, is common to KD and febrile exanthematous illnesses (FEIs).

Objective: To assess whether children with FEI, who do not meet the criteria for KD, have changes in coronary arteries dimensions.

Methods: Echocardiography was performed within the first two weeks of the disease in patients < 10 years with fever and exanthema without other KD criteria. To make a comparison with KD patients, we reviewed the echocardiograms and medical records of patients with a diagnosis of KD of the last five years. Coronary ectasia was assessed using Z scores of coronary arteries. The means of the dimensions of the coronary arteries were compared with a z test and a level of significance of 0.05 was adopted.

Results: A total of 34 patients were included, 22 (64.7%) with FEI, and 12(35.2%) with a diagnosis of KD. Using the Z scores of coronary artery, a dilation of any of the coronary artery branches was observed in six (27.2%) patients with FEI.

Conclusions: An important percentage of patients with FEI has coronary artery dilation. (Arq Bras Cardiol. 2019; 113(6):1114-1118)

Keywords: Child; Coronary Disease; Evanthema; Fever; Kawasali Disease; Mucocutaneous Lymph Node Syndrome; Echocardiography/methods.

Introduction

Up to some years ago, exanthema and fever in children were diagnosed as one of the diseases of the complex known as febrile exanthematous illnesses (FEI), including measles, rubella and scarlet fever. Thus, it was considered that, in most cases, symptoms would disappear by symptomatic treatment.[1] As vaccination schedule became universal, the epidemiology of FEIs has changed in a way that Kawasaki disease (KD), which was once an exception among these diseases, has become the primary illness to be considered in face of clinical signs including persistent fever and exanthema. Coronary abnormalities are the most serious complications of KD.[2,3]

Besides fever and exanthema, FEIs and KD share other clinical characteristics, such as conjunctival injection, swollen lymph nodes, and, in some cases, desquamation and swelling of the limbs, which supports the suspicion of KD in any of its forms.[4,5] It is paradoxical that, when the clinical presentation of incomplete KD is confused with self-limited diseases such as FEIs, the occurrence of a serious cardiovascular disease as a complication may be neglected.[6]

Studies have established that FEIs and KD have in common pathophysiologic mechanisms and clinical signs,[7] and therefore, some infectious agents have been proposed as responsible for causing KD. This implies that patients that have been diagnosed with FEIs without meeting the criteria for KD could develop coronary abnormalities.[7,8] These are considered an uncommon cause of cardiac disease among pediatric patients. However, the ensuing mortality, in some cases, makes them relevant in clinical practice.[9]

Given all of this, we intend to assess whether children with febrile illness who do not meet the criteria for KD have changes in coronary arteries dimensions.

Methods

In a cross-sectional study, we included patients under 10 years of age with a diagnosis of FEI in the pediatric outpatient settings

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of two hospitals belonging to the Health Services of Petróleos Mexicanos in Mexico. The parents signed an informed consent to participate in the study. The American Heart Association (AHA) criteria[10] were applied to all cases to confirm that the KD diagnostic criteria were not met, including cases that could be considered atypical or incomplete. All the patients underwent an echocardiogram within the first two weeks of the disease using a Vivid 7 General Electric® device.

Patients who had a fever ≥ 38°C, which had lasted for at least one day, and exanthema were considered. Subjects with previous known diseases, such as arterial hypertension, family history of cardiopathy, congenital cardiopathy, children with weight above the 95th percentile or below the 5th percentile according to their age, or who had been using steroids during at least one month before the disease were not included.

To establish a comparison with KD patients, we reviewed the echocardiograms and the medical electronic records of patients with a diagnosis of KD detected by the Pediatric Cardiology Service during the last five years.[11] Those who met the AHA criteria for KD were included in the analysis, and the children were then selected by convenience sampling.

Assessment of the coronary arteries

Echocardiography was performed according to that described by Muniz et al.[12] Coronary ectasia (CE) was defined as a dilation of the coronary artery > 1.5-fold in diameter, evidenced by an echocardiogram, when compared to the adjacent normal segments of the same arteries according to coronary artery Z scores.[11] The mean Z score for each coronary artery segment was 0, with a SD of 1.

Statistical analysis

Comparison of the means of the dimensions of the coronary arteries was performed with a z test, using a one-tailed analysis with a 95% confidence interval. Demographic and clinical characteristics were analyzed using an unpaired Student's t-test or a Fisher's exact test, depending on the type of variable, with a difference of $p < 0.05$. No adjustments were performed in the analysis, since the intention of the study is exploratory. The analysis of the results was done through the Stata program version 13.

Ethics

The study was approved by the Research and Ethics Committees at both hospitals. Informed consent signed was signed by the parents of the children included in the study.

Results

We included a total of 34 patients: 22 (64.7%) had a diagnosis of non-KD FEI; 11 of them (50%) were diagnosed as viral exanthema, the most common were hand-foot-and-mouth disease (n = 5; 22.7%) and exanthema subitem (n = 4; 18.1%); there was also one case of scarlet fever and one of Gianotti-Crosti syndrome. The remaining 12 patients were diagnosed with KD.

Distribution by sex was as follows: in the FEI group, 13 (59%) patients were male and nine (40.9%) were female; in the KD group, nine (75%) patients were male and three (25%) were female. In terms of age, in the FEI group, the mean age was 41.3 months (range: 7 to 120 months), and in the KD group, the mean age was 18.1 months (range: 6 to 36 months). Other demographic and clinical variables are described in Table 1.

Kawasaki disease criteria

Regarding the diagnostic criteria for KD in our sample, we found that the average duration of fever was 3.6 ± 2 days, only six subjects (27.2%) met the fever duration criterion of ≥ 5 days. The average of body temperature peak was 38.3°C.

Exanthema was present in all subjects, since it was one of the inclusion criteria in the study. One of them had conjunctival hyperemia; none of them had edema, desquamation of foot, hand or tongue, or swollen ganglia. The comparison with the KD patients is shown in Table 1, which shows a higher frequency of some clinical problems in children with KD, swollen lymph glands in the neck, swelling and redness in hands and bottoms of feet, peeling skin and swollen tongue. No difference was found in these percentages compared with those of patients with coronary dilation.

Assessment of coronary arteries in subjects with FEI

Measurements of the left main coronary artery (LMCA), proximal right coronary artery (PRCA), medial right coronary artery (MRCA), distal right coronary artery (DRCA), circumflex, left anterior descending coronary artery (LAD) were available in 22 patients with FEI. The PRCA showed the largest dilation (mean Z score = 0.45 ± 0.63, $p < 0.005$), followed by the LMCA (mean Z score = 0.14 ± 1.0, $p < 0.05$) (Table 2). According to the coronary artery Z-scores, six (27.2 %) patients diagnosed with FEI showed dilation in at least one of the coronary branches. Comparison between the groups are shown in Table 3.

Discussion

Previous publications have reported cases of increase in the dimensions of the coronary arteries among subjects with diseases such as polyarteritis nodosa, periodontal disease, Mediterranean spotted fever caused by *Rickettsia*, murine typhus, and even rheumatic fever. Furthermore, it has been shown that the dimensions of the coronary arteries of children with prolonged fever, who do not meet the criteria for KD, are larger than those of healthy subjects, but smaller than those of children suffering from KD.[12-15] These findings are in accordance with our study. We found a high percentage of subjects with FEI and coronary dilation, but the dimensions of their coronary arteries was smaller than those of subjects diagnosed with KD.

It is known that coronary abnormalities are present in 20% of the cases diagnosed with KD.[16] In our study, the percentage of coronary dilation among subjects with non-Kawasaki FEI was 26% using the Z score. This implies that coronary changes are more common in FEIs than in KD. It also suggests that it is likely that many of the cases diagnosed as atypical or incomplete KD (based on the presence of coronary alteration) could be, in fact, another FEI.

Table 1 – Demographic and clinical characteristics of patients with febrile exanthematous illness (FEI) and patients with Kawasaki disease (KD)

Variable	FEI (n = 22)	KD (n = 12)	p value
Male (%)	59	75	0.02
Age, in months (mean)	41.3	18.1	0.05
Fever duration, in days (mean)	3.6	6.5	0.06
Maximum body temperature (ºC)	38.3	38.7	0.9
Exanthema	22(100)	12 (100)	1
Conjuntivitis	2(6.2)	12 (100)	0.03
Swollen lymph glands in the neck	0(0)	12 (100)	--------
Swelling and redness in hands and bottoms of feet, n (%)	0(0)	12 (100)	--------
Peeling skin n (%)	0(0)	12 (100)	----------
Swollen tongue n (%)	0(0)	12 (100)	----------
Time between diagnosis and echocardiography, in days (mean)	12	25.3	0.05
Coronary dilatation n (%)	6 (27.2)	4(33.3%)	0.4

Table 2 – Z scores of coronary arteries of subjects with febrile exanthematous illness and dilatation of at least one of the coronary branches

Gender	Age (Months)	PRCA	Z	MRCA	Z	DRCA	Z	LMCA	Z	Circumflex	Z	LAD	Z	Diagnosis
F	7	2	*1.7	1.9	*2.1	1.6	1.57	3	*4.1	2	*2.5	2.8	*4.9	SE
F	27	2.4	*1.67	1.7	0.51	1.4	-0.1	2.2	0.49	1.6	0.29	1.5	-0.16	HFM disease
M	84	3	*2.21	1.9	0.27	1.5	-0.53	3.3	*2.3	1.7	-0.16	1.6	-0.6	Scarlet fever
M	120	3.4	*1.85	3	*1.7	2.3	0.47	3.5	1.48	2.6	0.94	2.5	0.74	Viral exanthem
F	36	2.3	1.16	2	1.09	1.8	0.82	3.1	*2.6	2.1	1.4	2	1.07	HFM disease
M	36	1.6	-0.57	1.2	-0.92	1	-1.34	2	-0.2	1.1	-1.16	1	*1.7	HFM disease
Mean	51.6	2.45	0.93	1.95	0.24	1.6	0.15	2.85	0.59	1.85	0.26	1.9	0.26	xx

**: Increased Z scores; F: Female; M: Male; PRCA: Proximal Right Coronary Artery; MRCA: Medial Right Coronary Artery; DRCA: Distal Right coronary artery; LMCA: Left main coronary artery; LAD: left anterior descending coronary artery; Z: Z values; SE: Sudden exanthema; HFM: Hand Food Mouth*

Pathogenesis of the dilation of coronary arteries in FEIs is not clear. However, it could be related with a greater myocardial demand for oxygen caused by fever and tachycardia. The consequent increase of coronary blood flow is produced through the compensatory dilation of the coronary arteries. Another potential dilation mechanism would involve pathogenic proteins that bind to the endothelial cells, activating immune response pathways that produce cytokines and promote additional cellular damage.

These findings make it clear that the etiology of coronary changes is not unique. There is a common pathophysiological mechanism that can cause temporary or permanent damage. Therefore, coronary changes should be carefully considered for the diagnosis of KD. An echocardiography should be performed in children diagnosed with FEI, and a timely prophylactic treatment should be considered.

Moreover, these findings have implications that should be defined and discussed. Even though the number of subjects is low, the results are important and give rise to some questions:

1. Should an echocardiography be performed to all patients diagnosed with FEIs?
2. If coronary changes are detected, should gamma globulin be administered?
3. Do coronary changes in non-KD FEIs persist or are they reversible?

Any affirmative answer would have an impact on public health and health economics. Maybe, many of the FEI cases primarily considered incompatible with KD should be reconsidered, and the number of the cases of atypical or incomplete KD would increase merely by the fact that the presence of coronary changes is determinant for the diagnosis of non-KD FEI. There is already a similar example in literature: patients without FEI criteria that were diagnosed with KD because of the coronary changes.[17,18]

Limitations

The main limitation of the study is its small sample size, but despite that, important differences were found. Moreover, it is noteworthy that in our country we do not have nomograms of the coronary arteries of Mexican children, which would allow a direct comparison and avoid the bias inherent to the use of nomograms from other regions. This study can encourage future studies to develop these nomograms with Mexican population. Also, the next step would be to perform a longitudinal study with follow-up of these subjects and assessment of the course of the diseases.

Table 3 – Comparison of Z scores of coronary arteries between subjects with febrile exanthematous illness and subjects with Kawasaki disease

	FEI (mean(IC 95%)	KD	p
PRCA	0.45 (–0.01–0.9)	0.2	0.05
MDCA	–0.004 (–0.3–0.3)	4.8	0.05
DRCA	–0.2(–0.8–0.3)	2.3	0.05
LMCA	0.13 (–0.2–0.5)	0.6	0.05
Circumflex	–0.01(–0.4–0.4)	0.6	0.05
LAD	–0.36 (–0.01–0.5)	0.5	0.05

PRCA: Proximal Right Coronary Artery; MRCA: Medial Right Coronary Artery; DRCA: Distal Right coronary artery; LMCA: Left main coronary artery; LAD: left anterior descending coronary artery.

Conclusions

In this study, we found an important percentage of patients diagnosed with FEI with an alteration in the dimension of the coronary arteries. This makes us conclude that coronary changes acquired in childhood are not exclusive to KD and should be carefully considered when establishing a diagnosis. Although the pathophysiological mechanisms underlying coronary changes in FEIs are not clear, it has been observed that they can cause temporary or permanent coronary damage.

Author contributions

Conception and design of the research: Reyna J, Limón AE; Acquisition of data: Reyna J, Reyes LM, Reyes L, Campos FH, Meza P, Lagunas A, Contreras C; Analysis and interpretation of the data: Reyna J, Reyes L, Meza P, Contreras C, Limón AE; Statistical analysis: Reyna J; Writing of the manuscript: Reyna J, Reyes LM, Campos FH, Meza P, Lagunas A, Contreras C, Limón AE; Critical revision of the manuscript for intellectual content: Reyna J, Reyes LM, Reyes L, Campos FH, Lagunas A, Limón AE.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Central Sur de Alta Especialidad under the protocol number 39/17. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Coronary Artery Dilation in Children with Febrile Exanthematous Illness without Criteria for Kawasaki Disease - An Enigmatic Disease

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Short editorial related to the article: Coronary Artery Dilation in Children with Febrile Exanthematous Illness without Criteria for Kawasaki Disease

More than half a century has elapsed since Prof. Tomisaku Kawasaki's did the first description of a unique disease. He saw the first 4-year-old patient with fever and rash in 1961…. At that time, he described the diagnosis "unknown". The published paper title was *Infantile acute febrile mucocutaneous lymph node syndrome with specific desquamation of the fingers and toes. Clinical observation of 50 cases.*[1] From This "unknown diagnosis", which now we call Kawasaki disease (KD) until the current era, this vasculitis of unknown cause became the leading cause of acquired heart disease among children in United States.[2]

Historically, the presence of coronary abnormalities was not noticed until patients died suddenly of cardiac complications. An angiographic study of 1100 patients showed coronary artery lesions in 24%, with aneurysms in 8% and a number of patients with stenoses and occlusions.[3] As soon as the Coronary arteries became the key structure for risk stratification, treatment and outcome, extensive research and worldwide effort has been done targeting the correct diagnostic. Unfortunately, to make things more challenging, there are forms of "uncomplete KD" which overlaps with other forms of febrile Exanthematous illness in children.

In this original paper, Dr. Reyna et al.[4] highlight the coronary arteries dilatation in the context of febrile Exanthematous illnesses, but not classified as KD.[4] Interestingly, Kawasaki's presentations and publication were initially met with skepticism as to whether his cases were a newly recognized disease entity or a variant of scarlet fever, Stevens-Johnson syndrome, or erythema multiforme. So, the most important and key step is a clear definition and criteria of KD and coronary artery lesions. In recognition of the challenges posed in the diagnosis of "incomplete" KD, The Japanese Ministry of Health Research Committee and the Japanese Circulation Society (JCS), and the American Heart Association (AHA) and American Academy of Pediatrics (AAP), in 2004, established their criteria.[2,5] The definitions and criteria for Kawasaki disease diagnosis slightly differ between the AHA/AAP and Japanese guidelines. The diagnostic criteria for classical Kawasaki disease in AHA/AAP guidelines include fever persisting at least 5 days and at least four of five other criteria. The criteria in the Japanese guidelines include fever as a sixth, equally important criterion, and patients must meet five of six criteria for diagnosis, including fever that subsides within 5 days in response to therapy. It is difficult to compare coronary lesions between these two countries because the definitions of are completely different in the respective guidelines. The Japanese JCS guidelines for Coronary artery lesions use the diameter of each segment of coronary arteries. However, in the AHA/APP guidelines aneurysms are classified using z-scores. In this paper, the author uses echocardiogram to assess the coronary artery luminal dimensions, converted to z – scores adjusted for body surface area (BSA).

As already mentioned before, another important topic related to this publication is the concept of atypical KD, which is very challenging diagnosis and management. The Japanese guidelines state that a KD diagnosis is possible even when five or more of the principal symptoms are absent, if other conditions can be excluded and KD is suspected, a condition known as incomplete KD. Indeed, approximately 15–20% of KD patients have incomplete KD in Japan.[6] However, even if a patient has four or fewer principal symptoms, the illness should not be regarded as less severe, because cardiovascular abnormalities are not rare in patients with incomplete KD.[7] The AHA/AAP guidelines include an algorithm for evaluation and treatment of suspected patients with incomplete or atypical KD. The algorithm indicates that incomplete KD should be diagnosed in a patient with a fever persisting at least 5 days, two or three additional clinical diagnostic criteria, and abnormal laboratory values typical of KD. The incidence rate of incomplete KD in the United States is reported to be approximately 20–27%. The AHA/AAP specifies that the term "atypical" should be used to describe patients who have a sign or symptom not typically seen in KD, such as renal impairment.

Previously, in a pilot study Muniz et al.[8] described that coronary arteries dimensions with non-KD febrile illness are larger than those in normative afebrile subjects but smaller than dimensions in patients with KD.[8] Some gaps still need to be filled, especially related to the pathology in those febrile illness: in the KD vasculopathy primarily involves muscular arteries and is characterized by 3 linked processes: 1 – necrotizing arteritis; 2 – subacute/chronic vasculitis and 3 – luminal myofibroblastic proliferation. Maybe, a better understanding of this process, which clarifies why the coronary arteries became dilated and don't progress to aneurysms.

So, the vasculopathy in KD and other febrile exanthemathous illness remains an enigmatic disease. Five decades of new findings and all research have not been enough. We still need more research to give us more answers….

Keywords

Doenças Cardiovasculares/ diagnosis; Coronary Artery; Kawasaki Disease; Fever; Exantemous; Echocardiography/ diagnostic imaging.

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Original Article

Nrf2, NF-κB and PPARβ/δ mRNA Expression Profile in Patients with Coronary Artery Disease

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Abstract

Background: Oxidative stress and inflammation are present in coronary artery disease (CAD) and are linked to the activation of the transcription nuclear factor kappa B (NF-κB). To attenuate these complications, transcription factors like nuclear factor erythroid 2-related factor 2 (Nrf2) and peroxisome proliferator-activated receptor-β/δ (PPARβ/δ) can be activated to inhibit NF-κB. However, the available data on expression of NF-κB, Nrf2 and PPARβ/δ in CAD patients are limited.

Objective: To evaluate the expression of the transcription factors NF-κB and Nrf2 and PPAR*β/δ* in CAD patients.

Methods: Thirty-five patients (17 men, mean age 62.4 ± 7.55 years) with CAD and twelve patients (5 men, mean age 63.50 ± 11.46 years) without CAD were enrolled. Peripheral blood mononuclear cells (PBMCs) were isolated and processed for mRNA expression of Nrf2, NF-κB, NADPH: quinone oxidoreductase 1 (NQO1) and PPARβ/δ mRNAs using quantitative real-time polymerase chain reaction (qPCR). $p < 0.05$ was considered statistically significant.

Results: There was no difference in the mRNA expressions of Nrf2 (1.35 ± 0.57), NF-κB (1.08 ± 0.50) or in the antioxidant enzyme NQO1 (1.05 ± 0.88) in the CAD group compared to the group without CAD (1.16 ± 0.76, 0.95 ± 0.33, 0.81 ± 0.55, respectively). However, PPARβ/δ was highest expressed in the CAD group (1.17 ± 0.86 vs. 0.56 ± 0.34, $p = 0.008$).

Conclusion: The main finding of this study was the PPARβ/δ being more expressed in the PBMC of patients with CAD compared to the control group, whereas no differences were observed in Nrf2 or NF-κB mRNA expressions. (Arq Bras Cardiol. 2019; 113(6):1121-1127)

Keywords: Coronary Artery Disease; Oxidative Stress; Inflammation; Obesity; Hypertension; Dyslipidemias; Risk Factors/prevalence; Myocardial Infarction; Heart Failure.

Introduction

Of all cardiovascular diseases (CVD), coronary artery disease (CAD) is the leading cause of death and high expenditure on medical assistance in the world, and is typically a chronic disease with progression over years or decades.[1–3] CAD, also known as coronary arteriosclerotic heart disease or coronary heart disease, is characterized by narrowing of the arteries in the heart that supply blood, oxygen, and nutrients to the cardiac tissue.[4]

Although there has been a steady decline in the incidence of CVD in recent years, the prevalence of CVD risk factors (hypertension, high cholesterol and obesity) has been increasing. Smoking, obesity, high blood pressure (BP), high total cholesterol and low-density lipoprotein, low high-density lipoprotein, diabetes and advanced age are the main risk factors for CVD[5,6] and are directly related to endothelial dysfunction with low bioavailability of nitric oxide, causing vasoconstriction, oxidative stress and inflammation.[7,8] Oxidative stress is present in both etiology and progression of myocardial infarction, congestive heart failure, atherosclerosis and hypertension.[9]

Oxidative stress arises when there is an imbalance between the reactive oxygen species (ROS) production and the capacity of the antioxidant defense systems of the body,[10] while inflammation is a biological response to oxidative stress where the cell starts producing proteins, enzymes and other compounds to restore homeostasis.[11] Oxidative stress is responsible for inflammation by several mechanisms, one of which is the direct activation of the nuclear transcription factor kappa B (NF-κB) by the ROS. NF-κB regulates the transcription of several genes encoding proinflammatory cytokines, chemokines and adhesion molecules of leukocytes.

In this direction, it is important to evaluate factors that attenuate both inflammation and oxidative stress. Nuclear factor erythroid 2-related to factor 2 (Nrf2) has been associated with cytoprotective effects and its accumulation leads to an increase in the transcription of antioxidant response elements (ARE)-regulated genes encoding antioxidant and phase 2 detoxifying enzymes and can be considered a protective factor against both oxidative stress and inflammation.[12-14] Under basal conditions, Nrf2 is inactive in the cytoplasm

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and is inhibited by its cytosolic repressor protein, Kelch-like ECH-associated protein 1 (Keap1), which through the action of certain substances, including the ROS, which alters the conformation, decouples Nrf2 and thereby facilitates accumulation and nuclear translocation of Nrf2. In the nucleus, Nrf2 binds to regulatory sequences called AREs acting on genes that encode antioxidant and phase II detoxifying enzymes, including NADPH: quinone oxidoreductase 1 (NQO1).[15] The role of Nrf2 in reducing inflammation is related to the ability to antagonize NF-κB indirectly by removing ROS. In addition, antioxidant enzymes appear to act directly on the reduction of inflammatory mediators.[15] Besides Nrf2, another target that has attracted interest and attention from research is the peroxisome proliferator-activated receptor-β/δ (PPARβ/δ). However, the biological functions of PPARβ/δ and its effectiveness as a therapeutic target in the treatment of hypertension and CVD have not been elucidated.[16] PPARβ/δ is the predominant subtype in the heart and several lines of evidence suggest a cardioprotective function of PPARβ/δ.[17] Preclinical studies suggest that PPARβ/δ activation promotes antihypertensive effects in established animal models[18] and the pharmacological activation of PPARβ/δ prevents endothelial dysfunction and downregulates inflammatory responses.[19,20] Furthermore, PPARβ/δ suppresses the activities of several transcription factors, including the NF-κB.[21] Based on the fact that there are no studies about gene expression of Nrf2, NF-κB and PPARβ/δ and its profile in CAD patients, the objective of this study was to evaluate the transcription factors NF-κB and Nrf2 and PPARβ/δ mRNA expression in patients with CAD.

Methods

Subjects

Forty-seven patients were enrolled in this study through a convenience sample where patients composed each group according to the presence or absence of CAD. Thirty-five patients (17 men and 18 women, mean age 62.4 ± 7.5 years, BMI 28.9 ± 4.9 kg/m^2) with CAD and/or abnormal findings of myocardial perfusion scintigraphy comprised the CAD group and twelve patients (5 men and 7 women, mean age 63.5 ± 11.5 years, 26.5 ± 6.2 kg/m^2) without CAD comprised the group without CAD. Eligible patients were older than 18 and attended the Nuclear Medicine Section at Hospital Universitário Antônio Pedro (Niterói, Rio de Janeiro, Brazil) to undergo myocardial scintigraphy. Patients with infection, cancer, chronic kidney disease (estimated glomerular filtration rate <60 mL/min), acquired immune deficiency syndrome (AIDS) and autoimmune disease were excluded. The control group consisted of hypertensive, dyslipidemic and/or diabetic patients not diagnosed with CAD, from the same hospital.

Anthropometric Measures

Anthropometric measurements were made by a trained staff member using standard techniques. Body mass index was calculated as weight in kilograms divided by height in square meters.[22]

Blood pressure assessment

BP was measured by the indirect method using auscultatory technique with sphygmomanometer and appropriate cuff in accordance with the dimensions of the patient's arm. Aneroid arterial pressure device – AD-2 was used on caster (pedestal), brand UNITEC Hospitalar (INMETRO ML 095 2007/ANVISA 10432300016). To assess BP, the procedure was initially explained to the patient who was resting for more than five minutes. The patient was sitting, feet resting on the floor, back resting on the chair, arm at heart level (mid-point of the sternum), supported, free of clothing, with the palm of the hand facing upwards and the elbow slightly flexed. HA was defined when systolic BP (SBP) values were greater or equal to 140 mmHg.[23]

Analytic procedures and sample processing

Blood was collected from each participant in the morning, after 12-hour overnight fasting, using a tube containing EDTA anticoagulant (1.0 mg/mL). Plasma was centrifugated and separated (15 min, 3000×g, 4°C) and stored at −80°C until analysis.

Peripheral blood mononuclear cells (PBMCs) were collected, blood samples with EDTA were diluted in PBS and cells were separated in 5 mL Histopaque (Sigma-Aldrich) by centrifugation at 1800 g for 30 min. PBMCs were collected and washed twice with cold PBS and re-suspended and stored (−80°C) with 1 mL of Recovery™ cell culture freezing medium (Thermo Fisher Scientific) for RNA isolation.

Biochemical and inflammation parameters

Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, glucose and ultra-sensitive C-reactive protein levels were determined using Bioclin® automatic biochemical analyzer kits (Bioclin BS-120 Chemistry Analyzer). LDL-c was calculated using the Friedewald et al. equation.[24]

Real-time quantitative PCR analysis

Nrf2, NF-κB, NQO1 and PPARβ/δ mRNA expressions were evaluated using real-time quantitative PCR (qPCR) from PBMCs according to Cardozo et al.[25] TaqMan® Gene Expression Assays (Applied Biosystems) were used to detect Nrf2 (Hs00975961_g1), NF-κB (Hs00765730_m1), NQO1 (Hs00168547_m1), PPARβ/δ (Hs00975961_g1) mRNA and the control gene GAPDH (Hs02758991_g1).

Statistical analysis

Shapiro-Wilk test was applied to test sample distribution. Results were expressed as mean ± SD (age, BMI, SBP, lipidic profile, glucose, Nrf2, NF-B, NQO1, PPARβ/δ), median (interquartile range) (CRP) or percentage (hypertension, dyslipidemia, diabetes), as applicable. Unpaired Student's *t*-test was used to compare the variables and groups with normal distribution and the Mann-Whitney-Wilcoxon test was used for nonparametric data. Correlations between variables were assessed by Pearson's or Spearman coefficient correlation according to the distribution of the

sample. A significance level of 5% was accepted. Statistical analyses were performed using the SPSS 19.0 software package (Chicago, IL, USA).

Results

In the CAD group, 82.8% presented abnormalities on myocardial perfusion scintigraphy (65.5% myocardial ischemia, 27.6% myocardial fibrosis, and 6.9% fibrosis and myocardial ischemia). Regarding the duration of disease, 71.4% were diagnosed with CAD from 1 to 5 years, 17.1% from 6 to 10 years and 11.5% from 10 to 15 years. According to the clinical history of patients with CAD, 54.2% performed some type of procedure before the study: 8.7% cardiac catheterization, 34.3% percutaneous transluminal coronary angioplasty, 5.7% percutaneous transluminal coronary angioplasty and cardiac catheterization and 5.7% percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. Moreover, 62.8% of the CAD patients and 30.8% of the control group were smokers. Considering the use of medication, in the CAD group, 68.5% used β-adrenergic blockers, 17.4% angiotensin-converting enzyme inhibitor, 77.1% statins, 28.5% calcium channel blockers, 51.4% diuretic, 37.2% nitrate, 54.3% acetyl salicylic acid, 62.8% losartan potassium, 34.8% oral hypoglycemic agents and 11.43% insulin. In the control group, 53.8% used β-adrenergic blocker, 15.4% angiotensin-converting enzyme inhibitor, 46.2% statins, 30.8% calcium channel blocker, 53.8% diuretic, 7.7% nitrate, 61.5% acetyl salicylic acid, 69.2% losartan potassium, 38.5% oral hypoglycemic agents and 7.7% insulin. No statistical differences were found between groups related to the use of medication or smoking.

Clinical profile and biochemical parameters are shown in Table 1. Also, the CAD group presented lower total cholesterol, LDL-cholesterol and HDL-cholesterol compared to the group without CAD (Table 1).

No differences were found in the transcription factors Nrf2 and NF-κB or in the NQO1 mRNA expression comparing the CAD group with the group without CAD. In contrast, the PPARβ/δ was more expressed in the CAD group (Table 2). We considered that the inclusion of diabetic patients did not interfere with the results. No correlations were found.

Discussion

Studies have evaluated systemic inflammation through PBMC gene expression.[26,27] The importance of studying PBMCs as a strategy to evaluate targets of inflammation-related metabolic pathways to explore CVD for a better understanding of the architecture of these diseases was emphasized. The hypothesis would be that the PBMCs could reflect inflammatory mechanisms in a more specific way compared to serum/plasma.[28] Thus, the present study investigates the transcription factors NF-κB and Nrf2 and PPARβ/δ mRNA expression in PBMCs of CAD patients. CVD patients are usually exposed to inflammation and oxidative stress. Nrf2 protects the body against these conditions because it is related to the synthesis of antioxidant enzymes and is capable of antagonizing NF-κB involved in inflammatory induction.

Several studies have shown that NF-κB plays an important role in the development of CVD.[29–31] It was demonstrated that ischemia rapidly induced NF-κB activation in the myocardium of rats.[29] Wilson et al.[30] showed that NF-κB was increased in the coronary atheromatous plaque in humans and its expression was predominantly associated with macrophages, foam cells and vascular smooth muscle cells. In addition, its expression was increased in acute coronary syndromes and associated with the intercellular adhesion molecule 1

Table 1 – Clinical profile and biochemical of the patients of the study

Parameters	Group without CAD (n = 12)	CAD Group (n = 35)	p value
Men/women (n)	5/7	17/18	0.99
Age (years)	63.5 ± 11.5	62.4 ± 7.5	0.70
Hypertension (%)	91.7	97.1	0.81
Dyslipidemia (%)	75	74.2	0.67
Diabetes (%)	16.7	37.1	0.84
BMI (kg/m^2)	26.5 ± 6.2	28.9 ± 4.9	0.17
SBP (mmhg)	137.5 ± 23.0	138.0 ± 18.6	0.69
DBP (mmhg)	82.5 ± 9.6	82.8 ± 8.2	0.90
Total cholesterol (mg/dL)	200 ± 59.4	163.3 ± 46.7	0.03
LDL-cholesterol (mg/dL)	109.3 ± 53.3	79.9 ± 33.3	0.03
HDL-cholesterol (mg/dL)	65.1 ± 21.3	45.3 ± 9.9	0.002
Triglyceride (mg/dL)	128.2 ± 57.3	130.6 ± 71.8	0.79
Glucose (mg/dL)	115.2 ± 44.6	103.7 ± 36.4	0.13
CRP (mg/L)	0.6 (0.4-4.0)	2.0 (0.12-8.7)	0.25

CAD: coronary artery disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure CRP: C-reactive protein. Parametric data expressed as mean±SD and nonparametric data expressed with median, 15th and 75th quartiles.

Table 2 – mRNA expression levels in the group without CAD and the CAD Group

Parameters	Group without CAD	CAD Group	p value
Nrf2	1.16 ± 0.76	1.35 ± 0.57	0.35
NF-B	0.95 ± 0.33	1.08 ± 0.50	0.58
NQO1	0.81 ± 0.55	1.05 ± 0.88	0.37
PPARβ/δ	0.56 ± 0.34	1.17 ± 0.86	0.008

Nrf2, NF-kB, NOQ1 and PPAR β/δ mRNA expression was performed in PBMC by real-time quantitative PCR. Data were expressed as mean ± SD. CAD: coronary artery disease.

(ICAM-1).[30] NF-κB inhibition in endothelial cells resulted in reduced development of atherosclerosis and was correlated with reduced expression of pro-inflammatory cytokines, chemokines and adhesion molecules in the aortas of mice fed with cholesterol-rich diet.[31]

Some studies demonstrate that, as a protection mechanism, in an early stage of diseases, Nrf2 has its activity increased in order to avoid damage induced by ROS. In the final stage, due to the chronicity and/or severity of the disease, this protection mechanism may become saturated by the excess of EROs leading to the reduction of Nrf2[32,33] or the Nrf2 appears to be insufficiently capable of antagonizing NF-κB and it remains high.[26]

Despite this, the effects of CAD on the Nrf2-Keap1 system are not well established. However, patients with CAD had lower gene expression of Nrf2/ARE and glutathione (GSH).[27]

An important phase of atherosclerotic plaque formation is endothelial infiltration well established by macrophages and formation of foam cells. In rats, Nrf2 is an important component in this process, as macrophages exposed to oxidized LDL promoted increased expression of Nrf2, which indirectly protected macrophages from oxi-LDL mediated lesions through phase II antioxidant enzymes.[34] In addition, the absence of Nrf2 in macrophages from mice consuming a high-fat diet increased the formation of foam cells and the progression of atherosclerosis, suggesting that Nrf2 is important in resistance to atherosclerosis.[35] Increased expression of Nrf2 at this stage of development of atherosclerosis is important because the effects on heme oxygenase-1 (HO-1) expression, which produces antiatherogenic effects as a reduction in the formation of foam cells[36] and NQO1 also proved to be important in the protection against atherosclerosis.[37]

In the present study, there were no differences in the Nrf2 or NF-κB mRNA expression between patients in the CAD group and the group without CAD possibly due to the fact that the patients in the two groups were elderly, hypertensive and/or diabetic, demonstrating that both groups did not include healthy patients. In addition, all the patients used several medications with potential antioxidant effect.[38,39] With age, expression of several Nrf2 downstream targets declined.[40] It is still important to emphasize that both hypertension and diabetes are related to increased oxidative stress, accumulation of reactive oxygen species and inflammation.[9,41]

In the present study, the PPARβ/δ was high compared to the patients without CAD. It seems to be protective since it has been shown that the adequate balance of PPARβ/δ activation in the different cardiac cell types may be important for potential cardioprotective effects of PPARβ/δ.[42] An *in vivo* study showed that cardiac specific overexpression of PPARβ/δ led to increased myocardial glucose utilization and did not alter cardiac function but exerted a protective effect on ischemia/reperfusion-induced myocardial injury.[43] In addition, cardiac PPARβ/δ deletion in mice resulted in cardiac dysfunction, hypertrophy and congestive heart failure.[17] Additionally, PPARβ/δ has been described in several biological functions, including cell survival.[44,45] Studies show that inflammation, ROS and oxidized LDLs induce endothelial cell apoptosis, representing the beginning of the development of atherosclerotic lesions.[45] Thus, assays performed on keratinocytes have shown that increased production of proinflammatory cytokines is capable of elevating PPARβ/δ expression, which in turn regulates the expression of apoptosis-related genes, resulting in increased resistance to cell death.[44]

Given the importance of PPARβ/δ and the transcription factors NF-κB and Nrf2 effects for the CAD patients – the Nrf2 orchestrating the production of antioxidant and phase 2 detoxifying enzymes being considered a protective factor against both oxidative stress and inflammation,[46] PPARβ/δ promoting cardioprotection[42] and NF-κB regulating inflammation[12] – a better understanding of how they are expressed in CAD patients is useful so that strategies can be used in an attempt to modulate these transcription factors. Some studies proposed that nutrients containing plant-based Nrf2 inducers may help to improve the Nrf2-Keap1 system.[25,47]

This study presented a range of limitations that warrant consideration. Firstly, this study should have a healthy control group for comparison. Secondly, it would be interesting to stratify the results by risk factor and scintigraphy results, but the sample was not large enough for this. Thirdly, unfortunately, we did not perform another Nrf2, NF-κB and PPARβ/δ target genes that encode antioxidant enzymes and proinflammatory cytokines to confirm the Nrf2, NF-κB and PPARβ/δ expression network. Furthermore, it was not possible to calculate non-HDL cholesterol. Further studies should be encouraged to explore this issue. Considering these limitations, this was a very well-controlled protocol, which allowed us to conclude that the results are considerably relevant.

Conclusion

The present study revealed increased expression of PPARβ/δ in the PBMC of CAD patients while no differences were observed in Nrf2 or NF-κB mRNA expressions. These findings may lead to possible therapies, targets and future research for treatment in these patients.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Barbosa JE, Stockler-Pinto MB, Cruz BO, Silva ACT, Anjos JS, Mesquita CT, Mafra D, Cardozo LFMF; Acquisition of data and Writing of the manuscript: Barbosa JE, Stockler-Pinto MB, Cruz BO, Silva ACT, Anjos JS, Cardozo LFMF; Statistical analysis and Obtaining financing: Stockler-Pinto MB, Mafra D, Cardozo LFMF; Critical revision of the manuscript for intellectual content: Barbosa JE, Stockler-Pinto MB, Mesquita CT, Mafra D, Cardozo LFMF.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal Fluminense under the protocol number 826.041 CAAE 35035414.8.0000.5243. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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PPARβ/δ: Benefits in Coronary Artery Disease and Beyond

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Short Editorial related to the article: Nrf2, NF-κB and PPARβ/δ mRNA Expression Profile in Patients with Coronary Artery Disease

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that participate in nutrient and energy metabolism.[1] In a recent paper entitled "Nrf2, NF-κB and PPAR β/δ mRNA expression profile in patients with coronary artery disease" (CAD), Barbosa et al. found that PPARβ/δ was highest expressed in the CAD patients when compared to patients without CAD.[2] Beyond its heart-protective effects associated to improvement of cardiac function and amelioration, the pathological progression of cardiac hypertrophy, heart failure, cardiac oxidative damage, ischemia-reperfusion injury, lipotoxic cardiac disfunction and lipid-induced cardiac inflammation,[3] others functions PPARβ/δ deserve be considered in the wide context of the cardiovascular disorders.

Obesity and dyslipidemia are risk factors for cardiovascular disease[4] and, in this sense, the modulation of PPARβ/δ can be interesting because it is associated with the improvement of fatty acid (FA) catabolism in skeletal muscle or alternating fibre type muscle during oxidative metabolism.[1,5] PPARβ/δ activation also reduces pre-adipocyte proliferation and differentiation, and attenuates angiotensin II-mediated dysfunctional hypertrophic adipogenesis and inhibits inflammation in adipose tissue.[5] Besides that, in the intestine, PPARβ/δ can induce the production of short-chain fatty acid (SCFA) production[1] and butyrate and propionate, two SCFA, were associated with reduction in food intake.[6] Moreover, PPARβ/δ improves hepatic FA oxidation which decreases the lipids availability for triglycerides synthesis and changes the expression of several apoproteins,[5] contributing for elevating plasma levels of high-density lipoprotein and decline levels of low-density lipoprotein.[1]

Thus, PPARβ/δ can be a potential target in metabolic disorders.[5] So, a question is pertinent: how to modulate PPARβ/δ? In the group of natural ligands, this subtype is activated by carbaprostacyclin, components of very low-density lipoprotein and unsaturated FAs.[7]

Unfortunately, PPARβ/δ has not been so intensely studied like the subtypes α and γ[7] and little is known about the potential natural activators, even in the case of unsaturated FAs that can be easily obtained by diet and supplements. So, let's look forward to this answer: it is possible to modulate PPARβ/δ by dietetic bioactive compounds? Nonpharmacologic strategies to modulate other nuclear factors, such as nuclear factor erythroid 2-related factor 2 (Nrf2), been pointed[8] and it is wanted to the same with PPARβ/δ. Caffeine,[9] genistein[10] and non-occidental diet pattern[11] already look promising.

Keywords

Coronary Artery Disease; Oxidative Strss; Inflammation, Obesity; Hypertension; Dyslipidemias; Risk Factors/prevalence; Myocardial Infarction; Heart Failure.

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Original Article

The Usefulness of Admission Plasma NT-pro BNP Level to Predict Left Ventricular Aneurysm Formation after Acute ST-Segment Elevation Myocardial Infarction

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Abstract

Background: **Left ventricular aneurysm (LVA) is an important complication of acute myocardial infarction. In this study, we investigated the role of N- Terminal pro B type natriuretic peptide level to predict the LVA development after acute ST-segment elevation myocardial infarction (STEMI).**

Methods: **We prospectively enrolled 1519 consecutive patients with STEMI. Patients were divided into two groups according to LVA development within the six months after index myocardial infarction. Patients with or without LVAs were examined to determine if a significant relationship existed between the baseline N- Terminal pro B type natriuretic peptide values and clinical characteristics. A p-value < 0.05 was considered statistically significant.**

Results: **LVA was detected in 157 patients (10.3%). The baseline N- Terminal pro- B type natriuretic peptide level was significantly higher in patients who developed LVA after acute MI (523.5 ± 231.1 pg/mL vs. 192.3 ± 176.6 pg/mL, respectively, p < 0.001). Independent predictors of LVA formation after acute myocardial infarction was age > 65 y, smoking, Killip class > 2, previous coronary artery bypass graft, post-myocardial infarction heart failure, left ventricular ejection fraction < 50%, failure of reperfusion, no-reflow phenomenon, peak troponin I and CK-MB and NT-pro BNP > 400 pg/mL at admission.**

Conclusions: **Our findings indicate that plasma N- Terminal pro B type natriuretic peptide level at admission among other variables provides valuable predictive information regarding the development of LVA after acute STEMI. (Arq Bras Cardiol. 2019; 113(6):1129-1137)**

Keywords: **Myocardial Infarction; Coronary Aneurysm/complications; Myocardial Revascularization; Indicators of Morbidity and Mortality; Stroke Volume.**

Introduction

Left ventricular aneurysm (LVA) is an important prognostic marker that is strongly correlated with mortality and morbidity after acute ST-segment elevation myocardial infarction (STEMI). LVA is also strongly related to adverse clinical outcomes. It is well known that LVA carries a high risk of arrhythmia, thromboembolism and heart failure. Additionally, patients with this complication have a high risk of death within 1 year, independent of left ventricular ejection fraction.[1,2]

The factors that are associated with LVA after acute STEMI have already been determined. However, most of these studies were performed before the modern treatment era for myocardial infarction. Additionally, the biochemical predictors of this complication have not yet been determined. Early detection prior to the development of LVA may be helpful in the management of patients with acute STEMI.

N terminal pro-B-type natriuretic peptide (NT-pro BNP) is a 32-amino acid peptide that is synthesized and released predominantly from the ventricular myocardium in response to myocyte stretching.[3] However, NT-pro BNP is secreted not only in response to increased left ventricular wall stretch but also to myocardial ischemia and infarction. Levels of NT-pro BNP correlate with left ventricular dilatation, remodeling, and dysfunction in patients after acute myocardial infarction.[4]

NT-pro BNP concentrations increase rapidly over the first 24 hours after acute myocardial infarction and then tend to stabilize. When measured 1 to 7 days after acute myocardial infarction, NT-pro BNP elevation identifies patients at risk for left ventricular dysfunction, heart failure, and death.[5-8] NT-pro BNP levels after acute myocardial infarction have proven useful for predicting prognosis and estimating infarct size, but the value of NT-pro BNP for the prediction of LVA formation has not yet been determined.

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The aim of this study was to evaluate the value of admission NT-pro BNP level in predicting LVA after acute STEMI.

Methods

A total of 1,519 consecutive acute STEMI patients admitted to our department were enrolled in this study from June 2011 to January 2017. The protocol for the study was approved by the local ethics committee. The study complied with the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients. The eligibility criteria included patients aged 21 to 75 years who presented within 12 h of chest pain. The exclusion criteria included previous heart failure, shock, pulmonary edema requiring intubation, and creatinine clearance < 30 ml/min. Acute STEMI was defined according to the third universal definition of myocardial infarction.[9]

Demographic information was collected, and a physical examination was performed for each patient. A 16-lead electrocardiogram recording was obtained from each patient immediately after admission.

Two-dimensional transthoracic echocardiography (TTE) was performed in all patients at admission and at the end of the first and six months of the index acute STEMI. The TTE measurements were performed using a Vivid 7 system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The echocardiographic assessment was performed according to a previous study by Weyman et al.[10] Complete 2-dimensional TTE, including Doppler flow interrogation, was performed according to standard techniques. LVA was defined as a demarcated bulge of the contour of the left ventricular wall during both diastole and systole, which showed akinesia and dyskinesia.

Blood samples were obtained immediately after admission to the coronary care unit using EDTA-containing tubes. The samples were stored for 3 days prior to NT-pro BNP assessment. Plasma NT-pro BNP level was measured using the Roche Diagnostics ElecsysproBNPelectrochemiluminescence immunoassay (ElecsysproBNP; Roche Diagnostics, Indianapolis, Ind). Baseline serum creatinine clearance was estimated using the Cockcroft–Gault formula. Fasting blood samples were taken in the morning after admission to determine fasting glucose and blood lipids. Blood samples for troponin I and creatine kinase-MB (CK-MB) assessment were taken every 8 h during the first 3 days after admission. The peak troponin and CK-MB levels during the hospital stay were also collected.

Reperfusion was achieved with primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy. The choice of reperfusion therapy type was made according to the patient's condition and the center's capabilities. Patients who were not suitable for reperfusion therapy because of late admission, comorbidities or contra-indications were followed medically.

All patients underwent coronary angiography except patients with serious comorbidities or contra-indications. Selective left and right coronary angiography was performed using the Judkins technique. Left ventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique projections and left ventricular end-diastolic pressure was measured before ventriculography.

The Rentrop grading scale was used to quantify the extent of collateral filling. The most opacified projection was used for grading. The following values were assigned according to the scale: 0 = no visible filling of any collateral vessel or collateral channels, 1 = filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2 = partial filling of the epicardial artery by collateral vessels, or 3 = complete filling of the epicardial artery by collateral vessels.

The mean collateral score was then calculated by dividing the sum of the Rentrop numbers by the number of patients.

The Gensini score was used to evaluate coronary lesion severity. Gensini score calculation was initiated by giving a severity score to each coronary stenosis as follows: 1 point for ≤ 25% narrowing, 2 points for 26 to 50% narrowing, 4 points for 51 to 75% narrowing, 8 points for 76 to 90% narrowing, 16 points for 91 to 99% narrowing, and 32 points for total occlusion. Thereafter, each lesion score was multiplied by a factor that considered the importance of the lesion's position in the coronary circulation (5 for the left main coronary artery; 2.5 for the proximal segment of the left anterior descending coronary artery; 2.5 for the proximal segment of the circumflex artery; 1.5 for the mid-segment of the left anterior descending coronary artery; 1.0 for the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, or the obtuse marginal artery; and 0.5 for the other segments). Finally, the Gensini score was calculated by the summation of the individual coronary segment scores in each group.

PPCI performed only for the culprit artery. Percutaneous coronary intervention (PCI) was performed for non-culprit stenotic lesions during index hospitalization. Patients who received fibrinolytic therapy and subsequently underwent coronary angiography, ad hoc PCI was performed in patients with suitable coronary anatomy, and drug-eluting stents were used in most of the patients. In patients without suitable coronary anatomy for PCI, medical therapy or coronary artery bypass graft were decided.

All patients received aspirin (300-500 mg), a loading dose of clopidogrel (300-600 mg), and a bolus of unfractionated heparin (60-100 U/kg). At discharge, medical therapy was prescribed according to the patient's individual status and guideline recommendations for secondary prevention.[11]

The patients were divided into two groups according to the presence of LVA within the six months of index MI. Group 1 consisted of patients with LVA, and group 2 included those without LVA.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 statistical software. Continuous variables with normal distribution were reported as the mean ± standard deviation, continuous variables with non-normal distribution were reported as median –interquartile range and categorical variables were expressed as the number of patients and percentages. Normality was tested using the Kolmogorov-Smirnov test. Comparisons between categorical variables were performed by the Pearson's chi-square test, or Fisher's exact test, as

appropriate. Continuous variables were compared by Student's t-test for independent samples or the Mann-Whitney test, as appropriate. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. We analyzed the effects of different variables on the occurrence of ventricular aneurysm in univariate analysis and determined the variables whose unadjusted p-value was < 0.10 as potential risk markers and these were included in the full model. We composed the model by using forward elimination at multivariate regression analysis, and we eliminated potential risk markers by using likelihood ratio tests.

Area under the ROC (receiver operating characteristic) curves, based on C-statistics, were performed to determine the optimal cut-off value for NT-pro BNP to predict the LVA.

Results

A total of 1,519 patients were enrolled (mean age 56.7 ± 11.7 years). Figure 1 describes the enrollment of patients for this study. The baseline characteristics of the patients are summarized in Table 1. The time from onset of chest pain to arrival at the hospital was 6 ± 12 hours. Of the 1,519 patients, primary PCI was performed in 67%, and 26% received fibrinolytic therapy. Seven percent of patients did not receive any reperfusion therapy. Among the patients who developed LVA, the myocardial infarction localization was anterior wall in 90.4%, isolated inferior wall in 1.3%, inferior-posterior in 2%, and inferior-right ventricle in 6.3%. In addition, anterior-located STEMI patients developed LVA more frequently than did patients with infarction on the other side (7.8% vs 1.2% p < 0,01). Patients who developed LVA had lower reperfusion rate than did patients without LVA (42.1% vs. 15.2%, p = 0.021) (Table 2). The LVA rate was lower in patients who received PPCI than in patients who received fibrinolytic therapy or no reperfusion therapy (5.3 vs. 9.2 p < 0.01, 5.3 vs. 14.7; p = 0.03). The type of fibrinolytic agent used had no effect on LVA development. Patients with LVA had a lower rate of P2Y12 inhibitor use (Table 3). When the culprit artery was the left anterior descending artery, the LVA risk was more than in the other coronary arteries (Figure 2). The Gensini scores were similar between groups (38.7 ± 30.8 vs. 37.9 ± 29.9, p = 0.924). However, Rentrop scores were significantly higher in patients without LVA (1.96 ±1.32 vs. 1.51 ± 0.76, p = 0.001). Time to reperfusion therapy was shorter in patients without LVA (4.1 ± 6.3 vs 6.2 ± 5.9, p < 0.05). The basal NT-pro BNP level was significantly higher in patients with LVA (523.5 ± 231.1 pg/mL vs. 192.3 ± 176.6 pg/mL, p < 0.001) (Figure 3). Multivariate logistic regression analysis determined the predictors of LVA after MI (Table 4). Previous CABG, post-MI heart failure, younger age, smoking, no-reflow phenomenon and high NT-pro BNP at admission predicted LVA formation after acute STEMI.

Roc analysis showed that the cut-off value of NT-pro BNP at admission for LVA development was 400 pg/mL. The sensitivity and specificity were 78.3% and 94.7%, respectively. (Area under curve: 0.860 0.751-0.968 95% CI) (Figure 4).

Roc analysis showed that the cut-off value for peak cTnI for LVA development was 78 pg/mL (Area under the curve: 0.720 0.541-1.320 95% CI) and for peak CK-MB was 312.86 IU/mL (Area under the curve: 0.640 0.314-0.986 95% CI).

Discussion

Our study showed two main issues: 1) the factors affecting the development of LVA in the new treatment era of acute STEMI, and 2) that NT-pro BNP measured during the acute phase of STEMI is useful for predicting LVA development.

Recent studies have determined that LVA incidence after acute STEMI was reduced from 10-30% to 8-15% after the developments in the treatment of acute STEMI.[12,13] In accordance with these data, we found that the incidence of LVA after acute STEMI was 10.3%. Although there are some controversial issues, previous studies have determined that single-vessel disease, total LAD occlusion, poor collateral supply to the infarct-related artery, hypertension and female gender were major determinants for the development of LVA after acute MI.[14-16] However, most of these data were reported before the modern treatment era. In our study, we determined that patients who received fibrinolytic therapy or no reperfusion therapy developed LVA more frequently than did patients who received PPCI. The type of fibrinolytic agent used had no effect on LVA formation. Patients who received reperfusion therapy earlier had less frequent LVA formation. These data showed that earlier reperfusion prevents the development of LVA. Moreover, in our study, P2Y12 inhibitors were found to be a determinant of LVA formations. Hirai et al.[17] showed that good collateral coronary circulation has a beneficial effect on the prevention of LVA formation.[17] Similarly, we found that the Rentrop score was significantly higher in patients without LVA. We also determined that the severity of coronary disease had no effect on the development of LVA. Additionally, gender and risk factors such as diabetes or hypertension had no effect on the development of LVA.

The biomarkers of cardiac function may provide useful information in evaluating cardiac outcomes after acute STEMI. Mayr et al.[18] found that NT-pro BNP on day 3 after admission correlated with acute and chronic infarct size and left ventricular ejection fraction after acute myocardial infarction.[18] Kleczyński et al.[19] showed that the assessment of NT-pro BNP level 6 months after STEMI is a useful marker of infarct size and left ventricle function at long-term follow up.[19] Fazlınezhad et al.[20] showed that BNP level is a predictor of acute MI complications such as left ventricular pseudoaneurysm.[20] We showed that NT-pro BNP assessment within the first 12 hours of chest pain is a good indicator to predict LVA. This relationship may be associated with ischemic remodeling of the left ventricle, which triggers NT-pro BNP secretion.

The answer as to why we observed high NT-pro BNP levels before the development of LVA may be associated with the properties of NT-pro BNP. The level of NT-pro BNP may reflect the severity of the ischemic insult, even when myocardial necrosis has not occurred. It has been shown that in experimental acute myocardial infarction, NT-pro BNP synthesis is augmented not only in infarcted tissue but also in non-infarcted tissue.[21] In addition, NT-pro BNP levels have been shown to increase transiently after uncomplicated percutaneous transluminal coronary angioplasty, even when intracardiac filling pressures remain unchanged.[22] Therefore, we may suggest that transient ischemia increases wall stress and induces BNP synthesis and the release in proportion to the degree of ischemic insult. Afterwards, this

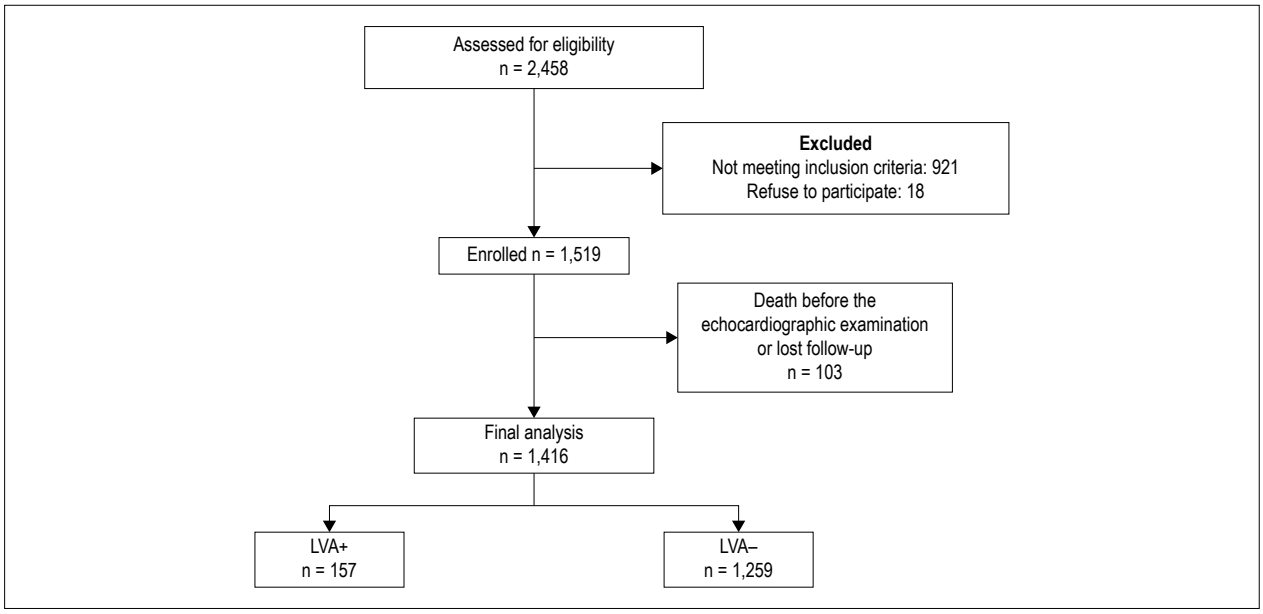

Figure 1 – *Patients flow chart demonstrating the number of patients eligible for inclusion into the study.*

Table 1 – Demographics of study group

	LV Aneurysm(-)	LV Aneurysm (+)	p-value
Age (years)	55.4 ± 11.0	61.0 ± 13.2	0.048
Gender (M) (n)%	(783)62.2	(106)67.5	0.070
BMI	27.4 ± 4.7	28.6 ± 2.9	0.030
Smoking (n) %	(673)53.4	(35)22.2	0.011
DM (n) %	(319)25.3	(36)22.9	0.803
Previous CABG (n) %	(23)1.8	(14)8.9	0.008
Previous PCI (n) %	(34)2.7	(2)1.3	0.439

LV: left ventricle; BMI: body mass index; DM: diabetes mellitus; CABG: coronary artery bypass greft; PCI: percutaneous coronary intervention.

ischemia causes infarct tissue and LVA. Thus, we observed high levels of NT-pro BNP before the development of LVA.

Conclusion

In this study, we found that in the modern treatment era of acute STEMI, there are new factors such as reperfusion therapy or P2Y12 inhibitors that affect the development of LVA. We also found that NT-pro BNP > 400 pg/dL measured during the first 12 hours of acute STEMI is a good predictor of LVA formation. To the best of our knowledge, no previously published studies have demonstrated the relationship between admission NT-pro BNP levels and LVA formation after acute MI. Therefore, we concluded that a single measurement of NT-pro BNP at admission in patients with acute STEMI proves useful for the estimation of LVA development.

Limitations

First, we measured the NT-pro BNP levels only at admission. Serial measurement may give more information about LVA development. Second, we only determined the LVA by TTE. Although TTE was performed by two blind echocardiographers, there will still be limitations in detecting the apical aneurysms.

Author contributions

Conception and design of the research: Celebi S, Celebi OO, Gokaslan S, Berkalp B, Aydogdu S; Acquisition of data and Statistical analysis: Celebi S, Celebi OO, Cetin HO; Analysis and interpretation of the data: Celebi S, Cetin S, Tek M; Writing of the manuscript: Celebi S, Celebi OO, Berkalp B, Aydogdu S; Critical revision of the manuscript for intellectual content: Celebi S, Cetin S, Cetin HO, Tek M, Amasyali B, Berkalp B, Diker E, Aydogdu S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Table 2 – Laboratory and angiographic parameters of the study group

	LV Aneurysm (-)	LV Aneurysm (+)	p- value
NT-BNP, pg/mL	192.3 ± 176.6	523.5 ± 231.1	0.000
Gensini Score	38.7 ± 30.8	37.9 ± 29.9	0.924
Rentrop Score	1.96 ± 1.32	1.51 ± 0.76	0.000
Revascularization, %	72	45.5	0.021
Succesful Reperfusion, %	84.5	62.8	0.01
Killip	1.1 ± 0.3	1.5 ± 0.5	0.001
LVEF (%)	4.2 ± 8.6	32.3 ± 4.8	0.001
C r e atinine, mg/dl	0.9 ± 0.7	1.3 ± 0.8	0.02
MPV, fL	8.6 ± 0.8	9.3 ± 0.8	0.000
MCV, fL	85.0 ± 9.8	86.2 ± 10.7	0.683
Glucose, mg/dl	98.7 (IQR 62.0–312.0)	101.5 (IQR 66.0–427.0)	0.211
HbA1c, %	7.2 (IQR 5.8–13.1)	7.8 (IQR 6.5–14.8)	0.098
Peak cTnI, ng/mL	28.6 ± 19.2	43.4 ± 26.8	0.000
Peak CK-MB, IU/L	82.0 ± 54.30	212 ± 96.80	0.003

LVEF: Left ventricular ejection fraction; MPV: Mean platelet volume; MCV: mean corpuscular volume; IQR: Interquartile range; cTnI: cardiac troponine I; CK-MB: creatinine kinase-MB. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test, and continuous numerical variables were compared by the Student's t test for independent sample or Mann-Whitney test, as appropriate.

Table 3 – In hospital Therapy and Adverse Events

	LV Aneurysm(-) (n = 1259) (%)	LV Aneurysm(+) (n = 157) (%)	p-value
P2Y12 inh.	(1226) 97.3	(112) 71.3	0.008
LMWH	(912)72.4	(97)61.7	0.008
Statin	(124)98.6	(142)90.4	0.128
b-bloker	(1208)96.0	(136)86.6	0.300
ACE inh	(1041)82.6	(128)81.5	0.927
ARB	(34)2.7	(9)5.7	0.075
Spironolakton	(92)7.3	(22)14.0	0.128
Furosemide	(167)13.2	(99)63.1	< 0.0001
Tiyazid	(27)2.1	(14)8.9	0.050
CCB	(59)4.7	(7)4.4	0.542
Amiodorone	(67)5.3	(16)10.2	0.190
Digoxin	(16)1.3	(21)13.3	0.035
Warfarin	(75)5.9	(15)9.5	0.050
Insülin	(101)8.0	(16)10.1	1.000
OAD	(185)14.6	(7)4.4	0.205
Post MI angina	(34)2.7	(8)5.0	0.542
Heart Failure	(185)14.7	(93)59.2	0.01
Acut Renal Failure	(44)3.3	(7)4.4	0.404
Pericarditis	(51)4.0	(9)5.7	1.000
Arrythmia	(251)20.0	(64)40.7	0.046
GIS bleeding	(21)1.7	(4)2.5	1.000
Hematuri	(14)1.1	(7)4.4	0.227
LV thrombus	(23)1.8	(29)18.4	0.002
Mitral Regurgitation	(167)13.2	57(36.3)	0.015

P2Y12 inh.: P2Y12 inhibitor; LMWH: Low molecular weight heparine; ACE inh.: angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel Blockers; OAD: Oral antidiabetic; MI: myocardial infarction; GIS: Gasrointestinal system; LV: left Ventricle. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test.

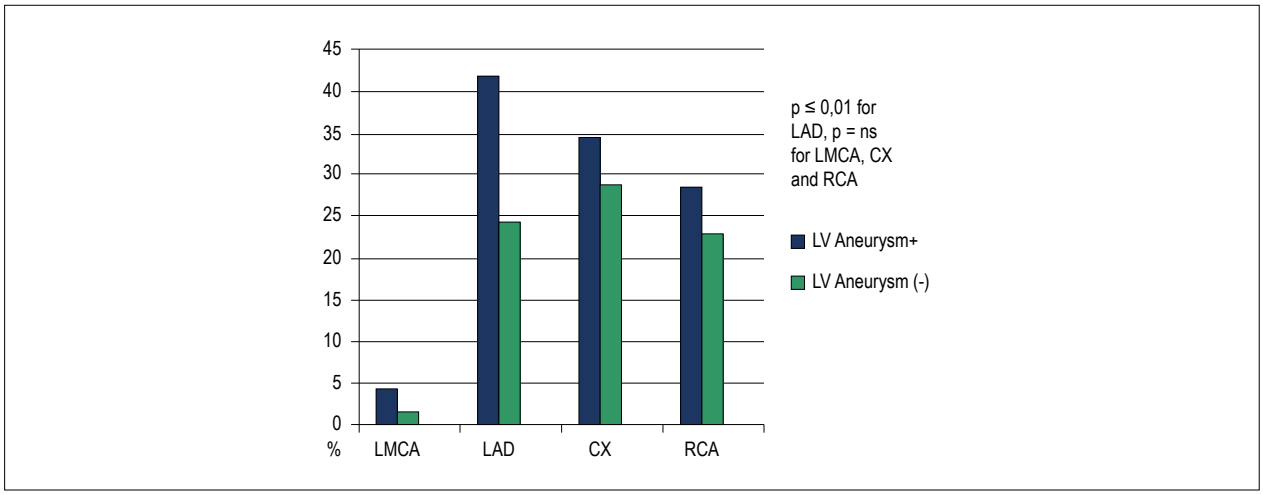

Figure 2 – *Culprit Artery in Patients with Left ventricular aneurysm. LV: left ventricle; LMCA: left main coronary artery; LAD: left anterior descending coronary artery; CX: circumflex artery; RCA: right coronary artery.*

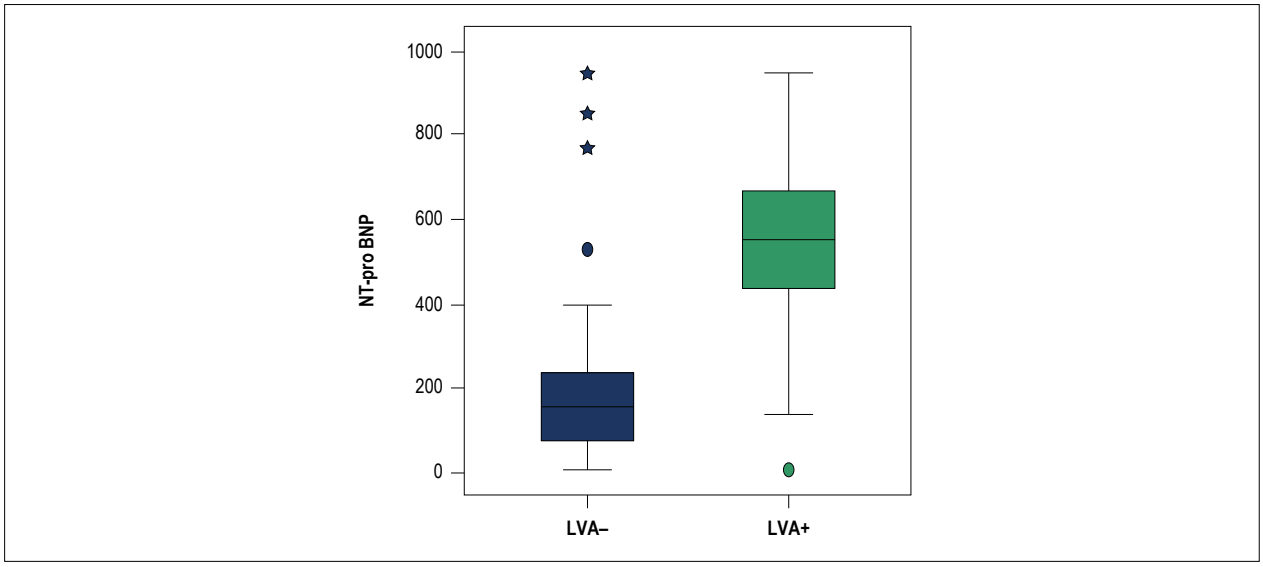

Figure 3 – *Patients who developed left ventricular aneurysm after acute ST-elevation myocardial infarction had higher NT-pro BNP levels at admission. NT-pro BNP: N terminal pro-B-type natriuretic peptide LVA: left ventricular aneurysm.*

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ankara Numune Training and Education Hospital under the protocol number 179. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 4 – Effects of variables on left ventricular aneurysm formation after acute MI in univariate and multivariate logistic regression analysis

Varible	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	95% CI	p	OR	95% CI	p
Age (> 65y)	1.04	1.00 – 1.09	0.051	1.04	1.00 – 1.09	0.030
BMI	1.06	0.96 – 1.17	0.263			
NT-proBNP (> 400 pg/mL)	1.01	1.00 – 1.01	0.005	1.01	1.00 – 1.01	0.001
Gensini Score	1.00	0.98 – 1.02	0.923			
Killip Class (> 2)	8.96	2.90 – 28.96	0.0001	9.71	3.10 – 30.43	0.007
Peak cTnI [ng/mL]	2.86	1.49 – 5.50	0.002	3.02	1.86 – 4.97	0.0 60
LVEF(< 50%) after MI	0.82	0.75 – 0.90	0.051	0.85	0.82 – 0.96	0.070
Peak CK-MB (IU/L)	0.36	0.01 – 0.65	0.005	0.23	0.12 – 1.02	0.001
Smoking	0.32	0.05 – 0.82	0.010	0.26	0.09 – 0.77	0.015
HT	1.81	0.65 – 5.01	0.253			
DM	0.87	0.28 – 2.67	0.803			
Medication						
Statin	0.14	0.01 – 1.57	0.109			
B Blocker	0.40	0.06 – 2.54	0.329			
ACE Inh.	0.94	0.27 – 3.25	0.927			
ARB	5.76	0.90 –	0.165			
Spironolactone	7.40	0.64 – 85.82	0.192			
Furosemide	5.94	1.0 – 36.33	0.180			
Fibrinolytic therapy	1.74	0.15 – 20.12	0.058	1.88	0.30 – 23.8	0.620
Post MI HF	9.10	2.97 – 21.12	0.003	8.40	2.90 – 24.35	0.001
ARF	3.52	0.21 – 58.76	0.080	3.65	0.28 – 56.32	0.100
Post MI Pericarditis	1.14	0.11 – 11.57	0.910			
Arrhythmia	2.77	1.00 – 7.69	0.510			
Previous CABG	11.37	3.81 – 33.98	0.001	4.29	1.19 – 15.50	0.026
Failure of reperfusion	0.34	0.20 – 1.46	0.050	0.32	0.12 – 0.86	0.024
No-reflow phenomenon	0.98	0.48 – 1.33	0.025	0.96	0.42 – 1.22	0.012

BMI: body mass index; cTnI: cardiac troponin I; LVEF: left ventricular ejection fraction; MI: Myocardial Infarction HT: Hypertension, DM: Diabetes Mellitus; CE: Angiotensin converting enzym inhibitor; ARB: angiotensin receptor blocker; Post MI HF: Post Myocardial infarction heart failure; ARF: acute renal failure; CABG: Coronary artery by-pass greft.

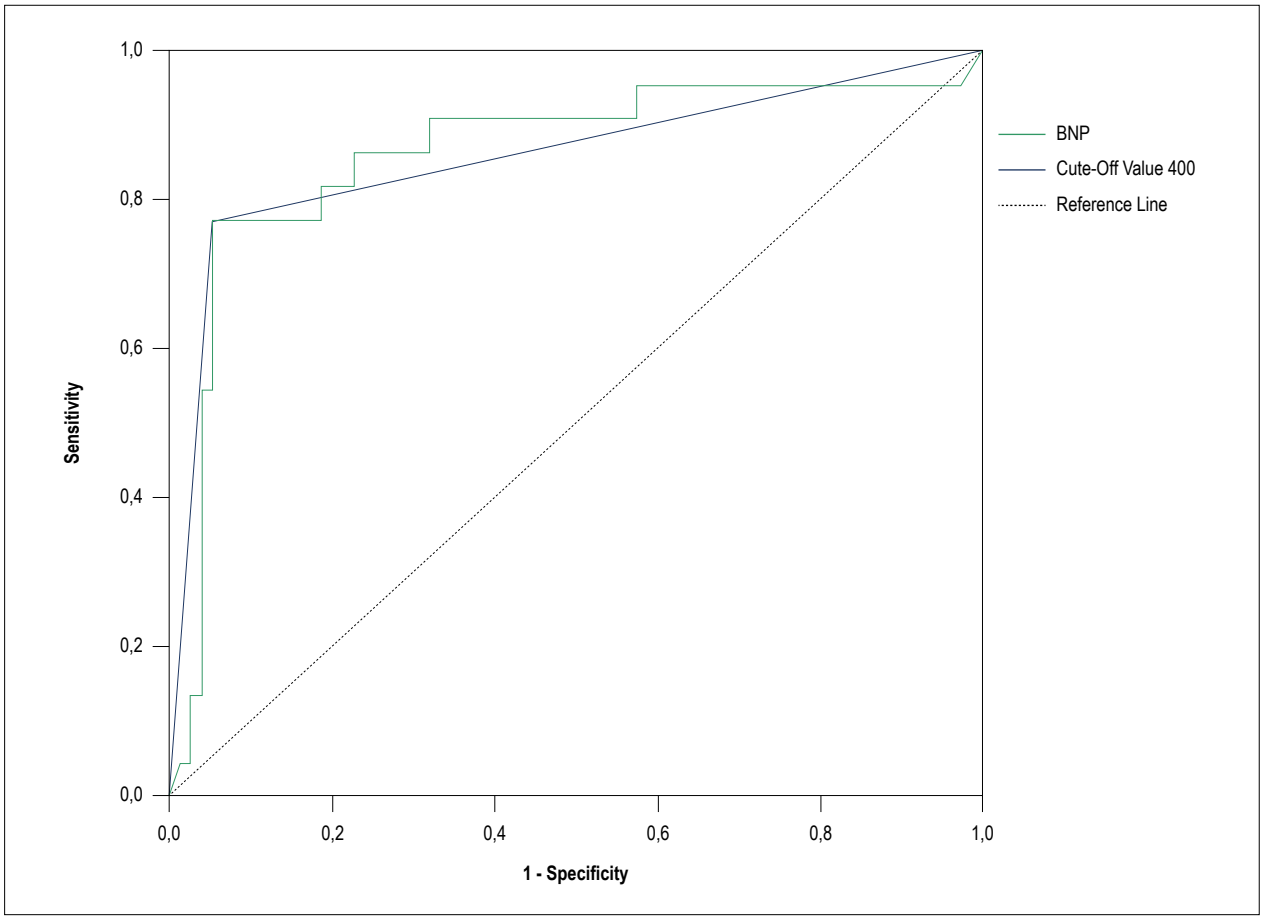

Figure 4 – *Receiver Operating Characteristic (ROC) Curve analysis shows the cut-off value of NT-pro BNP to predict left ventricular aneurysm.*

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Admission NT-ProBNP in Myocardial Infarction: an Alert Sign?

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Short Editorial related to the article: The Usefulness of Admission Plasma NT-pro BNP Level to Predict Left Ventricular Aneurysm Formation after Acute ST-Segment Elevation Myocardial Infarction

This issue of *Arquivos Brasileiros de Cardiologia* brings a paper entitled "The Usefulness of Admission Plasma NT-pro BNP Level to Predict Left Ventricular Aneurysm Formation after Acute ST-Segment Elevation Myocardial Infarction".[1] The authors bring a cohort of 1,519 post-acute ST-segment elevation myocardial infarction (STEMI) who were followed-up for at least six months. Despite its observational and retrograde design, the authors were straightforward in looking for predictive variables that could foresee the occurrence of left ventricular aneurysms (LVA). Among other major clinical aspects such as previous coronary artery bypass graft, post-MI heart failure, younger age, smoking and no-reflow phenomenon; authors highlighted the importance of high NT-proBNP at admission as a predictor of LVA formation after acute STEMI.

I would probably highlight one weakness and a potentially positive aspect of their work.

The weakness is that a LVA will never be diagnosed by a NT-Pro-BNP level and will always be found, confirmed and/or followed by an image test (Echo, CMR, etc.). NT-ProBNP usually and reliably identifies patients who are sicker or more congested, either in acute,[2] or in chronic heart failure,[3] or even without heart failure.[4]

The potentially positive one was, interestingly, what the authors have considered their limitation: that the NT-ProBNP values have been collected at admission. Having a high natriuretic peptide level at the admission of a STEMI patient could be a predictive variable of a clinical event, such as LVA formation, in six months. It was there, on the "Limitations" section, the best and most clinically relevant information.

Keywords

Myocardial Infarction; Heart Failure; Ventricular Dysfunction, Left; Natriuretic Peptides/metabolismo; Natriuretic Peptide Brain/metabolism; Echocardiography/diagnostic imaging; Magnetic Resonance Spectroscopy/methods.

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Review Article

Biochemical and Molecular Mechanisms of Glucose Uptake Stimulated by Physical Exercise in Insulin Resistance State: Role of Inflammation

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Abstract

Obesity associated with systemic inflammation induces insulin resistance (IR), with consequent chronic hyperglycemia. A series of reactions are involved in this process, including increased release of proinflammatory cytokines, and activation of c-Jun N-terminal kinase (JNK), nuclear factor-kappa B (NF-κB) and toll-like receptor 4 (TLR4) receptors. Among the therapeutic tools available nowadays, physical exercise (PE) has a known hypoglycemic effect explained by complex molecular mechanisms, including an increase in insulin receptor phosphorylation, in AMP-activated protein kinase (AMPK) activity, in the Ca2+/calmodulin-dependent protein kinase kinase (CaMKK) pathway, with subsequent activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), Rac1, TBC1 domain family member 1 and 4 (TBC1D1 and TBC1D4), in addition to a variety of signaling molecules, such as GTPases, Rab and soluble N-ethylmaleimide-sensitive factor attached protein receptor (SNARE) proteins. These pathways promote greater translocation of GLUT4 and consequent glucose uptake by the skeletal muscle. Phosphoinositide-dependent kinase (PDK), atypical protein kinase C (aPKC) and some of its isoforms, such as PKC-iota/lambda also seem to play a fundamental role in the transport of glucose. In this sense, the association between autophagy and exercise has also demonstrated a relevant role in the uptake of muscle glucose. Insulin, in turn, uses a phosphoinositide 3-kinase (PI3K)-dependent mechanism, while exercise signal may be triggered by the release of calcium from the sarcoplasmic reticulum. The objective of this review is to describe the main molecular mechanisms of IR and the relationship between PE and glucose uptake.

Keywords

Exercise; Insulin Resistance; Chronic Inflammation; Glucose Metabolism Disorders; Anti-Inflammatoty Agents; Glucose Transporter Type 4.

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Introduction

Insulin resistance (IR) at target tissues is directly related to chronic subclinical inflammation. When inadequately controlled, IR cause a permanent hyperglycemic status, characterizing the pathophysiology of type 2 diabetes mellitus (DM2).[1] Cardiovascular diseases are the main cause of morbidity and mortality in DM2 patients,[2] leading to annual costs per year of nearly 40 billion.[3]

Hyperglycemia, *per se*, is a devastating condition for the cardiovascular system. Among the complications caused by chronic hyperglycemia in patients with DM2, there is a reduction in endothelial vasodilator capacity (by reduced nitric oxide availability), increase in advanced glycation end products, in addition to increased oxidative stress, which leads to endothelial dysfunction and atherogenesis in long term, and increased cardiovascular risk.[4,5]

Physical exercise (PE), combined with pharmacologic therapy, is an effective strategy in the approach of DM2 patients, with direct effect on glycemic ontrol,[6,7] due to its capacity in reducing blood glucose concentrations[8] and its anti-inflammatory effect in long term,[9] with potential positive effect in reducing cardiovascular complications in these patients.

Muscle contraction acutely increases trigger biochemical reactions that culminate in increased glucose uptake by the muscle. This is caused by two important mechanisms – increase in insulin sensitivity[10] and translocation of the type 4 glucose transporter (GLUT4) to the cell surface independent of insulin use.[11] In addition, PE chronically increases intramuscular GLUT4 content[12] and reduces the inflammatory state, especially by the release of anti-inflammatory cytokines[13] and reduction in total lipid content.[14]

The objective of this review is to provide an overview of the regulation of glucose uptake in IR and chronic subclinical inflammation, and the role of PE in this situation. First, we present a discussion about biochemical and molecular mechanisms of the hypoglycemic effect of PE, with special attention to the increase in insulin sensitivity and translocation of de GLUT4 independent of insulin; then, we present evidence of the role of PE as an anti-inflammatory strategy and its association with IR.

Signaling of insulin and glucose uptake by skeletal muscle

Insulin is a peptide hormone released by the pancreas, specifically by beta cells of the pancreatic islets.[15] Intracellular signaling of insulin in insulin-sensitive tissues requires

binding of the hormone to a specific membrane receptor, named insulin receptor, composed by four subunits: two α subunits located in the external part of the membrane, and two transmembrane, β subunits. Insulin binds to the α subunits, and activate the kinase activity of beta subunits, which promotes the self-phosphorylation of tyrosine residues in the intracellular region of insulin receptor.[16] This generates the recruitment of adaptor proteins and phosphorylation of several protein substrate, including members of the insulin receptor substrate family – IRS-1, 2, 3 and 4.[17] Among these members, phosphorylation of IRS-1 and IRS-2 into tyrosine – by addition of a phosphate group – bind to and activate Src homology-2 (SH2) domains, such as the phosphoinositide 3-kinase (PI3K). The SH2 domain exhibits approximately 100 amino acids and is able to recognize and bind to phosphorylated tyrosine.[18] PI3K, in turn, catalyzes the formation of phosphatidylinositol (3,4,5)-trisphosphate (PI3P),[19] an allosteric regulator of phosphoinositide-dependent kinase (PDK).[20] PDK activates one of the isoforms of protein kinase B (PKB), also known as Akt, and the atypical protein kinase C (aPKC).[21] There is evidence that aPKC is essential for insulin-stimulated glucose transport in skeletal muscle; its activation seems to be compromised in IR,[22] and potentialized by PE.[23] Among the aPKC isoforms, the aPKC lambda/iota has shown an important role in glucose transport. This enzyme phosphorylates the double C2-like domain-containing protein (DOC2b), which regulates the soluble N-ethylmaleimide-sensitive factor attached protein receptor (SNARE), facilitating the interaction with syntaxin-4 and promoting the fusion of GLUT4-containing vesicles with the plasma membrane.[24] In addition to aPKC, other PKC isoforms are also involved in GLUT4 translocation, including PKCα and PKCθ, which are activated by the increase in intracellular calcium.[25]

Besides the PKC isoforms, the Akt enzyme promotes the phosphorilation of the Rab GTPase-activating proteins (RabGAPs), that involve the TBC1 domain family member 4 (TBC1D4) and TBC1 domain family member 1 (TBC1D1). This enables the dissociation of the Rab protein, and consequently, increased uptake of glucose by increased GLUT4 translocation.[26] The TBC1D1 and the TBC1D4 proteins act cooperatively regulating the translocation of GLUT4 in response to a stimulus, since both are co-expressed in skeletal muscle.[27] In summary, TBC1D4, previously known as Akt substrate of 160 kDa (AS160), is a protein that, when phosphorylated into treonin-642, helps in the translocation of GLUT4-containing vesicles to the membrane, in GLUT4 expression, leading to increased glucose uptake.[28] Akt also induces the phosphorylation of serine/threonine kinase with an atypical placement of the catalytic lysine, called with-no-lysine kinase (WNK1), with omnipresent expression, including the skeletal muscle. WNK1, in turn, phosphorylates the TBC1D4 enzyme, promoting the translocation of GLUT4 in the skeletal muscle.[29]

Therefore, activation of the cascade that involves PI3K/Akt enzymes allows the entry of glucose into cells by facilitated diffusion, by stimulation of translocation of GLUT4 from intracellular vesicles to the plasma membrane.[30] In addition to GLUT4 translocation, PI3K simultaneously stimulates the synthesis of hepatic and muscle glycogen.[31] In this context, another important mechanism was proposed. Previous studies using cell cultures have shown that inhibition of the endogenous Rac1 (member of the Rho-family of GTPases) blocked the insulin-induced GLUT4 translocation.[32,33] Rac1, in turn, was described as essential in the stimulation of insulin-mediated glucose uptake in skeletal muscle and glucose homeostasis in the whole body,[34,35] exerting a preponderant role in the regulation of insulin-induced GLUT4 translocation, as observed in cultured muscle cells.[36]

Also, when endogenous production of insulin is compromised (or in state of very high insulin resistance), the role of PE is even more important due to its insulin-independent hypoglycemic effect.[37]

Physical exercise in the regulation of glucose uptake in skeletal muscle

During PE, the utilization of energy substrates (mainly glucose and free fatty acids) considerably increases in relation to rest. These substrates originate from intramuscular stores, hepatic production and fat tissue mobilization by hormone-sensitive lipase.[38]

Both acute aerobic exercise and chronic exercise training can potentiate the action of insulin, and evidence from animal models has helped us to understand the mechanisms involved. In rats fed a high-fat diet, acute PE seems to affect the activation of insulin receptor, since a unique session of exercise increases insulin-stimulated IR phosphorylation in skeletal muscles.[39] In obese rats, both high-volume exercise (six-hour duration) and low-volume exercise (45 minutes) were effective in increasing insulin sensitivity, by increased phosphorylation of IR, IRS-1 and Akt.[40] Another experiment with rats showed an improvement in insulin sensitivity in adipocytes after seven weeks of daily aerobic exercise (60-minute duration), mediated by increased tyrosine phosphorylation in IRS-1 and IRS-2 and greater association of IRS-1 with PI3K and, consequently, increased phosphorylation of Akt protein.[41]

In addition, PE can increase glucose uptake in the muscle by other pathways that involve a key enzyme activated by muscle contraction, named AMP-activated protein kinase (AMPK). AMPK is a heterotrimeric molecule composed of a catalytic subunit (alpha) and two regulatory subunits (beta and gamma), with the following isoforms β1, β2, γ1, γ2 and γ3. It is activated by phosphorylation of a threonine-172 residue within the activation loop of the α subunit.[42] The activation of AMPK can result from an energy imbalance caused by muscle contraction.[43] Among the proteins that regulate AMPK, liver kinase B1 (LKB1) is currently considered the main protein involved in AMPK phosphorylation.[44] The activation of AMPK and LKB1 during exercise has been widely demonstrated in animals and humans.[43,45]

It is worth pointing out AMPK-stimulated glucose transport seems to be mediated by multiple factors – by increase of intracellular concentrations of Ca^{++} and bradykinin (plasma polypeptide that causes vasodilation), increased activity of endothelial nitric oxide synthase (which increases vasodilation and the availability of nitric oxide), by activation of mitogen-activated protein kinase (MAPK), activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMK), activation of protein kinase C (PKC), and even hypoxia.[46,47] All these factors are necessary for an effective translocation of GLUT4 and consequent entry of glucose into the cells.

In addition, there is evidence suggesting that activation of AMPK in skeletal muscle can increase lipid oxidation, and thereby glycogen resynthesis can adapt to PE (by sparing muscle glycogen) by stimulation of muscle contraction.[48] Some myokines, including interleukin-15 (IL-15) and interleukin-6 (IL-6), increase the expression of GLUT4 in adipose tissue, which can potentiate PE-induced glucose uptake,[49] and also activate AMPK and GLUT4 translocation to the cell surface.[50] Activation of AMPK is also important since as it promotes the phosphorylation of TBC1D1 and TBC1D4. Studies have shown that both acute and chronic exercise increase the expression of AMPK, TBC1D1, TBC1D4 and GLUT4 in skeletal muscles in humans.[51,52] It was also reported that in contracted epitrochlearis muscles of rats, TBC1D4 phosphorylation was increased, and this effect persisted for 3-4 hours after the animals swam for four 30-min bouts with a 5-min rest between bouts.[53] Kjøbsted et al.[54] corroborated this hypothesis in a recent study showing that increased phosphorylation of TBC1D4 stimulated by insulin in exercised muscles improves insulin sensitivity.

Another important event associated with PE and AMPK activation is the activation of the of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α),[55] mediated p38 MAPK and histone deacetylase-5 (HDAC5).[56] In addition, phosphorylation of Ca2+/calmodulin-dependent protein kinase (CaMKK) followed by activation of PGC-1α, can be induced by low-intensity, resisted exercise, suggesting that PE-induced GLUT4 translocation can be achieved by several modalities.[57] On the other hand, other important proteins, as the case of Pac1,[34,35] do not require activation of the AMPK pathway to promote PE-induced glucose uptake in skeletal muscle.[34,35]

Studies have indicated that muscle elongation contributes to activation of Rac1.[58,59] Silow et al.[58] have shown that Rac1 signaling is impaired in muscles resistant to insulin in rats and humans. The importance of Rac1 in this context is attributed to its effects on actin cytoskeleton. Thus, dysregulation of Rac1 and actin cytoskeleton in the skeletal muscle can be new molecular candidates that contribute to the phenotype of IR and DM2.[58] More recent data have supported these findings, suggesting that Rac1 essentially contributes to PE-stimulated glucose uptake.[60,61] However, it is important to mention that previous studies have shown that short exercise completely restored insulin sensitivity in Rac1-deficient muscle containing RI.[62] Therefore, although Rac1 is essential for regulation of glucose transport stimulated by PE, it is dispensable for the insulin sensitizing effect of exercise. This is important since Rac1 is dysfunctional in insulin-resistant muscle.[63] These findings indicate that other pathways different from the Rac1 pathway, can exhibit more pronounced effects of insulin sensitization during PE.[64]

A schematic illustration of GLUT4 translocation mediated by insulin and by muscle contraction is presented in Figure 1.

Other important and complex mechanisms related to the AMPK pathway need to be mentioned. For example, its relationship with autophagy, a process involved with glucose metabolism and insulin sensitivity. Autophagy is a self-degradative process that occurs via lysossomal pathway that plays a role in the removal of malformed or aggregated proteins, eliminating damaged organelles, similarly to mitochondria and sarcoplasmic reticulum. Autophagy is generally considered a survival mechanism, although its dysregulation has been associated with non-apoptotic cell death.[65,66]

The relationship between autophagy, PE and metabolic regulation is still a little explored area. However, there is increasing evidence that the autophagic process is strongly induced during physical training,[67,68] and seems to play an important role in the metabolism of skeletal muscle.[69] In this regard, autophagy can regulate the homeostasis of muscle glucose and contribute to the reduction of RI in response to PE.[70] These data are corroborated by He et al.,[71] in an experiment conducted with mice, showing that mice with induced allelic loss of *Beclin 1*, an autophagy-related gene that promotes a decrease in autophagy in the skeletal muscle, had impaired exercise-induced GLUT4 plasma membrane localization. These data suggest an important role of autophagy and *Beclin 1* in improving glucose uptake in response to PE. For example, a single bout of running for 90 minutes on a treadmill was sufficient to induce autophagy in the skeletal muscle and in the brain of mice.[68] One of the hypotheses that may explain the mechanisms involved in this scenario is that PE can increase the concentrations of proteins of the sestrins (SESNs) induced by stress, such as SESN1 and SESN3, which not only increase the autophagic activity, but also interact with AMPK, and stimulate its activation.[72,73] The induction of SESNs inhibits the mechanistic target of rapamycin complex 1 (mTORC1) activity by stimulation of AMPK.[73] Thus, the interaction between sestrin and AMPK induced by PE may be involved in the beneficial metabolic effect of training, activating autophagy. This interaction provides a molecular mechanism that is a potential target in metabolic syndromes.

Obesity, inflammation and insulin resistance

IR develops silently and may lead to pancreatic failure, starting with a resistance to insulin activity in the target-tissues, followed by an increase in pancreatic insulin production in response to such IR, and ultimately with incapacity of the pancreas to continue insulin production. This fact opens the door to DM2, characterized by an acquired chronic hyperglycemia associated with other diseases including hypertension and dyslipidemia. The main factors that cause this syndrome are obesity, sedentary lifestyle and genetic factors.[74] IR is characterized by pathological changes in several steps of insulin metabolic pathway,[75] with simultaneous increase in endogenous production of hepatic glucose, leading to chronic hyperglycemia.[76] Today, obesity, especially visceral obesity, is recognized as one of the main risk factors of IR.[77]

Several mechanisms are involved in the etiopathogenesis of obesity-related IR, characterized by changes in several steps of insulin signaling, with reduction in IR concentration and kinase activity, in IRS-1 and IRS-2[78] phosphorylation into tyrosine, and in PI3K activity.[79] In addition, a significant increase in abdominal adipose tissue induces the delivery of free fatty to the liver through the portal vein, aggravating hepatic insulin resistance,[80] thereby increasing the release of proinflammatory cytokines through the portal vein, which acts as a feedback to the process.[81]

The role of chronic inflammation in this scenario cannot be excluded. IR is related to obesity-induced inflammation,

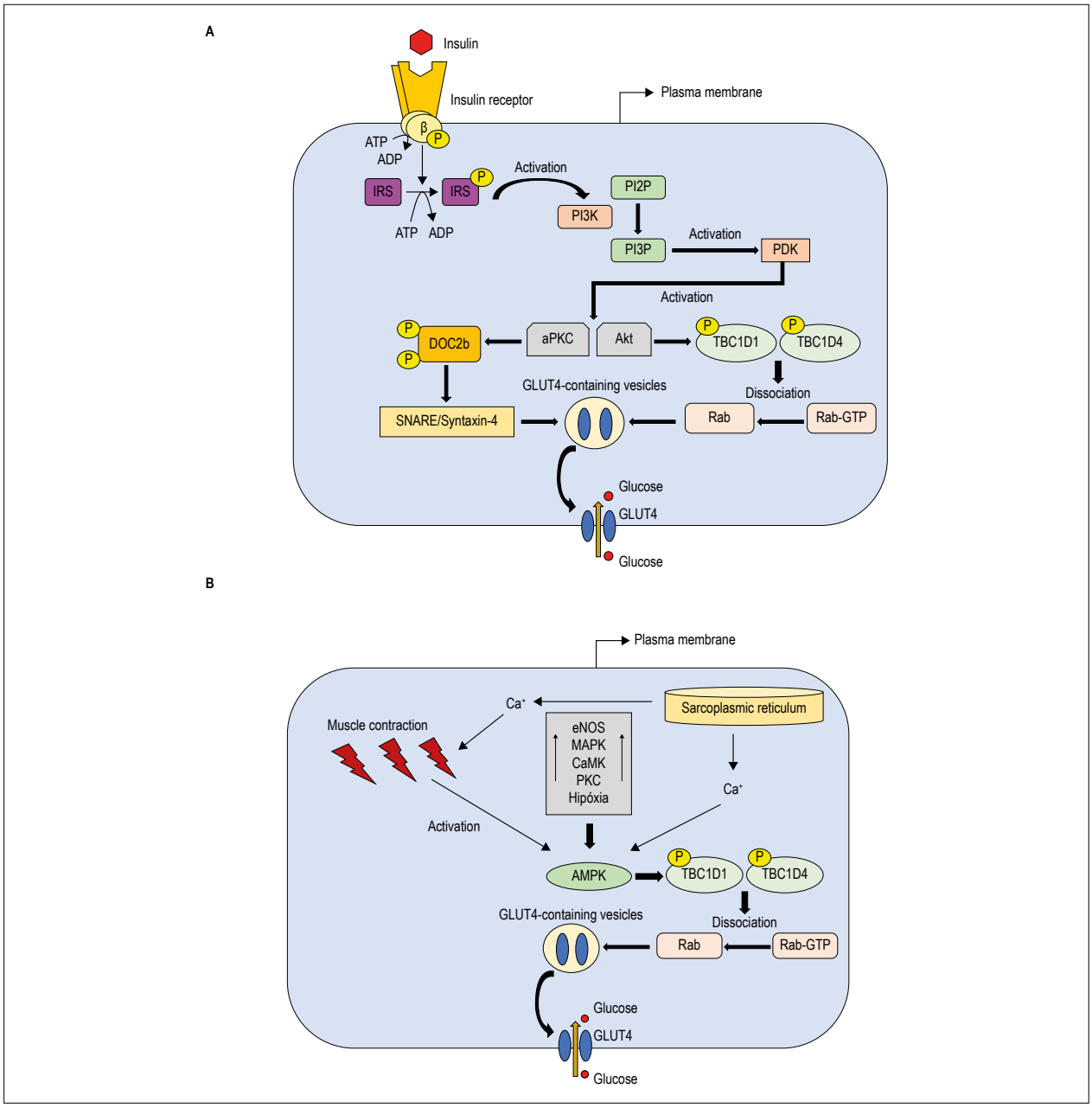

Figure 1 – *Schematic representation of the main pathways that promote the translocation of GLUT4-containing vesicles to the membrane in the skeletal muscle induced by insulin (A) and insulin-independent pathways during physical exercise (B) P: Phosphorylation; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; IRS: insulin receptor substrate; PI3K: phosphoinositide 3-kinase; PI2P: phosphatidylinositol-4,5-bisphosphate; PI3P: phosphatidylinositol (3,4,5)-trisphosphate; PDK: phosphoinositide-dependent kinase; aPKC: atypical protein kinase C; DOC2b: double C2-like domain-containing protein; SNARE: soluble N-ethylmaleimide-sensitive factor attached protein receptor; TBC1D1: TBC1 domain family member 1; TBC1D4: TBC1 domain family member 4; GLUT4: glucose transporter type;Ca+: Calcium; eNOS: nitric oxide synthase; MAPK: mitogen-activated protein kinase; CaMK: Ca2+/calmodulin-dependent protein kinase; PKC: protein kinase C; AMPK: AMP-activated protein kinase.*

process already described in the 90's. In this decade, several studies evaluated the association of IR with traditional inflammatory markers, such as tumor necrosis factor-alpha (TNF-α) and showed that adipocytes treated with TNF-α had impaired insulin signaling. This response was associated with reduced IRS-1 and GLUT-482 transcription.[82]

Pro-inflammatory cytokines, such as the TNF-α, can lead to activation of c-Jun N-terminal kinase (JNK), a critical enzyme in inflammation associated with obesity and IR,[83] by activating serine or threonine kinase, thereby reducing insulin signaling by phosphorylation of proteins into serine or threonine residues.[84] Besides, activation of this enzyme is related with signaling pathways that activate nuclear factor-kappa B (NF-B) which, in turn, stimulates the production of pro-inflammatory cytokines.[85] The activation of JNK also promotes NF-B activation in pancreatic islets, and therefore, perpetuating a vicious cycle of β-cells

dysfunction induced by inflammation, which in turn aggravates the chronic inflammatory process.[86] This feedback causes more macrophage recruitment, which together with hypertrophic adipocytes, release more pro-inflammatory cytokines.[87]

Additionally, circulating free fatty acids, as well as other ligands such as bacterial lipopolysaccharides, are able to activate transmembrane proteins known as toll-like receptor 4 (TLR-4), that trigger inflammatory pathways, reducing glucose uptake by insulin signaling[88] in a process called metabolic inflammation.[89] TLR-4 is ubiquitously expressed throughout the cells, including the adipose tissue. In the development of obesity, there is greater infiltration of immune cells in this tissue, particularly macrophages, which show increased expression of TLR4.[90] Free fatty acids bind to TLR-4, activating JNK and IκB kinase (IKK).[91] Because IRS-1 are target of both enzymes, this process affects tyrosine phosphorylation, resulting in reduced GLUT4 translocation.[92]

Activation of IKK causes phosphorylation and subsequent proteasomal degradation of IKKβ, inducing activation of NF-κB. Degradation of IKKβ triggers the gene transcription of inflammatory mediators, such as TNF-α and interleukin-6 (IL-6).[93] Also, IKKβ promotes serine phosphorylation of insulin receptor and IRS-1 and IRS-2 substrates, which reduces insulin signaling in different tissues.[94] These processes are schematically illustrated in Figure 2.

In summary, the increase in circulating free fatty acids is a metabolic characteristic of insulin-resistant state, which may cause IR by several mechanisms. Evidence has suggested that excess adipose tissue reduces insulin receptor phosphorylation and promotes chronic activation of pro-inflammatory cytokines and circulating fatty acids, which may lead to deterioration of the tissue response to insulin. Adipose tissue, previously believed to be a mere place of energy storage, has shown to be an important endocrine and pro-inflammatory organ. It is more evident with visceral white adipose tissue that exhibits macrophage infiltration with local production of interleukins, which can help in the development of local and systemic IR.[95-97] Therefore, strategies targeting anti-inflammatory responses in the adipose tissue, such as PE, may have beneficial effects on individual's health status, alleviating the burden of obesity in endocrine dysregulation.

Physical exercise in obesity and insulin resistance

The beneficial role of PE has been increasingly recognized in increasing insulin sensitivity, independent of body fat reduction by the training.[98] The protective effect of PE may be attributed to the anti-inflammatory effect of physical training mediated by a reduction in visceral fat and/or induction of an inflammatory environment, with elevation in IL-10 and interleukin-1 receptor antagonist (IL-1Ra) concentrations, and reduction in IL-6 and TNF-α.[99]

As previously mentioned, visceral obesity is an important factor for the development of DM, which may be related to the increase in IL-6 and TNF-α.[100] Regular exercise can reduce baseline production of IL-6, by decreasing its plasma concentration at rest.[101] After acute moderate-intensity exercise, plasma IL-6 can increase in up to 100 times after a marathon (even though this is not adequate for obese individuals), but rapidly decreases compared with pre-exercise values.[101] This cytokines also stimulates proliferation of β-cells, and increased IL-6 concentrations in response to PE can stimulate the release of glucagon-like peptide-1 (GLP-1), an important hormone that stimulates insulin secretion.[102,103] These evidences support a beneficial effect of IL-6 in the regulation of insulin secretion, which undoubtedly contributes to DM prevention.

Regarding AMPK in DM2 and IR scenario, many studies have suggested that muscle contraction plays a central role, regardless of insulinemic status, where the activity of AMPK-α2 in skeletal muscle in response to PE was similar to that in individuals without DM2, indicating a normal functioning of muscle AMPK in diabetics, which is particularly important in IR conditions.[104] In another study, an acute bout of aerobic exercise (one hour duration) at 75% of VO_2max did not increase insulin sensitivity in obese diabetic subjects. Nevertheless, after seven sessions, there was an increment in glucose uptake rate, possibly stimulated by increased AMPK activity. It is of note that no difference was observed in the expression of proteins of insulin signaling pathways post-exercise compared with baseline.[105]

The action of Akt protein, previously mentioned as an important mediator of GLUT4 mobilization from GLUT4-containing vesicles to the membrane, may be impaired by the mammalian homolog of Ddosophila tribbles TRB3, whose expression is increased in obesity.[106] However, PE seems to be able to reduce the expression of this protein TRB3. A study showed that acute exercise reduced TRB3 expression and reversed Akt phosphorylation in the skeletal muscle of obese animals.[107] On the other hand, one session of swimming reduced TRB3 levels in the hypothalamus of obese rats.[108] In a recent study by Wang et al.,[109] the authors showed that aerobic training contributed to reduce inflammatory factors in mice with induced DM2. In addition to reducing body weight, there was a inhibition of TLR4 in hepatic cells of these animals, which, in turn, increased AMPK expression, ultimately contributing to the improvement of inflammation and IR.[109] Therefore, this pathway would also explain the importance of aerobic exercise in improving insulin sensitivity and glycemic control in DM2. These findings may lead to further studies, especially in humans, and open new horizons for the treatment of obesity and IR.

PE can also exert beneficial effects on cardiovascular system by mechanisms including the increase in adiponectin.[110] Among its several functions, adiponectin can greatly suppress hepatic glucogenesis, stimulating the oxidation of fatty acids in the skeletal muscle and inhibiting the transcription of genes involved in glucose production. In insulin-responsive tissues, adiponectin improves the sensitivity to this hormone.[111,112] Hypoadiponectinemia, defined by plasma adiponectin levels lower than 4.0 μg/mL, was associated with decreased levels of circulating high-density lipoprotein, triglycerides and glucose, and increased risk of metabolic syndrome. Also, the risk for atherosclerosis was twice as high in individuals with low adiponectin levels.[113]

The improvement in adiponectin levels has been associated with loss of subcutaneous and visceral adipose tissue induced by PE.[114] Studies have shown that aerobic PE alone[115] or combined

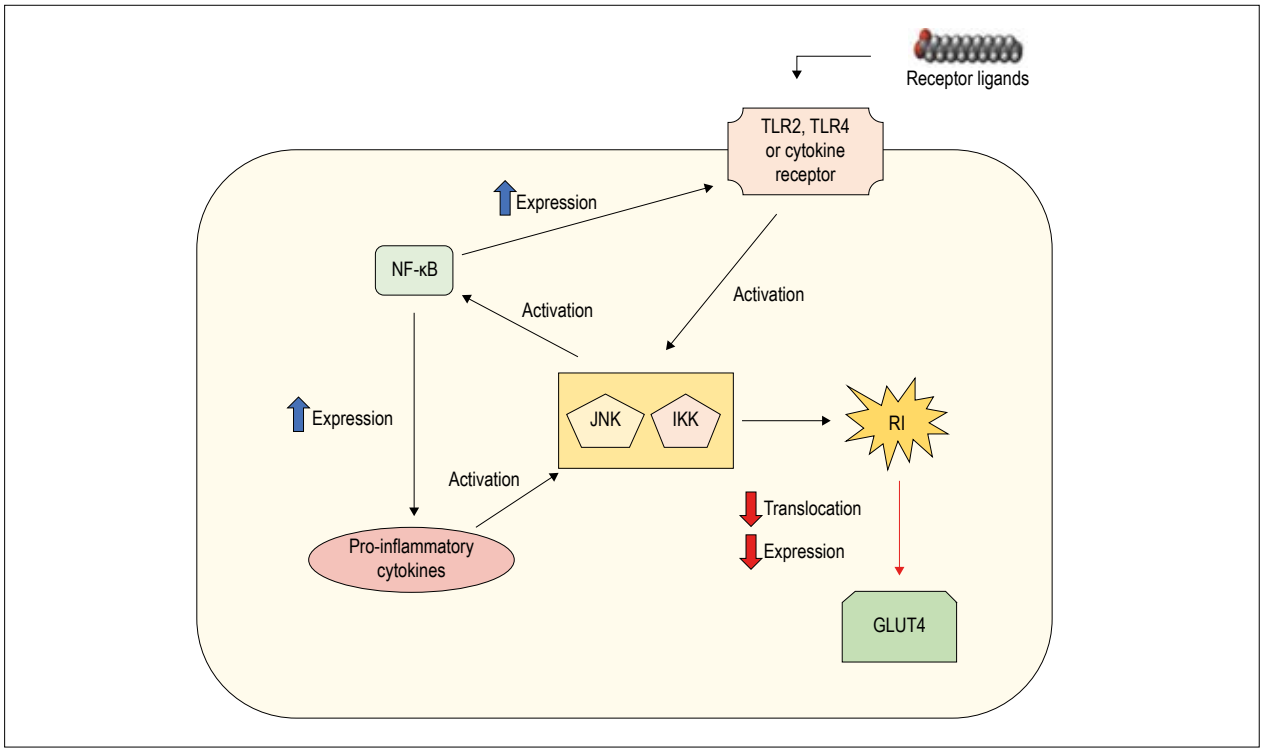

Figure 2 – *Schematic representation of activation of TLR 2, TLR4 or cytokine receptor by extracellular ligands and induction of inflammation and insulin resistance in an adipocyte. TLR2: toll-like receptor 2; TLR4: toll-like receptor 4; NF-κB: nuclear factor-kappa β; JNK: c-Jun N-terminal kinase; IKK: IkB kinase; GLUT4: glucose transporter type 4; IR: insulin resistance.*

with diet[116] significantly increase adiponectin levels in adipose tissue in obese subjects, regardless of changes in body composition. In addition, PE, particularly aerobic exercise, was able to change the body fat distribution, by reduction of pro-inflammatory cytokines and improvement of insulin sensitivity.[112]

Finally, plasma levels of resistin (protein related to IR and glucose intolerance), decreased after PE programs.[117,118] Resistin is commonly found in obese individuals, and seems to be involved in IR.[119] It was recently demonstrated that accumulation of this protein is associated with lower survival of DM2 patients, and concentrations above 11 ng/mL indicate increased risk in these patients.[120] Reduction in resistin concentrations by interventions, such as PE, may be related to reduction in inflammation via release of anti-inflammatory cytokines rather than changes in glucose metabolism and reductions of body mass.[121]

Therefore, obesity, in consonance with inflammatory process, can contribute to the increase in important inflammatory markers, such as pro-inflammatory cytokines. Available evidence has indicated that PE reduces these markers, regardless of a reduction in body weight.

Final considerations

PE stimulates many complex molecular and biochemical mechanisms, which promote a substantial improvement in insulin signaling and glucose uptake in IR states. It is important to highlight that evidences for the role of PE in reduction of the inflammatory process in IR associated with obesity were also presented.

Author contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Ferrari F, Bock PM, Motta MT, Helal L; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Ferrari F, Bock PM, Helal L.

Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Another Cause of Acute Cardiogenic Shock

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Clinical Case

A 64-year-old woman with a history of Diabetes and Hypertension was admitted to the emergency department with acute dyspnea and chest pain. Physical examination revealed hypertension, sinus tachycardia (150 bpm), acute pulmonary edema and poor extremity perfusion. In the context of respiratory failure and hemodynamic instability, she required invasive mechanical ventilation. Blood works showed increased levels of hs-TroponinT (rising from 800 to 1600 ng/L) and the ECG showed poor R wave progression and incomplete right bundle branch block. The echocardiogram revealed a hypertrophied left ventricle, with severe systolic dysfunction and akinetic apical and middle segments. Considering the possibility of acute coronary syndrome, the patient was referred for emergent coronary angiography, which revealed normal coronary arteries. She was admitted to the intensive care unit with the presumed diagnosis of Takotsubo cardiomyopathy. Through the rest of the day, she presented with fluctuating blood pressure and required elevated levels of positive end-expiratory pressure due to pulmonary edema. Despite an apparent favorable evolution, she suddenly developed asystole, refractory to resuscitation efforts, dying less than 24 hours after admission.

Post-mortem examination

Macroscopic examination revealed: myocardium with softened hyperemic anterolateral wall, suggestive of myocardial infarction; mild pericardial effusion; bilateral pulmonary congestion with hepatization of the lung basal lobes; left retroperitoneal mass, with 10x7x5 cm, with a cystic appearance and a necrotic core, located above the left kidney.

Microscopic examination revealed: necrotic myocardium with inflammatory infiltrate (Figure 1A), with no evidence of coronary artery disease; lungs with extensive alveolar edema and passive vascular congestion; left suprarenal gland tumour consistent with pheochromocytoma (Figure 1B), with intratumoral hemorrhage and necrosis.

Anatomopathological diagnosis: left suprarenal pheochromocytoma; catecholamine-induced cardiomyopathy; acute pulmonary edema.

Comments

In this case, the patient developed progressive ventricular dysfunction in the context of stress cardiomyopathy, leading to low cardiac output and cardiogenic shock. The pathology examination revealed a pheochromocytoma. This rare neoplasia has been described in the literature as a possible cause of stress cardiomyopathy due to an excess of circulating catecholamines, causing acute heart failure[1] or cardiogenic shock.[2]

Contemporary literature reviews have found a higher complication rate for pheochromocytoma-induced stress cardiomyopathy when compared with idiopathic Takotsubo cardiomyopathy. Patients with pheochromocytoma are more likely to develop cardiogenic shock (34.2% vs. 4.2%)[3] and less likely to recover left ventricular function on follow-up (40.8% vs. 64.9%).[4] In such patients, circulatory support with extracorporeal membrane oxygenation has been demonstrated as feasible but is still associated with a significant mortality rate.[5]

The case is a reminder that pheochromocytoma should be a differential diagnosis in the context of stress cardiomyopathy, particularly in patients presenting with cardiogenic shock.

Keywords

Takotsubo Cardiomyopathy/complications; Heart Failure; Pheochromocytoma; Respiratory Insufficiency; Shock, Cardiogenic.

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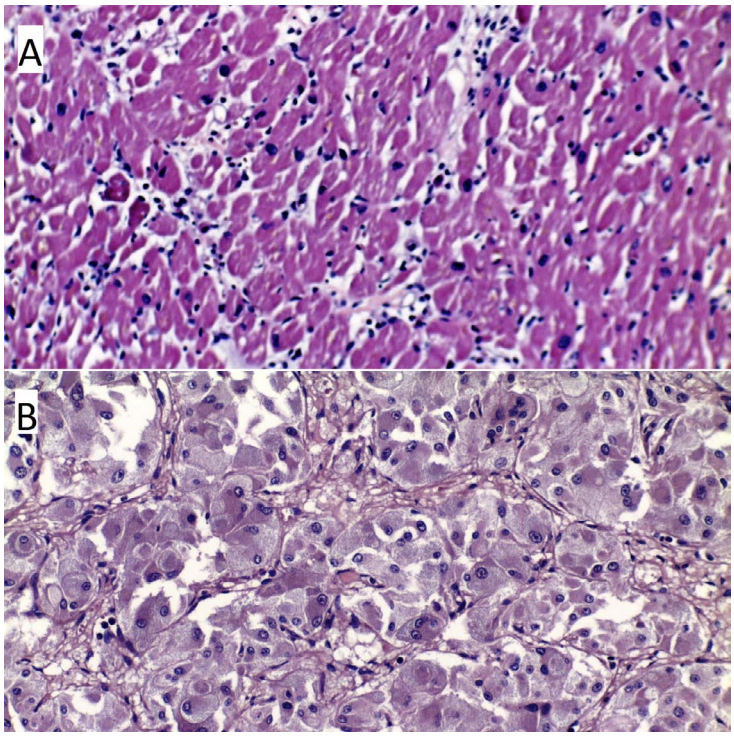

Figure 1 – *A) Histopathology specimen of the heart, haematoxylin and eosin stain: necrotic myocardium with inflammatory cells infiltrate. B) Histopathology specimen of a friable mass adjacent to the left adrenal gland, haematoxylin and eosin stain: nests of chromaffin tumour cells, with numerous membrane-bound granules, surrounded by a fibrovascular stroma.*

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Emergent Percutaneous Rotational Atherectomy to Bailout Surgical Transapical Aortic Valve Implantation: A Successful Case of Heart Team Turnaround

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Abstract

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis (AS) in patients with elevated surgical risk. Concomitant coronary artery disease affects 55-70% of patients with severe AS. Percutaneous coronary intervention in patients with TAVI can be challenging. We report a case of acute coronary obstruction immediately following transapical TAVI deployment requiring emergent rotational atherectomy.

Introduction

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis (AS) in patients with elevated surgical risk. Concomitant coronary artery disease affects 55-70% of patients with severe AS.[1] Percutaneous coronary intervention (PCI) in patients with TAVI can be challenging. Rotational atherectomy (RA) before or after TAVI has been described in an elective setting, but not as an emergent procedure.[2,3] Coronary artery occlusion or obstruction is a rare but serious complication of TAVI. We report a case of acute coronary obstruction immediately following transapical TAVI deployment requiring emergent RA to restore adequate perfusion.

Case Report

An 86-year-old male, with prior coronary artery bypass grafting and severe peripheral arterial disease (PAD), presented with New York Heart Association class III exertional dyspnea. Echocardiography revealed severe calcific AS with normal left ventricular systolic function. Cardiac computed tomography (CT) showed adequate left (14 mm) and right (21 mm) coronary heights. Previous coronary angiography had demonstrated non-occlusive triple-vessel coronary artery disease with a functional left internal mammary artery graft to the left anterior descending artery and a dominant native left circumflex artery. A Symetis Acurate 'Large' (Boston Scientific, Boston, MA, USA) TAVI prosthesis was deployed transapically in the hybrid operating theatre. Immediately thereafter, the patient became hypotensive and developed posterolateral ST-segment elevation. Emergent coronary angiography showed a critical, calcific filling defect at the junction of the distal end of the short left mainstem and proximal-mid circumflex arteries (Figure 1, Panel A). Through the radial access, a 6-French Cordis XB 3.5 guide catheter (Cardinal Health, Vaughan, ON, Canada) was used to cannulate the left main coronary artery. Heparin was administered to maintain ACT > 250 seconds and clopidogrel 600mg was administered. The lesion resisted extensive attempts at balloon delivery. A 0.009" RotaWire Floppy guidewire was inserted to facilitate the 1.5 mm Rotablator Rotational Atherectomy System (Boston Scientific Corporation, Boston, MA, USA) burr passage at 180,000 rpm. Three passes were undertaken into the mid-circumflex artery (Figure 1, Panel B). A 2.5 x 20 mm non-compliant balloon was subsequently inserted unimpeded in the left main coronary artery (post-RA and balloon dilatation-figure 1, panel C) extending into the proximal circumflex segment over a Pilot 50 guidewire (Abbott Vascular, Abbott Park, IL, USA). A 3.25 x 38 mm Xience Xpedition (Abbott Vascular, Abbott Park, IL, USA) drug-eluting stent was successfully deployed extending from the ostium of the left main coronary artery into the proximal-mid circumflex lesions and post-dilated with a 3.5 x 20 mm non-compliant balloon at high pressures with a good angiographic result (Figure 1, Panel D) and resolution of electrocardiographic changes along with marked hemodynamic improvement. The patient subsequently recovered uneventfully in the intensive care unit and was extubated the following day and transferred to the ward uneventfully. Peak creatine kinase and high-sensitivity troponin T levels were 961 U/l and 1921 ng/l respectively.

Comments

PCI post-TAVI can be challenging. The case report describes emergency RA immediately after deployment of a transapical TAVI prosthesis and highlights the feasibility and challenges of complex, high-risk PCI in such patients.

Choice of vascular access for PCI can be limited to only transradial in patients with severe PAD. Anatomical variants and tortuosity can impede guide manipulation. The valve prosthesis can obstruct coronary ostia or alter annular geometry and a trial with multiple guides might be necessary for selective engagement. Valves jailing the coronary ostia can make selective intubation more difficult.[1] The Symetis Acurate TA TAVI prosthesis pulls the native valve leaflets away from the coronary ostia making coronary obstruction unlikely.[4] However, coronary flow can be compromised by displacement of annular calcium

Keywords

Aortic Valve Stenosis; Atherectomy, Coronary; Atherectomy; Peripheral Arterial Disease; Coronary Angiography.

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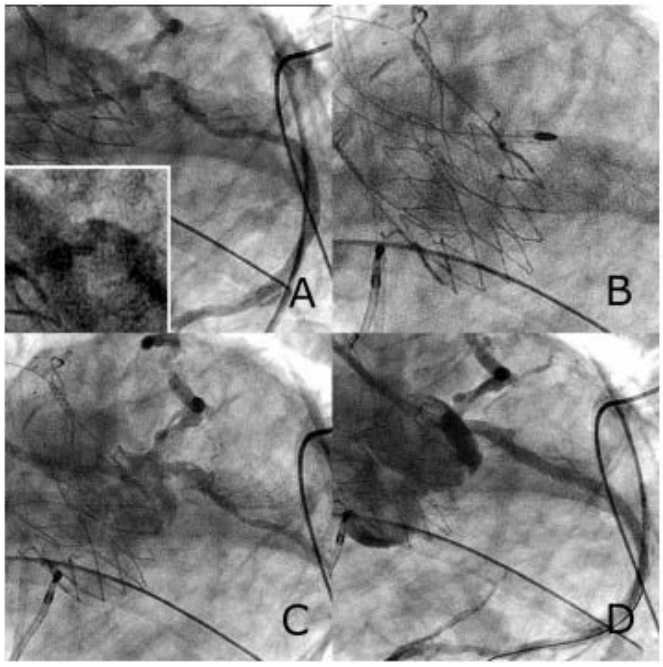

Figure 1 – *Percutaneous coronary intervention to circumflex artery lesion. A) Emergent coronary angiogram showing the new ostial left circumflex filling defect and prior mid-circumflex lesion. Inset view shows ostial left circumflex lesion at greater magnification. B) Rotablator 1.5 mm burr entering culprit ostial left circumflex artery lesion. C) Ostial left circumflex lesion after rotational atherectomy shows angiographic improvement. D) Final angiographic result after stent insertion and high-pressure post-dilatation.*

into the ostium, as in our case (Figures 2-4). Modification of coronary lesions may require RA to debulk calcific deposits permitting passage of stents and adequate expansion. The rate of major RA-related complications (in-hospital death, cardiac tamponade, and emergent surgery) was 1.3% according to a Japanese registry, increased with age and was approximately 4 times higher if RA was performed in an emergency setting of coronary artery disease per se.[5] Previous use of RA in TAVI patients have been in an elective setting unlike our report. RA in a TAVI setting poses additional challenges, particularly with suboptimal guide engagement.

Conclusion

This case highlights the complexity of coronary obstruction following TAVI and the need for availability of alternate arterial access (i.e. radial) and various modalities of revascularization (i.e. RA). Importantly, it highlights the necessity of a heart team approach with the seamless and unencumbered transition from a surgical domain (transapical TAVI) to the interventional realm (PCI with RA). Pre-procedural CT guided planning in terms of prosthesis selection, implantation technique, and bailout strategy in case of coronary compromise is also of critical importance.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Choudhury T, Bakar S, Kiaii B, Teefy P; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Choudhury T, Bakar S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

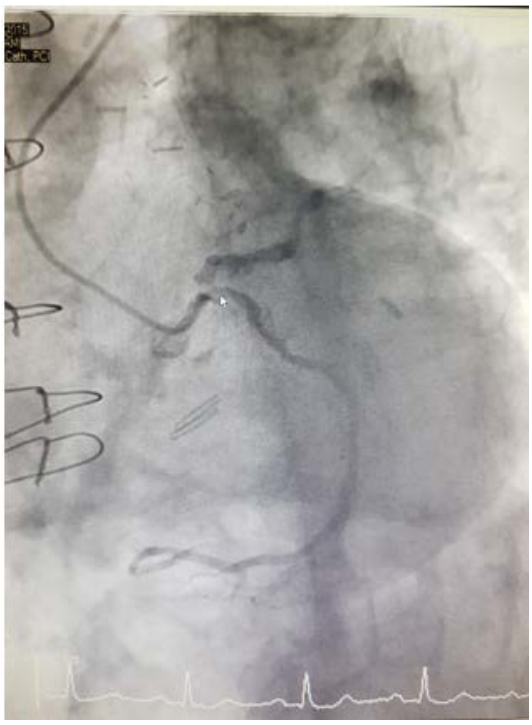

Figure 2 – *Baseline Coronary Angiogram. Baseline, pre-TAVI coronary angiogram showing calcified left coronary system, including calcified left main, ostial left circumflex and left anterior descending arteries.*

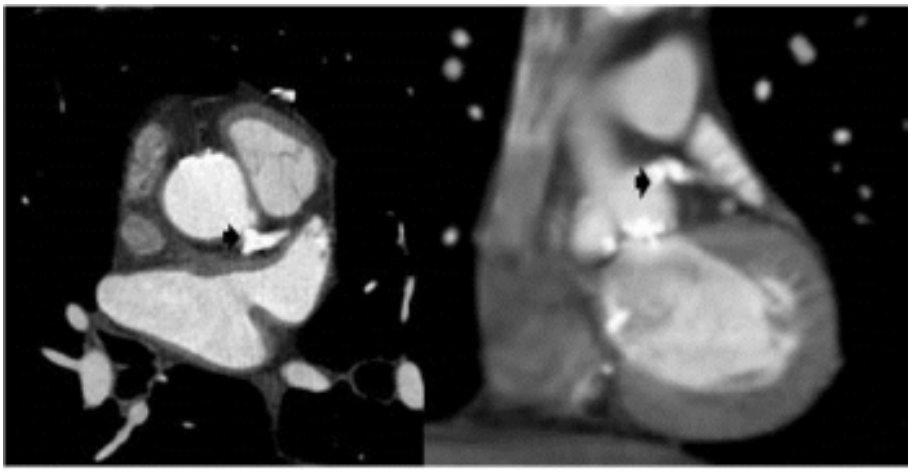

Figure 3 – *Cardiac CT. Pre-TAVI cardiac CT showing heavy calcification (arrow) extending into the left main ostium, left anterior descending artery and left circumflex artery as well as annular calcium.*

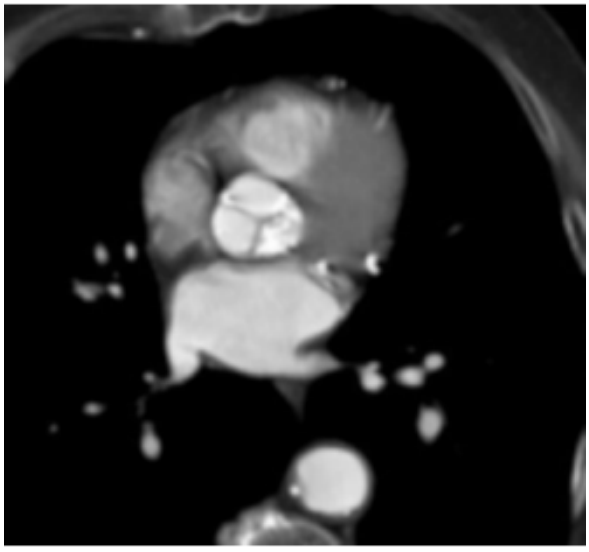

Figure 4 – *Annular calcium. Pre-TAVI cardiac CT demonstrating heavy aortic valve annular calcification.*

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Longitudinal Data and Correlated Measures Bias: The Alternative of Mixed Models

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Longitudinal studies have two important data typologies: single outcomes or repeated measures.[1] Single outcome, such as death or disease onset, should have a different data treatment than those studies with repeated measures outcome. But, they have in common the detection of changes over time and the contributing factors for this change. Cohort differs from cross-sectional studies that desire only variables relationship, without causal effect.

Fernandes et al.[2] wrote an article entitled *The Relationship between Lifestyle and Costs Related to Medicine Use in Adults*, published in this journal, volume 112, number 6, 2019, and they used behavioral independent variables to estimate their effects on drug costs outcome, collected as repeated measurements in a prospective cohort design.

The aim of this exposition is to show that, probably, there was a mistake in the Fernandes et al.[2] data analysis, which compromises the causality inferences due to the great possibility of the estimates' accuracy to be mistaken.

Let's get to the facts. Considering the prospective cohort design with repeated measures, there is a hierarchical structure in the outcome data due to their clustering in the same participant after various measures. Data cluster leave to the model error, that is the difference between what was predicted by the model and the actual measurement, of the same participant, at different times, to be correlated.[3] This is a condition for not using multiple linear regression (MLR) which assumes the independence of the model error given by the assumption that the distribution of each participant is equal. MLR does not extract from the data which is variability within the individual from variability between individuals (population).[3]

Keywords

Cohort Studies; Longitudinal Studies; Cross-Section,Studies; Epidemiology; Biostatistics.

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Using RLM in repeated measures generates regression coefficients with standard errors biased. This requires covariance matrix application that will produce more reliable estimates, in others words, narrower confidence intervals from Mixed Effects Models.[4] This is the best alternative to verify changes over time or the conditioners effects on repeated measures outcomes in longitudinal studies, controlling for individual effects.

There is greater variability between individuals than within individuals, mainly due to biological and social conditioning differences, it's observed that drug costs will be more correlated over time in the same individual than among participants. To think that this distribution is the same among the participants ignores theoretical assumption in the social determination on people's behavior.[5]

Build distinct MLRs (A, B, C and D), see Fernandes et al.[2], does not control this covariance effect, and therefore may be producing coefficients with confidence intervals biased in independent variables and can not detect the rate of change from basal either.[3] In addition, with mixed models it would also be possible to take advantage of measurements that were measured on lost participants, increasing modeling sensitivity.[4]

From another perspective, the objective of the research being to estimate the interrelation of drug cost and behavioral habits, without establishing causality, would only require a cross-sectional design of the participants with the collection of outcome data and independent variables at a single moment. Thus, the basal regression model would be sufficient to estimate gross and adjusted associations.[1]

Thus, the use of RLM should be restricted to cross-sectional research designs and longitudinal studies with repeated measures outcomes need to differentiate the individual effect of the population effect in the identification of temporal changes and their conditioning. Possibly, the findings of Fernandes el al.[2] should be based regarding their conclusions about the inverse relationship between alcohol use and drug costs or the statistically non-significant relationships with body fat, gender and smoking status that have great impact on other health situations, especially chronic diseases.

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Reply

I appreciate the opportunity to answer the questions concerning our manuscript recently published in Arquivos Brasileiros de Cardiologia.[1] Academic discussion is always healthy and welcome.

Firstly, thank you for your interest in our study. The question raised refers to the use of linear regression in the treatment of data from a prospective cohort with repeated measures, which is believed to have caused mistaken estimates (mixed linear regression is suggested instead). Linear regression is debated as it fails to detect intra-individual variability properly, as it focuses on variability between individuals. From a theoretical point of view, this statement is correct, but it does not reflect the way the data were analyzed in the study.

The dependent variable of the study was defined as "drug spending over 12 months." In the study, we did not analyze the history of drug spending over the year[2] (and how this history would be affected by behavioral variables), nor did we seek to identify the relationship between changes compared to baseline (for dependent and independent variables). We did try to analyze the relationship of behavioral variables with the final amount spent over the year.

In fact, this dependent variable is unusual in its construction, as it was longitudinally designed (expenditures on drugs computed over 12 months), but treated cross-sectionally (total amount spent over 12 months). The total amount of drug spending reflects a cross-sectional construct, although its construction considers the 12 months of follow-up. This particularity of the dependent variable, added to the fact that the behavioral variables were collected at only two moments (baseline and at the end of 12 months), led us to create the four models proposed in the study, which characterize a cross-sectional view of the problem (especially models A [baseline data] and B [at the end of 12 months]). Unfortunately, the monthly assessment of behavioral variables was not an available methodological option.

In an ideal model, the dependent variable and the independent variables should be collected monthly, allowing to identify the impact of changes on behavioral variables on changes in drug spending history over the year. However, I repeat, this was not the purpose of the study.[1] For this type of analysis, specific structural equation modelling (latent growth curve analysis) would be more suitable (even more so than mixed linear regression), as they would make it possible to analyze the direct impact of changes on independent variable (slope)over changes observed on dependent variable (slope).[3] The "impact" measures generated by the model are easily interpreted, as they can be expressed as correlation coefficients, which additionally provide effect-size measurements.[4]

Additionally, the dependent variable as it was presented (cross-sectionally, with spending accruing over follow-up time) was necessary due to the particularities observed in its structure. Unlike other variables usually measured in different areas of health sciences (height, blood pressure, lipid profile components), which do not have zero value, drug spending occurs irregularly, reflecting the high occurrence of zero values (that is, spending can be reported in the first month of collection, then no spending can be reported over the subsequent months). Against this background, analyses considering the month-to-month variable would be problematic. Likewise, the issue of intra-individual variability needs to be considered with caution in this study because drug spending in the previous month does not recur in the following month, unlike what was observed for variables like height[5] which, even without any gain, the amount of the previous month will repeat in the following month.

Finally, the absence of significant relationships for obesity and smoking is not surprising in this study, as the sample is relatively young, without the presence of chronic diseases and low occurrence of smoking.

Rômulo Araújo Fernandes

Letter to the Editor

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