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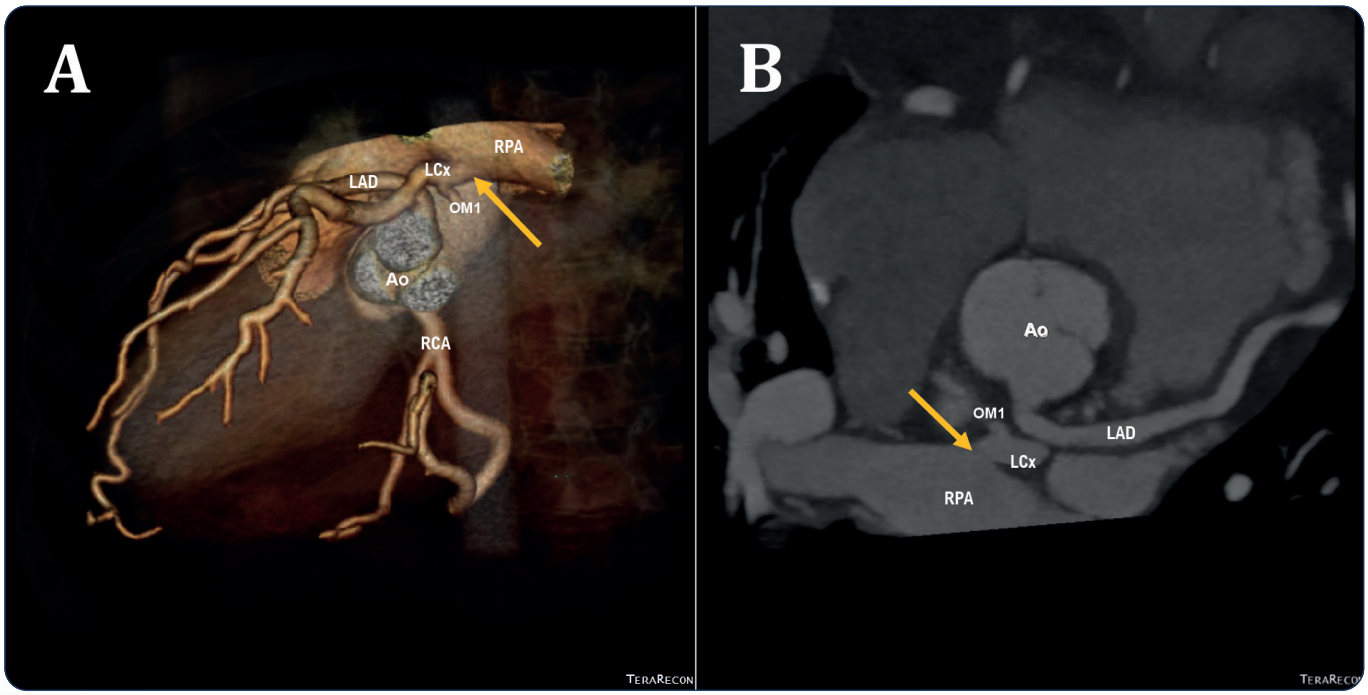

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Arquivos Brasileiros de Cardiologia
JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Chagas Disease: Are Kissing Bugs the Only Culprit?

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Preface

Chagas disease, first described by Carlos Chagas in 1909, is caused by a single-celled parasite (*Trypanosoma cruzi*). Throughout history, the main mechanism of transmission has been via contact with the feces of an insect infected with the parasite. This insect, known as the "kissing bug" in English, is popularly known as "*barbeiro*," "*chupão*," or "*chupança*" in Brazil. The "kissing bugs" are not born with the parasite in their intestine; rather, they acquire it by feeding on the blood of infected mammals. (This disease only affects mammals). When taking a blood meal, the insects eliminate feces, where the parasites are present, and the parasites can contaminate the bite, allowing the parasite to enter the organism. In this manner, the disease begins. The kissing bugs mainly make their nests in cracks in clay walls of houses made in a style known as "*pau-a-pique*" in Brazil. These houses are very common in diverse regions of Brazil, especially throughout the *sertão* of the Northeast Region. Other mechanisms of transmission can occur, for example, via blood transfusion, organ donation, mother-to-child transmission, ingestion of contaminated foods, etc.

During the acute phase of the disease, complaints may be mild or even non-existent. They may include general manifestations, such as low fever, malaise or more severe ones, such as shortness of breath and swelling.[1] As bites from kissing bugs usually occur on the face, swelling of the eyebrows, known as the Romaña sign, may occur. As the years pass, generally after 10 years or more, cardiac complaints appear in one third of patients, such as fatigue, shortness of breath, and swelling in the body (heart failure).[2] In some cases, the electrical system of the heart may be compromised, with alterations in cardiac rhythm, fainting, and even sudden death. Dilatation of the esophagus and the colon can also occur, with progressive difficulty in swallowing food and defecating.[1]

Since the first issues, which date back to 1948, the *Brazilian Archives of Cardiology* have registered advances in medical knowledge regarding this specialty. Even with few technical resources, diverse researchers of that time showed brilliant clinical reasoning. The first 10 articles on Chagas disease in this journal date from 1948 to 1958.[3-12]

At the end of the 1940s, the figures included in the articles, such as those published in 1948 and 1949 (Figure 1), already reflected groundbreaking didactic interest on the part of the *Brazilian Archives of Cardiology*.

My story

When we were still eggs, my mother left my siblings and me in a dark place that smelled like clay. Lucky for us. When I came out of the egg, I noticed that many of my siblings had already come out, but others weren't reacting. Later, I would understand that they would never come out. I don't know who my mother is, or my father either.

When I was still little, exploring the territory where I was born, I saw that my nest was in a small crack in a very strange house. It was made with interlaced sticks of bamboo that were filled in with red clay. There was a peculiar smell, a mixture of sweat and burnt wood. There were several very old objects. A little lamp that was turned off, on top of a wooden shelf that was nearly rotten close to the door, which was wide open and made of pieces of planks, with lots of cracks between them. There was a wood-burning stove with embers on top and a pot that was almost empty, just boiling water and a few pieces of manioc. Next to the wall, right below my nest, I could see a double bed that was patched up around the feet and the head, on the verge of collapsing. On top, there was a threadbare mattress with a blanket that was also in tatters, with clumps of straw sticking out of the parts that were torn. On the other wall, an open window with a table beneath it, also worn down, with all four legs on the verge of falling apart. There were no towels, just two empty pea tins that were used as drinking cups. Next to them, two plates that were chipped all over with a worn-out spoon on top of each. The floor was made completely of raw earth, with pieces of wood and leftover food, as well as splattered contents from the wood-burning stove. The roof was made entirely of dry straw with a lot of holes that let sunbeams in. There was no one home. Looking at this scenario, I though that my nest was pretty comfortable by comparison.

Several of my siblings had already gone and I didn't hear from them anymore. The ones who were there with me and I found the environment very sad. We didn't even know who we were. I would later learn that we were insects known as "kissing bugs."

Leaving my nest, I started to explore the house and I went out the window, afraid of what I might find there. The sun was blazing and there was not even a little breeze to cool us off. The earth was covered with red clay, and we rarely saw patches of brush with yellow leaves that were twisted by the heat. I thought that the inhabitants must not feel thirst, because

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Chagas Disease/history; Trypanosoma Cruzi; Chagas Cardiomyopathy; Myocardites; Mortality.

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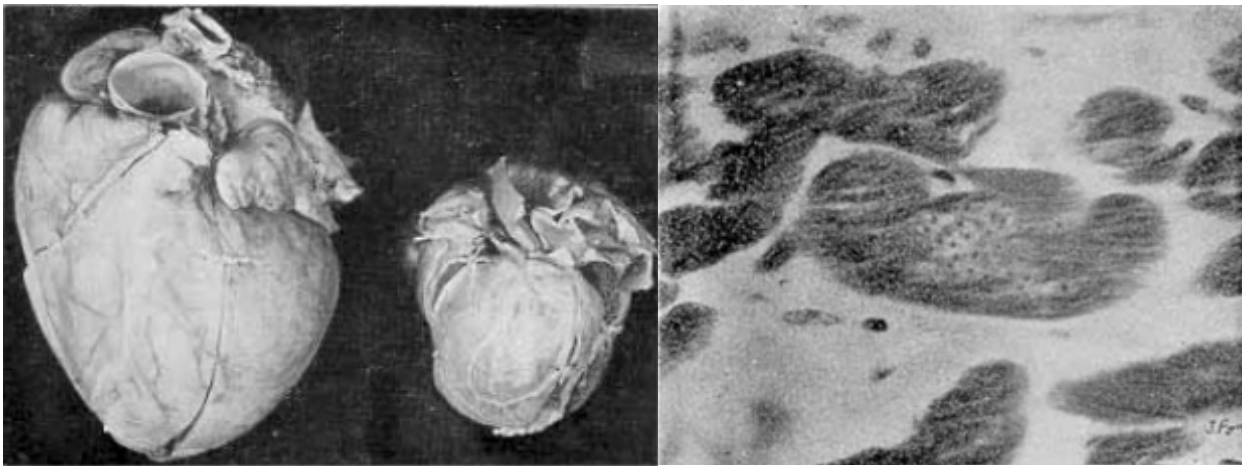

Figure 1 – *(A) Left, heart of case 26; right, normal heart. On radioscopy: large myogenic heart, almost completely stopped. (B) Parasite cluster in the cardiac fiber (S. cruzi).*[3,5]

I couldn't see any traces of water. A little later I heard a noise and I saw an emaciated dog with its tongue hanging out lazily slinking along the burning ground. I noticed that it scarcely had the strength to walk and bark at the same time. It came close and, in fear, I hid in a crack that I found on the outside of that little hut. I stayed still there while the dog sniffed incessantly, as though it were hunting something to eat. A little while later it left, went into the house, and lay down on the ground next to the door, sleeping heavily, perhaps to take its mind off of how hungry it felt. Continuing my exploration, I saw another animal. It was very strange, and I later learned that it was called a skunk. When it saw me, it immediately ran toward me with a horrifying expression, demonstrating the intent to, at my expense, sate its hunger. Once again, I hid in the strategic haven in the crack in the wall, which also provided an opening that went inside the house. As it was already nighttime, I decided to go back to the nest where I would be safe. I admit that I fell asleep. I don't know how long. I woke startled by a loud noise inside the house. It was very dark, and I couldn't see anything. Then, a faint light came on and I saw that the lamp had been lit. Imagine how frightened I was when I saw a man, a woman, and four children speaking loudly inside the house. The man was short and very lean, and the skin of his face was wrinkled, showing signs of suffering from constant exposure to the sun. He wore busted up sandals on his feet. His pants hardly covered his ankles, and they were all patched up, with several tears that couldn't take another stitch. His hands, which were calloused from the daily toil on the small farm, were incapable of finer movements, and they handled everything with brutality. He was smoking a straw cigarette that spread a foul-smelling smoke, but still seemed comforting to him.

The woman wore a resigned expression, and she was equally thin. She walked barefoot, and her feet were calloused. On her head, she wore a cloth that must have been white one day, but was yellow by then. The cloth hid almost all of her dark hair and the locks that weren't covered looked like straw. She wore a blouse that was similarly in rags. It was missing several buttons and it was held closed by a knot in the front. Her black skirt also covered her knees, and it was tied around her waist with a thin rope. Her hands bore the signs of the difficult life she led. She lamented when she saw the pot on the wood-burning stove with so little to offer to eat. What a life, my God.

The four children seemed more like four cherubim, given their sad and innocent appearance in view of everything that was going on. The youngest seemed to be around three, and the oldest wasn't older than seven. All of them walking barefoot. One of them had a rag tied around her foot, in the attempt to treat a cut made by a branch that she had stepped on in her daily struggle. The two girls, who appeared to be three and five, were wearing dresses made of very thin cloth that was worn-out, and the boys, who were older, were wearing pants that reached their knees and nothing else. All of them had stomachs sticking out, and the rest of their bodies were skeletal. The oldest boy, with a great deal of effort for his age, dragged a tin container of water, which was not very clean, into the house. All six sat around the table or on the bed, and they ate what there was to eat, the largest portions being for their parents. After this paltry dinner, they turned out the lamp, and all six piled into the only bed they had. I observed all of this with great sadness. How was it possible to live like that? Shortly thereafter I fell asleep too, because I wasn't hungry thanks to the food reserve I had received while I was inside the egg.

All of a sudden, I woke to angry shouts from the man, "Kill that kissing bug that's on the girl…"

Instantly, I looked at the bed where that little child was fast asleep with the expression of an angel and I saw one of my older siblings "stuck" on the little girl's face. He was very fat, in contrast to how I'd seen him the day before. I couldn't grasp what was going on or what my brother was up to there. The only thing I saw was the woman who grabbed him and

threw him in the embers of the wood-burning stove. Terrifying scene. Then I saw the man come close to my nest with the lamp on and he started putting it in the cracks in the wall. I was afraid, and I hid, along with the rest of my siblings, in the far corner. Not finding anything, the man turned off the lamp and started swearing, "Darn kissing bugs." Shortly thereafter, they all left the house without having anything to eat, taking their tools with them to the backbreaking work on the farm. I stayed there, trying to get a grip.

A little while later, I decided to leave the house and wander around the surrounding area. I saw a pile of wood outside and I went in. It was a dark, warm place with a bad smell. I was frightened when I saw that skunk, the one that had chased me the day before, coming close. He started smelling around as if he knew there was food there. I stayed still, but I had the feeling my legs were shaking. When he didn't find anything, he went away. Continuing my exploration of that hiding place full of dry sticks, I found an old kissing bug who could scarcely walk, and I went over to him. He was glad to see me because it had been a long time since he had met one of his own to talk to. He asked me where I came from and why I was putting myself in harm's way. I told him that I wanted to get to know the region and that I couldn't grasp what was going on around me. Then I told him what had happened to my brother and he asked me to sit by his side so he could explain.

"Many years ago, there were no humans here and this region was inhabited by us and many other animals. There was a thick scrubland and lots of trees with thorns. We lived in harmony. We made our houses in other animals' nests, mostly skunks and rats, and that's where our children grew up, because we had a lot of food."

"What do we eat?" I asked curiously.

Seeing my innocence and curiosity, the old kissing bug went on, "Young one, we only eat blood. We suck blood from other animals and we are satisfied with that."

I confess that I was horrified, and then I understood what my brother was doing on that child's face and why he was so fat; he was feeding on her blood. He went on.

"Every time we eat, we get very fat and then we can't keep our feces in, and we end up defecating right there."

"That's gross," I exclaimed.

"Back to what I was saying," the old kissing bug went on. "Our peace came to an end. Human beings arrived, and they cut down the bushes and trees. They made little huts, and our friends the skunks and rats and many others fled in fear. So many of us had nothing to eat and some of us died out. Others went looking for new places, and that's how we spread throughout this place."

"As time went on, we learned that the walls of those houses, made of clay, cracked in the intense heat. Some of us, in despair, out of hunger and lack of a place to hide, made up our minds to make a home in those cracks. They got used to the place and started to notice that those humans also had warm blood, just like the skunks and rats. At night, while they sleep, kissing bugs can eat and almost always get back safely to the cracks in the walls. Sometimes they take too long and get caught and end up in the wood-burning stove. All the same, we started expanding throughout the region."

I was satisfied with the explanation he had given me, so I started back to my nest. It was already getting dark and the sky was bright with stars, without any clouds. When I got home I spent a long time observing those people. Once again they ate a measly soup that didn't seem to have much to satisfy their hunger. I kept growing, but I still didn't feel the need to eat. So I fell asleep.

In the middle of the night, I was awoken again by the woman who was yelling, "Darn kissing bugs!" The sun had not come up and the house was already lit by the faint light of the lamp. Now there were five of my siblings who were sucking the children's blood. All five of them ended up in the embers of the wood-burning stove. In despair, I couldn't fall asleep. When the sun came up, the man, the woman and the children left again without eating anything.

I thought about leaving there and never coming back. I couldn't get the scene with the wood-burning stove out of my head. I looked around and saw several of my siblings sleeping, fat from eating so much. They had done a good job of eating at night without being discovered.

I went outside looking for my friend, the old kissing bug, but I couldn't find him. I roamed around the perimeter, always hiding so as not to be noticed. I was afraid of what I might find, especially after the old man's stories. I came across a lot of strange animals. Some of them were rather large compared to me and they were flying high up in the sky, which was blue and showed no signs of rain. I didn't like the way they looked at me at all, and I thought it would be wise to stay beneath the leaves in the path. There I found many of my own kind who seemed to be my age or a bit older, but they already had more experience, and they were roving around those parts. We quickly became friends, and we talked a lot. I told them what had happened with my siblings and how they met their tragic end.

Many of them gave me advice.

"When you eat, go for the children, because they sleep more heavily and they generally sleep up against the wall. That way, it is easier to run away inside other openings in the clay or even to hide beneath the mattress. Avoid the adults, because they wake up more easily and catch us, and it's hard to get away from them when they are in a deadly rage."

I still didn't know what it meant to feel hungry and I had never had a blood meal, but I was getting more and more curious about it.

"But out here, how do you hide and find food?" I asked.

"If you look around, you'll see that, in this field, there are a lot of nests that belong to birds, skunks, and rats, all very well hidden. We live there. We're always warm and at night we have all the blood we want. We just need to pay close attention, because we can end up on their menu. In those nests, especially the ones that belong to the skunks and the rats, there are usually babies and they are delicious. We can eat all we want, and they hardly react; when it comes to the parents, we hide between the straw and that's where we stay."

I thought hard about this type of life, which seemed more interesting to me, and some of the kissing bugs even commented in a worried tone of voice that these birds, skunks,

and rats were getting rarer and rarer around the region, just like that old kissing bug had already told me.

"They are running far away, afraid of human beings, and we have less and less choice of where to live and what to eat. It's very likely that soon we'll have to go inside the house to look for food and shelter, even if we have to run the risk of the wood-burning stove."

It was getting dark. I thought it wise to get home. I said goodbye to my new friends and set off on the way home. I was almost there when I was startled by a dark, strange creature. It was much larger than me. It had eight legs, in contrast to us, who only had six. Its body was dark and covered with short hair. It had two giant fangs in its mouth. It was a spider. I was terrified when I saw it and even more so when it turned toward me in a way that wasn't friendly at all. The only thing that went through my mind was to run away as fast as I my feet would let me and go into the first crack in the wall that was small enough for the spider not to be able to come in after me. Finally, I found a little crack that also extended into the house. I stayed there for a few moments in fear, gathering my thoughts after that frightful scene that I'd just faced, and then I went toward my nest, which seemed safe to me.

When the sun was already starting to heat up the ground, I woke up and I noticed that the humans were getting ready to head out toward their daily toil. Something there drew my attention. The man was moving more slowly and his breathing was laborious and noisy, but he leaned on his shovel, which gave him some support. But they went off.

I noticed several of my own kind between the rags that covered that pitiable bed, and they were all fat and satisfied. For the first time I had a strange feeling. I didn't know what it was, but instinctively I understood that I was hungry. Since it was daytime, there were no human beings in the house, and, even if there were, it would not have been wise on my part to wander out because the stove was there, and it was frightening. So I went looking for food. When I got outside I noticed a great deal of commotion. When I got closer, I saw a skunk lying down next to a bush. It was very quiet. It was having difficulty breathing and its body seemed very swollen. Several of my own kind were taking advantage of the poor animal's lack of resistance and they were sucking its blood, even though they saw that it was getting weaker and weaker. Sometimes it moved slowly, but it wasn't able to reach the animals that were causing it so much suffering. I thought it was very sad and even though I was hungry I couldn't bring myself to take advantage of the situation.

Continuing my exploration I noticed a nest on top of a bush, and I went to see what it was. I climbed very slowly, keeping my eyes open to see if there was any danger nearby. To my surprise there were three baby birds. They were very small, and they have almost no feathers.

"Might they have any blood?" I asked myself. "I'm going to check."

I was able to put my sucker in the skin that was thin and soft, without any difficulty. The baby bird scarcely moved. That was when I noticed that, when I sucked their blood, it was practically painless. I stayed there for a long time enjoying my first blood meal. When I came to myself, it was already getting dark, and it was time for me to go home. Like the old kissing bug had told me, I noticed that my feces were close to the place where I had bitten it. I walked with a certain difficulty on account of the size of my stomach. When I got back to my nest, I fell asleep and had a very peaceful night.

In the morning, still satiated from eating so much the day before, I looked around the inside of the house and noticed that the man did not feel well. He was having difficulty breathing. He could scarcely walk, and his legs were very swollen. He wasn't able to lie down, and he remained seated in the bed, dangling his legs. Just that day, the woman and the children went out to work on the farm. Fascinated by the scene, I couldn't take my eyes off that man who seemed to be suffering a lot. I spent the whole day in my nest watching that poor creature. At the end of the afternoon, the woman and the children came back and found the man in the same situation. She prepared corn mush with what little was left or their dried meat, gave a good part of it to the children and set some aside for herself and her husband, but he wasn't able to eat on account of how uncomfortable he was. So they all went to sleep, but the man remained seated in the bed.

When it was morning, I found it strange that no one was getting ready for work, and I heard the woman telling her children that it was Sunday and that they would go to church for mass and talk to the priest about her husband's health. And then they went away. I had already been there on one of my excursions around the territory and I went there too.

Sunday mornings, the whole community, which was around thirty people, got together in the church for mass and to spend time together. They shared their difficulties and concerns, which were numerous, and often without any prospective solution. The walls of the church were made of interweaved bamboo sticks that were filled in with the same red clay that the houses were made of, maintaining the same setting of misery, desolation, and abandonment. A cross made of two thicker branches was placed on top of an altar made of nothing more than a plank on top of two wooden stands and a white cloth. The worshippers sat on very rustic benches that were patched together and that seemed like they were about to collapse under the weight of the people. Lit candles surrounded a small vase where we could see a few branches arranged as though they were flowers.

I found out that, when the ceremony was over, the woman went up to the priest and explained her husband's situation to the priest. When the priest heard about the severity of the situation, which he had already seen many times in many of the inhabitants of the diverse communities he had visited, he said that he would visit the sick man. So, the woman and her children went home where they found the man in the same state.

Later, the priest arrived at the family's home, accompanied by an elderly woman, who was the midwife, blessing-giver, and the region's leading authority on health. They talked with the poor man who felt so uncomfortable. He could hardly speak on account of how exhausted he was and his difficulty breathing, and his body was very swollen. The woman, with a knowing air, took hold of the patient's wrist and realized that his heart was beating in a very irregular manner. She looked at his eyes and throat and quickly made her diagnosis.

"It's the kissing bug disease," exclaimed the elderly woman who knew everything about diseases in the region and she stated with certainty, "He needs a doctor."

That scared me very much. Kissing bug disease? What type of disease is that? How was it possible? Could we cause someone sickness? We are so small. How could we put a man that big in such a situation?

My first reaction was complete disbelief in her words, and I curled up in my nest and soon fell asleep. I woke up in the middle of the night, and I was very hungry. I looked down and saw that the house was totally dark. The man had fallen asleep sitting up, and there, up against the wall, was a little child fast asleep.

I went down carefully, constantly worried that someone might wake up and throw me in the stove. Finally, I reached the little girl. Her skin was so warn and soft that I couldn't help myself. I started eating her blood, which was fresh and delicious, until I couldn't eat anymore. I noticed that I had eliminated feces close to the bite wound. How embarrassing. I left the place as quickly as I could and climbed the wall with some difficulty on account of how fat I had gotten. On the way, I noticed that the child was scratching where I had bitten her, and she was spreading my feces across her skin. That night, I also slept very soundly.

As soon as the sun came up, they were already moving about the house. The man, accompanied by his wife and the priest, were going to seek medical attention. I heard they say that the only hospital in the region, where there was only one physician, was three hours away and they were going on a cart drawn by an old donkey that went very slowly. That was the only way to go look for medical treatment. The children stayed there alone, and the oldest one took care of them. That day, they didn't work on the farm, and they could play a little bit, which was a rare sight to see. I stayed there observing how happy those children were. They had absolutely nothing, but they had fun with a ball made of rags and some dry sticks that they pretended were dolls. I watched closely and I realized that they were also playing with an old "kissing bug." They were picking it up, letting it walk on their arms and even letting it bite their skin, which was damaged by the sun. I really liked that, but I didn't have the courage to go over to them. A little while later, they started playing something else and they left the "kissing bug" alone. It disappeared into the woodpile.

In the evening, the priest, the wife, and the husband came back from the physician. The priest helped the man get out of the cart and, with difficulty, helped him sit down in the bed. He went back to the cart and left. I realized that the woman had a sad and very concerned expression. Tears were rolling down her face. She was carrying a little box with a medication that she had received at the hospital. She immediately got the cup, filled it with water, and gave it to her husband so that he could take the medication, in the hope that he would get better. That night, he got up to urinate several times, and it bothered me so much I almost couldn't get to sleep. When I woke up, everyone had already left, and I imagined that the man had gotten better.

Once again, I went out to explore the region. I found an old dog lying down on the ground. It didn't seem well at all. It was having difficulty breathing, and it was so swollen it could hardly move. The sun was already very hot, but it didn't seem to bother the dog, or maybe it couldn't even react to the heat, given how weak it was. Again, I felt hungry and I saw, in that debilitated animal, a chance to eat. So I found a place its feet and mouth couldn't reach and started eating. When I was full, I realized that that poor animal wasn't moving. I paid attention to its breathing, and it was getting slower and slower, until it stopped. For the first time, I understood what death was. What might have happened to that dog? I couldn't understand that, but what drew my attention was the difficulty breathing that resembled the man in the house. Could it also be the "kissing bug disease," like the elderly woman had said before? Worried, I went back to my nest. Later the children, the woman, and the man came back. I noticed that the man was panting less, but his legs were still very swollen. Difficult as it was, he didn't stop going out to work on the farm. He sat on the bed while the children played a bit outside and the woman prepared something to eat. I noticed that she was carrying a dead bird. She started to break it into pieces, and then she put it in a pot with boiling water on the stove. A little later, they ate, and, as it had already gotten dark, they got comfortable in the bed to sleep. The man remained seated. I fell asleep worried. I couldn't get the scene with that poor dog out of my mind, or the one of that bird that had been so mercilessly devoured.

When I woke up everyone had already gone out. I felt strange, as though the feast from the day before wasn't good for me. I didn't know exactly what it was, but I realized that something strange was happening to me. I spend the whole day in the nest. At the end of the afternoon, when it was already getting dark, they all came back, and I didn't like the way the man looked. He looked very tired, and he was panting. He was still very swollen, even in his stomach, and he was having difficulty buttoning his torn shirt, which he left totally open. That evening, he didn't feel like eating and he went to relax in bed, sitting with his legs dangling, nodding off.

The days passed, but that monotonous scenario was interrupted by a frightening event. Standing up next to the door, the man suddenly fell unconscious on the ground. He was alone at home, because his wife had gone to wash some rags in a tub outside the house, and the children were gathering wood for the stove. All of a sudden, he stood up as if nothing had happened. When they all came home, the man stayed quiet and he didn't say anything about what had happened. This happened other times, and he was always alone. So as not to worry the others, he didn't say anything about it.

Another hot day, I realized that the little child who had provided me with so much food also seemed strange. She didn't want to get out of bed, she seemed tired, and I noticed that her right eye was swollen. I remembered the elderly woman and her words, "It's the kissing bug disease." I confess that I felt scared and guilty, without knowing exactly how that had happened. On many other occasions, I had fed on her blood after having bitten that poor dying dog, and had I, just now, given this child that disease? How could that be possible? What might have happened? Could I be the one to blame?

The days went on and I noticed that that child was getting weaker and weaker. She didn't play. She scarcely ate because of how tired she was. That went on for several weeks until she started getting better, going back to normal. Her recovery was a relief to me, because I imagined that I hadn't hurt that little angel after all. To my fright, all the other children, except for one, starting showing the same symptoms. I hadn't fed off of any of them, but my siblings had.

One day, walking around the area, I met that old kissing bug, who I hadn't seen for a long time, who had answered all my questions before. So I asked him about what had happened to those children. What he told me was terrifying. I had certainly become contaminated by the blood of that sick dog and for the rest of my life I would contaminate those I fed from. I was shocked, and I promised myself that I would never bite anyone from that household again. And so it was… When I felt hungry, I looked around for a bird's nest with baby birds or an old skunk that was hardly moving. I never fed from anyone in that family again. The remorse hurt too much.

From my nest, I could see that man getting more tired and thinner every day, but he never stopped working, even when it was painful. The scenario was sadder and more hopeless every day. Food and water were scarcer and scarcer. The furniture around the house progressively falling apart. The children growing up without prospective. What a horrible situation, my God!

One day, a piece of promising news: A young teacher had arrived in the little village, and she was going to take charge of that old school that was in ruins and give an opportunity to anyone, especially to the children, who wanted to learn to read and write, and then they would be able to understand all those letters arranged on those old newspapers they used as rugs. I thought to myself, "Could this be a spark of hope?"

The following days, the children's behavior changed. Three times a week, early in the morning, they went to school happy, and they stayed there until around eleven in the morning, when they came home. Those days, they only worked on the farm in the afternoon. I sat there impressed, watching them teach their parents how to put together letters to form words, but it was very difficult for them. They were already trying to read the big pieces of newspaper on the floor, and that made them very happy.

The days went by, and I started noticing that the man was fainting more often. Now everyone in the house witnessed it. After the episodes, he would stand up as if nothing had happened. That bothered me a lot, because he seemed tired and very swollen. I couldn't get the image of that dying dog out of my head, and the man's situation seemed very similar. His wife, getting more worried by the day, didn't want the children to see how concerned she was. They didn't notice the slight worsening of their father's condition.

One day, I woke up before the sun came up, worried about the whole scenario from the preceding days. Shortly thereafter, the woman got up, together with the children, but the man didn't move. The woman tried to wake him up, shook him, but he didn't move. The scene was very painful. The woman yelling and crying desperately. The children crying and hugging their father. He was dead. He died in his sleep, like few people deserve. Their despair was terrifying. No one left his side as he lay there in bed with his feet dangling over the ground. What would become of that woman and those children now?

After that motionless scene continued for some time, the mother told the oldest child to go and call the priest. The child was still crying in despair, but he obeyed his mother and went looking for the priest, crying in a way that hurt to see.

Finally, the priest arrived at that house and confirmed that the man had died. He prayed for his soul to rest in peace and tried to comfort the woman and the children, but there was little to say in the face of so much misery.

The only thing left for that man was to be buried in the land where he had always lived. The woman and the children would have to continue their tragic lives, without a husband and a father.

Day after day went by, in an agonizing monotony, until a group of men came to town, proposing to kill all the kissing bugs in the region. My siblings and I, all adults by then, were very apprehensive about this news, trying to imagine a defensive strategy. Should we leave the house and look for an equally dangerous area?

I personally decided to stay, because, out of cowardice, I didn't want to face the dangers of skunks, spiders, and dogs, without having a safe haven to return to. I remembered when the man with his smoking lamp would look for us between cracks in the wall, and I would hide way in the back. That seemed safer to me.

One day, two men came to the house wearing strange clothes, with masks on their faces that made them look scary. They asked the woman and the children to leave the house and come back a few hours later. I was curious when they started mixing liquids in a tin container. The smell was unbearable.

Then I started thinking of running away, but it was too late. I hid as far as possible in that crack.

"What's happening?" They were coming toward me spraying that liquid that went back into my nest, soaking my siblings and me completely.

All of a sudden, I saw my siblings fall on the ground without moving. Few of us were left. I felt dizzy and weak, and I could hardly move. I stayed still.

The strange men went away and a few hours later the woman and the children came back, gathered many dead kissing bugs from the ground and threw them in the stove. Sad end.

That noxious smell decreased progressively, until the environment went back to normal. Why had so many of my own kind died and I hadn't? Was it possible that I had been given a second chance not to make the same mistakes that caused the "kissing bug disease" in those people who suffered so much?

A year had already gone by since I had left that egg. I feel very weak. It is hard to walk, and I don't have the strength to go out and find food. My vision is blurry and everything is very dark. I feel very sleepy and I am going to fall asleep.

Looking back on my trajectory, I understand that all the

harm that I caused was not intentional, but just a means of survival. I hope that this can be fixed some day. "I'm not able to breathe anymore…"

"In blaming kissing bugs for the spread of this horrible disease, we have to analyze humans' role in history in an impartial manner. In trying to survive, we often adopt thoughtless attitudes that don't hurt just us."

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Fragata Filho AA.

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References

1. Ortiz JV, Pereira BVM, Couceiro KN ,Silva e Silva H, Doria SS, Silva PRLet al. Avaliação cardíaca na fase aguda da doença de Chagas com evolução pós-tratamento em pacientes atendidos no estado do Amazonas, Brasil. Arq Bras Cardiol. 2019; 112(3):240-6.
2. Mesquita ET, Souza ALAG, Rassi S. Dia de alerta da insuficiência cardíaca: um tributo ao gênio Carlos Chagas. Arq Bras Cardiol. 2019; 113(1):5-8.
3. Pondé A. A cardiopatia crônica da doença de Carlos Chagas. Arq Bras Cardiol. 1948; 1(1): 27-70.
4. Rodovalho OA, Dias JC, Tisi OG,Décourt LV, Ramos Jr J, Correia IA. Miocardite crônica chagásica. Arq Brasil Cardiol. 1948; 4(1):333-46.
5. Ramos J, Freitas JLP, Borges S. Moléstia de Chagas, estudo clínico e epidemiológico. Arq Bras Cardiol. 1949; 2(2):111-62.
6. Marques RJ, Gomes AP. Moléstia de Chagas em Pernambuco. Arq Bras Cardiol. 1950; 1(3):159-68.
7. Péra JR. O eletrocardiograma na cardiopatia chagásica crônica. Arq Bras Cardiol. 1952; 4(5): 428-36.
8. Borrotchin M, Carvalho SM, Veloso DP. O eletrocardiograma em 70 pacientes com a forma crônica da doença de Chagas. Arq Bras Cardiol. 1954; 1(7):26-39.
9. Borba P, Gomes AP, Sherb J. Aspectos epidemiológicos da doença de Chagas em Pernambuco. Arq Brasil Cardiol. 1954; 3(7):191-200.
10. Franco AG, Pelosi AM, Silva JN, Costa C. A cardiopatia chagásica na Bahia. Arq Bras Cardiol. 1955; 4(8):415-22.
11. Borba P, Gomes AP, Sherb J. Aspectos epidemiológicos da moléstia de Chagas em Pernambuco. Arq Bras Cardiol. 1956; 3(9):191-200.
12. Castro JM, Uvo D. Incidência da doença de Chagas em doadores de sangue do Hospital São Luis Gonzaga, Jaçanã, São Paulo. Arq Bras Cardiol. 1958; 11(2):114-20.

Anomalous Origin of the Circumflex Coronary Artery from the Right Pulmonary Artery: Diagnosis Through Cardiac CT

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Introduction

Anomalous origin of the left circumflex coronary artery (LCx) from the right pulmonary artery (PA) is an extremely rare coronary anomaly. Although the clinical course may be silent, the risk of sudden cardiac death is increased. The symptoms are related to collateralization and amount of myocardium that it supplies, and some patients need surgical treatment.[1,2]

Case report

A 44-year-old woman with a family history of Brugada syndrome and no other relevant medical background was examined in our hospital due to Canadian Cardiovascular Society class I exertional angina. She had no coronary risk factors and no family history of premature coronary artery disease or congenital heart disease.[3] Physical examination was unremarkable. Transthoracic echocardiography only revealed mild mitral regurgitation, and ECG was normal.

She underwent an exercise echocardiogram that revealed wall motion abnormalities in the inferolateral wall, with worsening of the degree of mitral regurgitation. Brugada syndrome was excluded after pharmacological test with ajmaline.

Coronary computed tomography angiogram (CCTA) was performed (*Siemens Somatom Sensation 64 CT Scanner*®). A preliminary scan for scoring the amount of coronary calcium was obtained, and the Agatston score was zero. Seventy milliliters of iodinated contrast (*Ultravist 370*®) were administered. Nitroglycerin 0.3 mg was sublingually administered immediately before contrast injection. The patient was in sinus rhythm with a heart rate of 50 to 60 beats/min. A retrospective gated CCTA was performed, with reconstruction of cardiac phases at 70% of the R-R interval. The post-processing image was performed on *Aquarius Intuition TeraRecon*®.

CCTA imaging revealed an anomalous LCx arising from the proximal right PA (Figure 1 A and B; arrow). Figure 1A illustrates a three-dimensional volume-rendered image of the coronary tree demonstrating the anomalous connection of the LCx to the right PA, coursing inferior to the proximal left anterior descending (LAD) coronary artery. We can also observe the normal origin of the LAD and right coronary artery (RCA), with dilation of the main arteries, but no significant collaterals are observed. Figure 1B is an oblique multiplanar reconstruction with maximum intensity projection 1 mm thick, demonstrating the anomalous origin of the LCx from a right PA. This finding was confirmed on a subsequent coronary angiogram, where ectasia of the coronary arteries was observed, with an extensive network of collaterals originating in the RCA and LAD supplying retrograde perfusion of the LCx (Figure 2).

Our patient had exertional angina, with a positive stress test; therefore, she was referred for cardiac surgery. Surgical ligation of the anomalous LCx was performed to decrease competitive flow, which can cause the graft to fail, followed by coronary bypass graft with left internal mammary artery to the LCx. There were no complications and the patient remained asymptomatic since then.

Discussion

Normal coronary anatomy is characterized by two ostia located in the right and left Valsalva sinuses and is universally defined as follows: the RCA originates from the right Valsalva sinus and the left coronary artery in the left sinus, usually below the sinotubular junction, and it usually divides into the anterior descending artery and the circumflex artery.[1]

Determining what is normal in the anatomy of coronary arteries is a challenge. Angelini et al.[4] classified any anatomy present in more than 1% of the general population as normal. Thus, by definition, congenital coronary artery anomalies (CCAAs) occur in less than 1% of the population.[3] CCAAs were first described two millennia ago by Galen and Vesalius and are abnormalities in the origin, structure, and course of these arteries.[3]

There are several classifications. Clinically speaking, CCAAs can be divided into two types, those that cause significant hemodynamic instability, occurring at an early age and requiring early surgical intervention, and those that are asymptomatic until old age, which remain unidentified unless they present with other cardiac symptoms or are found accidentally.[2]

The classification initially proposed by Angelini in 1989 has subsequently been updated, and it is currently one of the most used. It divides CCAAs into a) anomalies of origination and course; b) anomalies of intrinsic coronary arterial anatomy; c) anomalies of coronary termination;

Keywords

Coronary Artery Disease; Congenital Abnormalities; Heart Defects, Congenital; Coronary Vessels; Pulmonary Artery; Tomography, Computed/methods.

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Case Report

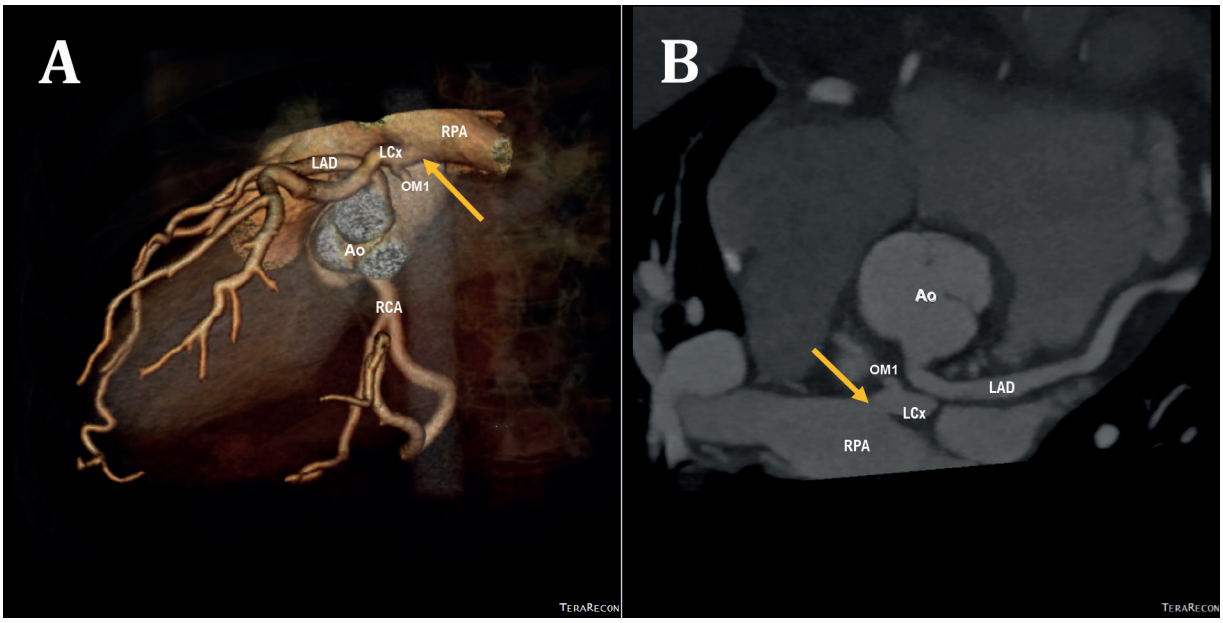

Figure 1 – *Multislice cardiac CT using a 64-slice scanner showing anomalous origin of the circumflex coronary artery from the right pulmonary artery (arrow). LCx: left circumflex coronary artery; LAD: left anterior descending artery; RPA: right pulmonary artery; Ao: aorta; RCA: right coronary artery; OM1: first obtuse marginal.*

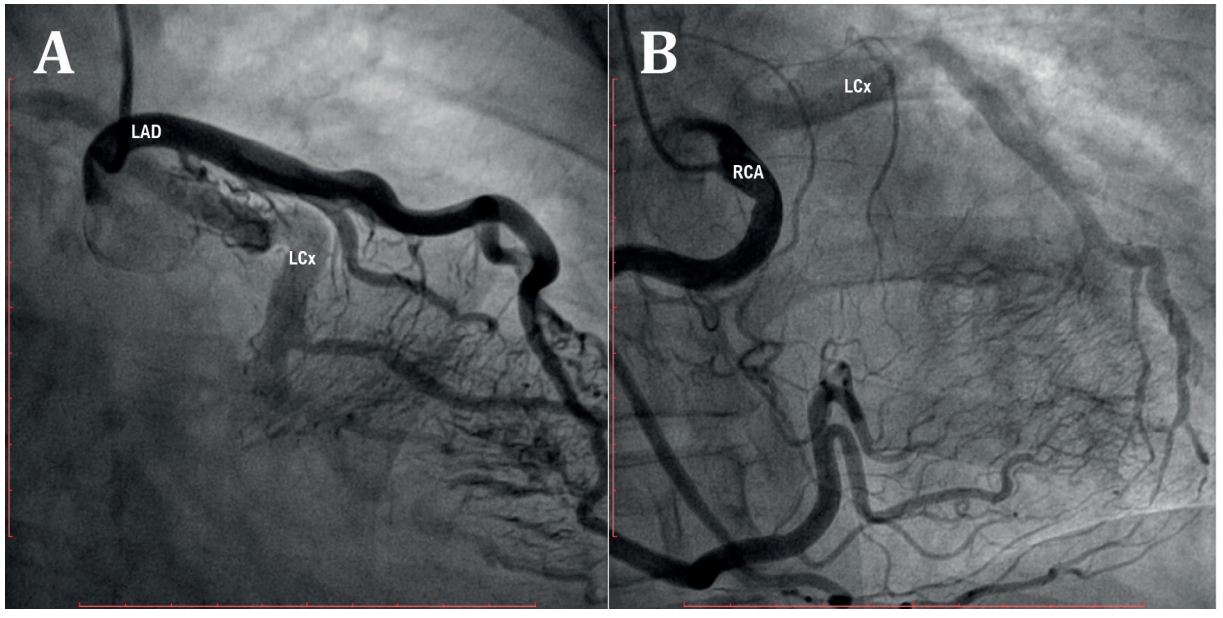

Figure 2 - *Coronary angiogram showing ectasia of the coronary arteries and an extensive network of collaterals originating in the LAD (2A) and RCA (2B) supplying retrograde perfusion of the LCx. LCx: left circumflex coronary artery; LAD: left anterior descending artery; RCA: right coronary artery.*

and d) anomalous anastomotic vessels. The basic principle of this system is that the name of an artery is determined by the territory to which it supplies blood and not based on its origin or initial course.[3,4]

The real incidence of CCAAs in the general population remains unclear; coronary anomalies occur in 0.3% to 0.9% of patients without heart disease and in 3% to 36% of those with structural heart defects.[1] CCAAs are often only detected in autopsy. In young athletes, these anomalies are the second most common cause of sudden cardiac death (in 12% of deaths), and they are generally triggered by vigorous physical exercise.[3]

Bland-White-Garland syndrome or anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) was described in 1933, following the autopsy of a 3-month-old infant with difficulty feeding, cardiomegaly and evidence of left ventricular lesion on ECG, and it is the coronary anomaly most often associated with sudden death.[1,3]

ALCAPA has an incidence of 1 in 300,000 live births. This anomaly is an important differential diagnosis in children with heart failure.[3] It usually presents as an isolated anomaly, but, in 5% of cases, it may be associated with other malformations (septal defect, ventricular septal defect, or coarctation of the aorta), and, if left untreated, its mortality rate in the first year of life is 90%.[3,5,6]

Less commonly, the RCA, LAD coronary artery, or LCx coronary artery have been reported to arise from the PA in rarer variants of this syndrome.[7,8]

Anomalies in the origin of the right coronary artery from the pulmonary artery (ARCAPA) are extremely rare, with an incidence of 0.002%. These abnormalities are asymptomatic in more than 75% of cases, with no evidence of myocardial ischemia.[3]

Anomalous origin of the LCx artery from the pulmonary artery (ALCxCAPA) can be considered an exceedingly rare variant of ALCAPA, with the first adult case reported in 1992 by Garcia et al. and with just over 20 cases described in the literature to date.[7,9] It is usually associated with other congenital heart defects, with isolated cases being extremely uncommon. The described cases range from neonates to adults, with varied clinical presentations, including reports of asymptomatic heart murmur, dyspnea, and angina. The most severe forms found in the literature include myocardial ischemia, with few reported cases of severe myocardial dysfunction and cardiac arrest secondary to this anomaly.[1,2]

During the first month of life, physiological pulmonary hypertension and fetal hemoglobin provide perfusion and oxygenation to the myocardium; consequently, individuals are asymptomatic.[3] In older children and adults, relatively low pressures in the normal pulmonary artery create a gradient through which blood flows, directed from native coronary circulation, through the extensive collateral network, to the anomalous artery and pulmonary artery. This results in coronary-pulmonary artery fistula, with the coronary steal phenomenon.[1] Patients become symptomatic and may experience angina, fatigue, dyspnea, palpitations, ventricular arrhythmias, pulmonary hypertension, and sudden death.[3] Symptoms and prognosis depend on the development of collateral vessels in the other two arteries.[1,2]

Our patient remained asymptomatic throughout the first 40 years of her life. We hypothesize that this is a result of the combination of the relatively small area of myocardium supplied by the LCx artery, the degree of coronary collateralization, and the lack of significant previous cardiac challenges.

CCTA provides a noninvasive imaging tool to demonstrate the origin and relationship of anomalous arteries to other mediastinal vascular structures, and it enables the use of three-dimensional reformation for delineation of subtle variations in the position and morphology of anomalous vessels. Moreover, it plays an important role in surgical intervention planning, and it may be a valuable postoperative follow-up tool for adult patients.[10]

ECG-gated CCTA was shown to be superior in sensitivity to invasive angiography in several series.[6] The ACC/AHA 2018 Guidelines for the Management of Adults with Congenital Heart Disease recommend the use of CCTA as a screening method for diagnosis and patient management in congenital coronary anomalies of ectopic arterial origin.[11]

The indication for surgical treatment of anomalous origin of the LCx is not yet well established. The criteria for treatment are the presence of symptoms, the ventricular area that is supplied by the artery, and collateralization from the LAD and/or the RCA.[12] When surgery is indicated, ligation and bypass grafting are recommended in adults; re-implantation yields substantially better results in infants and children.[13] In this case, as the patient had angina and documented ischemia, surgery was performed.

Conclusion

CCAAs are a heterogeneous group of rare congenital abnormalities, whose manifestations vary greatly. The anomalous origin of the LCx artery from the PA is masked by the presence of collateral circulation and the relatively small area supplied by this vessel. Although most of the patients with this anomaly are asymptomatic and their physical examinations are unremarkable, they are at risk of sudden death. As such, this condition requires a high degree of clinical suspicion and CCTA is the imaging modality of choice.

Author contributions

Conception and design of the research and Writing of the manuscript: Faria B; Data acquisition and Analysis and interpretation of the data: Faria B, Calvo L, Ruivo C; Critical revision of the manuscript for intellectual content: Ribeiro S, Lourenço A.

Potential Conflict of Interest

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References

1. Pretto J, Daros C, Medeiros C, Roman R. Origem anômala da artéria coronariana circunflexa na artéria pulmonar em adulto jovem. Arq Bras Cardiol: imagem cardiovasc. 2014;27(3):212-5.
2. Harky A, Bashir M, Garner M, Hsia T. Anomalous origin of the circumflex coronary artery presenting with ventricular fibrillation cardiac arrest. BMJ Case Rep. 2017. doi:10.1136/bcr-2016-219184.
3. Silva A, Baprista MJ, Araujo E. Congenital coronary artery anomalies. Rev Port Cardiol. 2018;37(4):341-50.
4. Angelini P, Velasco J, Flamm S. Coronary anomalies: incidence,pathophysiology and clinical relevance. Circulation.2002;105(20):2449-54.
5. Peña E, Nguyen E, Merchant N, Dennie C. ALCAPA Syndrome: Not Just a Pediatric Disease. RadioGraphics. 2009; 29(2):553–65.
6. Agarwal P, Dennie C, Pena E,Nguyen E,La Bounty T, Yang B, et al. Anomalous Coronary Arteries That Need Intervention: Review of Pre- and Postoperative Imaging Appearances. RadioGraphics. 2017; 37(3) 740-53.
7. Liu B, Fursevich D, O'Dell M C, Flores M, Feranec N. Anomalous left circumflex coronary artery arising from the right pulmonary artery: a rare cause of aborted sudden cardiac death cureus. 2016:8(2):e499. DOI 10.7759/cureus.499.
8. Graidis C, Dimitriadis C, Karasavvidis V,Argyropoulou E, Economou F, George G, et al. Prevalence and characteristics of coronary artery anomalies in an adult population undergoing multidetector-row computed tomography for the evaluation of coronary artery disease. BMC Cardiovasc Disorders. 2015;15:112.
9. Garcia C, Chandler J, Russell R. Anomalous left circumflex coronary artery from the right pulmonary artery: First adult case report. Am Heart J. 1992:123(2):526-8.
10. Vizzuso A, Righi R, Zerbini M,Gamanji S, Cucchi P, Gallo F, et al. An unusual presentation of anomalous leftbcoronary artery from the pulmonary arteryb(ALCAPA) syndrome in a 70-year-old man: a case report. J Med Case Rep. 2018;12(1):308.
11. Stout K, Daniels C, Aboulhosn J,Broberg BB, Colman JM, Crum b SR, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol.2019;73(12):e1-e192.
12. Bolognesi R, Alfieri O, Tsialtas D, Manca C. Surgical treatment of the left circumflex coronary artery from the pulmonary artery in an adult patient. Ann Thorac Surg. 2003;75(5): 1642–3.
13. Aktaş D, Erdem A, Çelik N, Kamalı Z, Sarıtaş T. A rare coronary anomaly with masked diagnosis: Anomalous left circumflex artery from right pulmonary artery. Turk Kardiyol Dern Ars. 2015;43(6):551–3.

Family Screening in the Diagnosis of Short QT Syndrome after Sudden Cardiac Death as First Manifestation in Young Siblings

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Introduction

In 2000, Gussak et al.,[1] published a case series in which atrial tachyarrhythmias, syncope, and sudden cardiac death (SCD) were associated with a short QT interval, being the first to correlate all of these finding in one single study. Since then, efforts have been made to better understand the behavior of and find alternatives to treat short QT syndrome (SQTS); however, researchers face the barrier of the rarity of the disease, the difficulty in establishing diagnostic parameters, and its complex clinical manifestation. This article reports on the case of young siblings with SCD and SQTS and discusses the syndrome's diagnostic and therapeutic difficulties.

Case Report

An 18 year old boy had a sudden death during sexual intercourse. Autopsy examination was within normal. After six months, his young brother, at 11 years old, had an aborted cardiac arrest while walking home from school. He died after 9 days in a local hospital. The autopsy, once again, was inconclusive.

Their family members (Figure 1) sought out medical assistance to conduct a diagnostic investigation. Their medical history revealed the father's long-term drug addiction and the 18-year-old son. had a past history, during childhood, of syncope without prodromes, no triggered by autonomic circunstances. The 20-year-old daughter had hypothyroidism and reported palpitations, lasting seconds. The mother also reported the medical condition of hypothyroidism and her cardiac evaluation was normal. The father, the son, and the grandfather presented *pectus excavatum* and an increased arm span, without fulfilling the criteria for Marfan Syndrome. The electrocardiogram (ECG) of the father showed a QTc of 371 ms and of the living son of 323 ms (Figure 2), while the living daughter presented a QTc of 380 ms. The high resolution ECG (HR-ECG), aorta angiotomography, and of all of the first degree relatives were within normal. No atrial or ventricular arrhythmias were observed in the stresse testing or in the 24-hour Holter monitoring.

Keywords

Short QT Syndrome; Sudden Cardiac Death; Implantable Cardioverter-defibrillator; Genetic Testing; Cardiac Channelopathies.

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A Next-Generation Sequencing (NGS) test of the father was performed, and no pathogenic or possibly pathogenic variants were identified in a panel of 101 genes correlated with SCD, including SQTS (KCNH2, KCNQ1, KCNJ2, CACNA1C, and CACNB2) and Marfan (FBN1 and TGFBR).

Due to the implanted loop recording unavailability in the Brazilian Unified Health System (SUS, in Portuguese), we opted for the implantable cardioverter defibrillator (ICD) in the 18-year-old son, due to his medical history of syncopes without prodromes, associated with a family history of SCD and short QTc interval, favorable to the diagnosis of SQTS. In an 18-month follow-up, the patient presented no syncope or ICD therapy.

Discussion

SCD in young patients with structurally normal hearts, defined by autopsy examination, can presumably be considered arrhythmic, specifically due to cardiac channelopathies.[2] The main channelopathies include long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, progressive heart disease, and finally, SQTS.

Most of these disorders are associated with the gene mutations that codify the alphaform subunits of the channel pores and their interactions with auxiliary proteins, responsible for the functioning of the sodium, potassium, and calcium channels.[2] Therefore, the evaluation of family members in a context of two SCDs in young individuals with inconclusive autopsy includes an extensive clinical analysis of the survivors, along with post-mortem genetic tests.

The only relevant finding in the familiar screening, specifically in the surviving son who presented a "off-on" syncope, as well as in the father, was a short QT interval. The SQTS diagnosis is the target of debate in the literature even today. The criteria proposed by Gollob et al.,[3] in 2011, were the first to be implemented.[3] In 2015, new criteria were proposed,[4] with the SQTS diagnosed when the QTc interval $\leq$340 ms or when the QTc interval $<$360 ms, in association with the medical or family history or with the presence of pathogenic mutation. In the case explained above, the ECG of the surviving son presented a QTc of 323 ms, associated with a strong history of SCD in family members of $\leq$40 years of age, in addition to the past medical history of unexplained syncopes. In an isolated manner, a QTc interval $<$340ms is diagnosed as an SQTS and, by the Gollob score, would add up to 5 points,[3] fulfilling high-probability diagnostic criteria for SQTS. To date, we have not documented atrial fibrillation that would reinforce the diagnosis of SQTS.

Case Report

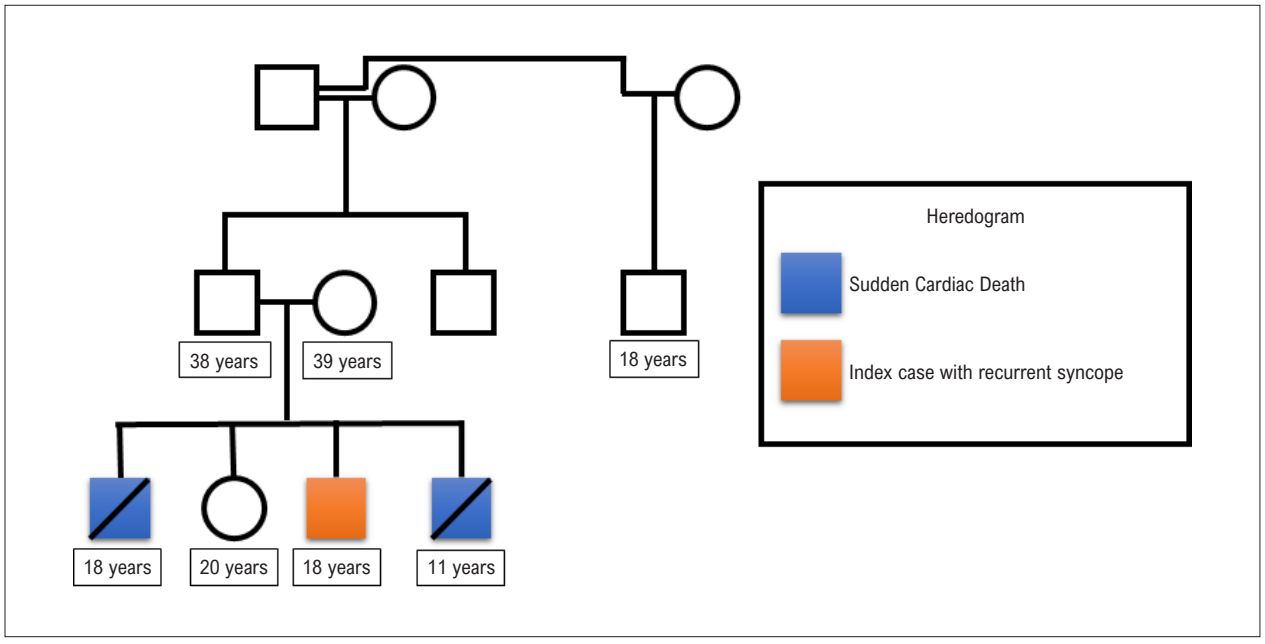

Figure 1 – *Family Heredogram, showing the index case in orange with the manifestation of syncopes. Their brothers, marked in blue, suffered sudden cardiac death at 18 years old (during sexual intercourse) and at 11 years old (walking home from school), respectively, from left to right. Sudden cardiac death defined according to Priori et al:[4] no obvious extra-cardiac cause occurred in the post-mortem exam and, therefore, an arrhythmic event is the most probable cause of death.*

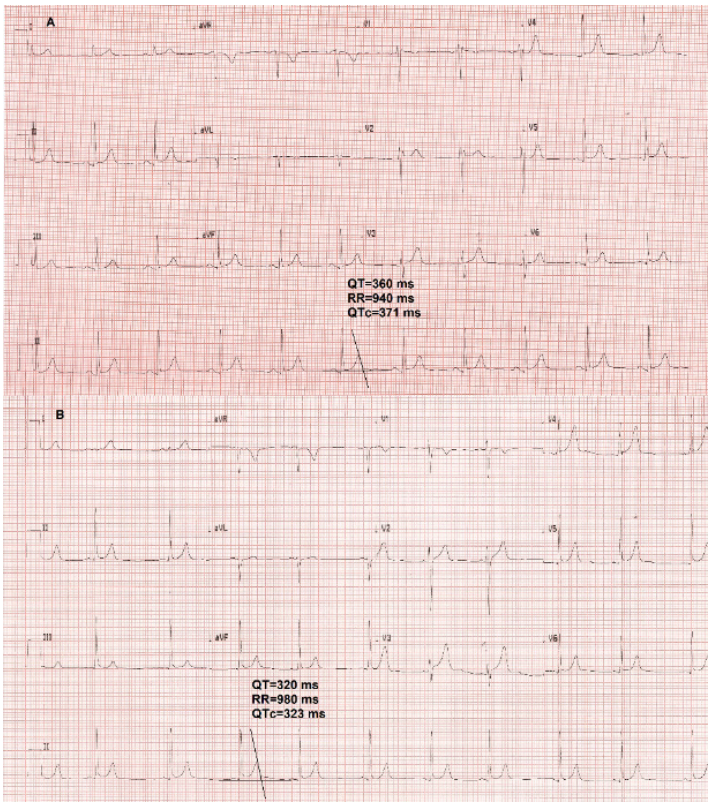

Figure 2 – *Electrocardiogram of the arrival of the patients to the health service, showing short QT intervals. A. Electrocardiogram of the father, with QTc = 371 ms. B. Electrocardiogram of the living son, with QTc = 323 ms.*

The sudden death in these two young brothers, without prior additional family medical history of SCD, suggests the presence of recessive disease, however parents were non-consanguineous. Paternity test was not performed, but the father short QTc interval and dismorphic features suggested a paternal inheritance. Another possibility is the occurrence of a de novo mutation in one of the parents, with a lighter clinical expression. The father presented a shorter QT interval than the general population average but was asymptomatic. As it is a dominant autosomal disease of incomplete penetrance and variable expressivity,[5] the father might be a silent carrier. Moreover, the death and the syncope of the survivor occurred in the second decade of life, which is more common for other channelopathies.[4] The clinical and genetic evaluation did not identify it.

The real prevalence of SQTS is doubtful due to its rarity. The short QT interval reflects accelerated repolarization, generating a dispersion of the repolarization within the heart chambers, favoring the mechanism of functional re-entrance in the atrium and ventricles, predisposing the patient to atrial and ventricular fibrillation.[6]

In channelopathies, the genetic test plays a limited role in the Brugada syndrome and in the SQTS (approximately 25%),[3,7] differently from SQTL (80%)[8] and from cathecolaminergic polymorphic ventricular tachycardia (CPVT) (90%).[9] Hence, a genetic test without the identification of pathogenic mutations in patients with SQTS does not preclude the clinical diagnosis,[3] and does not exclude the diagnosis of SQTS.

ICD has proven to be the most effective and safe treatment for SQTS patients, since it presents a high risk for SCD.[10] The ICD is recommended for patients with SQTS diagnosis who are survivors of an SCD or who have a documented spontaneous sustained ventricular tachycardia.[4] In our case, the treatment proposed was the ICD implant in the symptomatic son (with syncopal episodes) and close follow-up for the others, according to more recent recommendations, which suggest that the ICD should be considered in SQTS patients with a strong family history of SCD and evidence of short QTc as a IIb class of recommendation.[4]

Conclusion

The etiological diagnosis of SCD in young patients can be challenging, especially when there is the suspicion of sudden arrhythmic death, due to its incomplete penetrance and variable expressivity. The QT syndrome is a very rare channelopathy and, therefore, with a limited phenotypical characterization, which should be taken into consideration in a scenario of SCD of unknown etiology in young patients. Its diagnosis is based only on the ECG, the medical and family history, and genetics. The ICD is the main therapeutic tool, proving to be an effective and safe treatment for the reduction of mortality in these patients.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Athayde GAT, Olivetti NQS, Darrieux FCC, Sacilotto L, Scanavacca MI; Acquisition of data: Athayde GAT, Olivetti NQS, Pessente GD; Analysis and interpretation of the data: Athayde GAT, Darrieux FCC, Sacilotto L, Pessente GD; Writing of the manuscript: Athayde GAT, Darrieux FCC, Sacilotto L.

Potential Conflict of Interest

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References

1. Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology. 2000;94(2):99-102.
2. Gray B, Ackerman MJ, Semsarian C, Behr ER. Evaluation After Sudden Death in the Young: A Global Approach. Circ Arrhythm Electrophysiol. 2019 Aug;12(8):e007453.
3. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. J Am Coll Cardiol. 2011 Feb 15;57(7):802-12.
4. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac Death. The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J. 2015 Nov 1;36(41):2793-867.
5. Giudicessi JR, Ackerman MJ. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. Transl Res. 2013;161(1):1-14.
6. Tse G, Chan YW, Keung W, Yan BP. Electrophysiological mechanisms of long and short QT syndromes. Int J Cardiol Heart Vasc. 2016 Nov 26;14:8-13.
7. Yamagata K, Horie M, Aiba T, Ogawa S, Aizawa Y, Ohe T, et al. Genotype-Phenotype Correlation of SCN5A Mutation for the Clinical and Electrocardiographic Characteristics of Probands With Brugada Syndrome: A Japanese Multicenter Registry. Circulation. 2017 Jun 6;135(23):2255-70.
8. Giudicessi JR, Ackerman MJ. Genotype- and phenotype-guided management of congenital long QT syndrome. Curr Probl Cardiol. 2013;38(10):417-55.
9. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. Europace. 2018;20(3):541-7.
10. Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol. 2014 Apr 8;63(13):1300-8.

Dilated Cardiomyopathy: New Variant in the Filamin-C Gene

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Case Report

This is a case report of a 50-year-old male patient who came to the emergency department of our institution with a complaint of progressive dyspnea for a week. The patient reported a previous history of fibromyalgia and denied other comorbidities, such as myocardial infarction or stroke. He denied current smoking, but occasionally used alcohol. His routine medications included duloxetine, pregabalin and zolpidem. His mother and cousins had a history of heart failure due to idiopathic dilated cardiomyopathy, with no other cardiovascular comorbidities in his family history.

On physical examination, he showed stable vital signs, crackles in the lung bases and edema in the lower limbs. Cardiac auscultation showed normal heart sounds. The electrocardiogram showed sinus rhythm, with no signs of atrial or ventricular overload (Figure 1). The chest radiography revealed cardiomegaly. The laboratory tests showed an NT-pro-BNP of 2335 pg/mL, and the series of ultrasensitive T-troponins revealed consecutive values of 0.074 ng/mL and 0.072 ng/mL (reference value < 0.014 ng/mL).

The patient was admitted for investigation. His echocardiogram revealed dilated heart disease, an ejection fraction of 37.1%, with diffuse hypokinesia of the left ventricular walls. A cardiac catheterization revealed coronary arteries without significant stenoses. Cardiac magnetic resonance imaging showed an ejection fraction of 27%, with global systolic dysfunction and absence of fibrosis, suggesting an idiopathic dilated cardiomyopathy. A 24-hour Holter was also performed, which did not show ventricular arrhythmias during the monitoring period.

After the patient was compensated with measures for heart failure at the institution, the patient underwent genetic testing for hereditary cardiomyopathies, and the genes listed in Table 1 were analyzed. The analysis was performed with genomic DNA extraction and fragmentation followed by identification, capture and enrichment of the regions of interest. The result of such examination revealed a likely pathogenic variant c.1595delIT in heterozygosity in the Filamin-C gene - *FLNC*. This gene has been associated with a number of heart diseases, such as: (1) familial hypertrophic cardiomyopathy, of undetermined inheritance; (2) familial restrictive cardiomyopathy,[1] of autosomal dominant inheritance [OMIM: 617047]; (3) distal myopathy, of autosomal dominant inheritance [OMIM: 614065] and (4) myofibrillar myopathy, of autosomal dominant inheritance [OMIM: 609524].[2] The identified variant is characterized by the deletion of a nucleotide that, predictably, leads to a change in the reading frame (frameshift) by promoting the replacement of the amino acid valine at codon 532 by a glycine, with consequent early stop of protein translation 16 positions ahead (p.(Val532Glyfs*16)) resulting in a truncated protein. The variant is absent in the population frequency databases (Exome Aggregation Consortium – ExAC and The Genome Aggregation Database - GnomAD),[3] it has never been described in the medical literature and has never been observed in the ClinVar database.[4] Filamin-C is a protein expressed mainly in cardiac and skeletal muscle, being encoded by the *FLNC* gene. The protein is responsible for the crosslinking of actin filaments in orthogonal networks in the cortical cytoplasm of cells and participates in the anchoring of membrane proteins to the actin cytoskeleton.[5] Due to these functions and its expression predominantly in the cardiac muscle, the *FLNC* gene has been related to dilated or arrhythmogenic cardiomyopathies.[6] According to the metrics available in the GnomAD database, the *FLNC* gene does not tolerate loss-of-function alterations. Furthermore, frameshift mutations have been related to arrhythmogenic/dilated cardiomyopathy diseases.[7] According to the criteria of the American College of Medical Genetics and Genomics – ACMG,[8] this found variant is classified as likely pathogenic.

The patient showed clinical improvement with the treatment and was discharged with furosemide, sacubitril-valsartan and carvedilol. Genetic counseling was recommended to the family, since first-degree relatives of individuals with heterozygous pathogenic variants of the *FLNC* gene have a 50% probability of being carriers of the same variant. Despite the risk of major ventricular arrhythmias, in this specific case, the patient chose not to receive an implantable cardioverter defibrillator (ICD) at first. Regarding this aspect of sudden cardiac death prevention, we recall that the DANISH[9] study showed no benefits in terms of mortality reduction in patients with heart failure with reduced ejection fraction of nonischemic etiology. However, it is important to emphasize that, according to the guidelines of the Brazilian Society of Cardiology, patients with heart failure of non-ischemic etiology, with an ejection fraction ≤ 35% may have an indication for an ICD, including for primary prophylaxis (Class IIa).[10] In addition, the Heart Rhythm Journal guidelines from 2019[11] mention that in patients with arrhythmogenic cardiomyopathy

Keywords

Cardiovascular Diseases/physiopathology; Cardiomyopathy Dilated/genetics; Heart Failure; Filamins.

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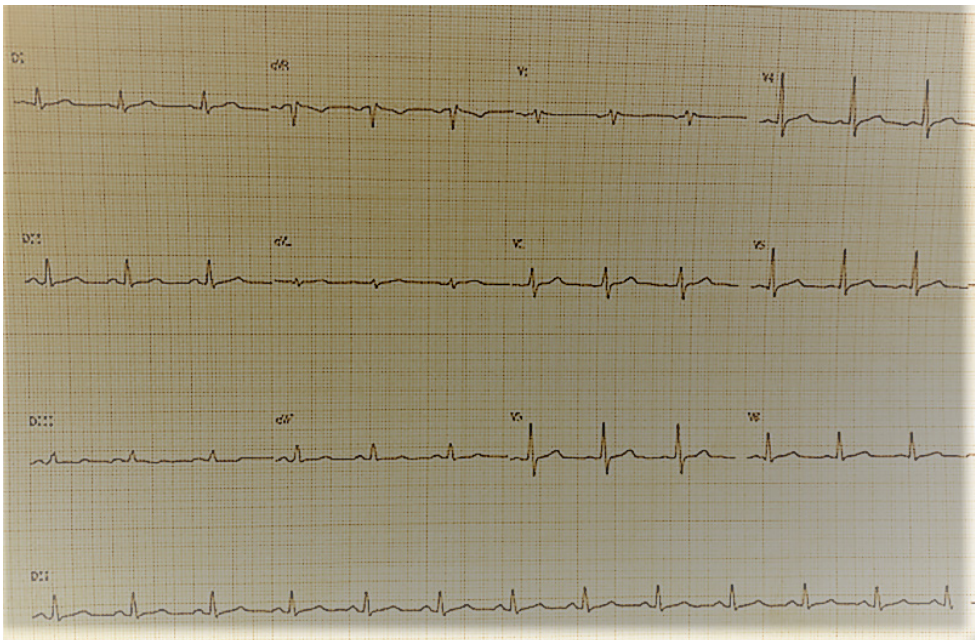

Figure 1 – *Electrocardiogram.*

Table 1 – Analyzed Genetic Panel

ABCC9; ACTC1; ACTN2; ANK2; BAG3; BRAF; CALR3; CAV3; CBL; CRYAB; CSRP3; DES; DSC2; DSG2; DSP; DTNA; EMD; EYA4; FHL1; FKTN; FLNC; GAA; GLA; HRAS; JPH2; JUP; KRAS; LAMP2; LDB3; LMNA; MAP2K1; MAP2K2; MYBPC3; MYH6; MYH7; MYL2; MYL3; MYLK2; MYOT; MYOZ2; NEBL; NEXN; NRAS; PKP2; PLN; PRKAG2; PSEN1; PSEN2; PTPN11; RAF1; RBM20; RPSA; RYR2; SCN5A; SGCD; SHOC2; SLC25A4; SOS1; SPRED1; SYNE1; SYNE2; TAZ; TCAP; TGFB3; TMEM43; TMPO; TNNC1; TNNI3; TNNT2; TPM1; TRIM63; TTN; TTR; VCL.

linked to a mutation in the *FLNC* gene and ejection fraction < 45 %, the ICD implantation is a therapy to be considered (Class IIa/C). This would be a more specific recommendation, as it takes into account the genetic characteristic of the patient's pathology. We feel that the decision as to whether or not implant an ICD should take the literary evidence into account, but that it should also be individualized, always in compliance with the patient's wishes and their quality of life and life expectancy.

In view of this report, we consider the importance of establishing the etiology for cases of presumed idiopathic heart failure, including genetic research, as there is the possibility that a causal factor for a patient's disease may be found, a patient who often may be deprived of a more specific diagnosis. Evidently, there are certain difficulties in offering genetic screening, such as the low availability of the test in many places, high price and the lack of dissemination of genetic knowledge among general cardiologists. It should be noted that genetics is a field still undergoing great development, in which certainly many mutations and pathogenic variants still need to be catalogued, allowing much more precise advice to be provided to patients and their families, once the origin of the pathology in question has been determined.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Frasson MZ e Jaeger CP

Potential Conflict of Interest

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

Sources of Funding

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References

1. Brodehl A, Ferrier RA, Hamilton SJ, Greenway SC, Brundler MA, Yu W, et al. Mutations in FLNC are associated with familial restrictive cardiomyopathy. Human Mutation. 2016; 37(3):269-79. doi:10.1002/humu.22942
2. OMIN Online Mendelian Inheritance in man: an online catalog of human genes and genetic disorders: update June 23, 2021. [Internet] [Cited in 2021 June] Available from:omnium.org.
3. The Genome Aggregation Database (gnomAD). [Internet] [Cited in 2021 June 21] Available from: https://gnomad.broadinstitute.org/.
4. ClinVar. Clin Var aggregates information about genomic variation and its relationship to human health. [Internet]. [Cited in 2021 June 23]. Available from: ncbi.nlm.nih/clinvar/
5. Maestrini E, Patrosso C, Mancini M, Rocchi m, Repetto M, Villa A, et al.Mapping of two genes encoding isoforms of the actin binding protein ABP-280, a dystrophin like protein, to Xq28 and to chromosome 7. Hum Molec Genet.1993;2(6):761-6. doi:10.1093/hmg/2.6.761.
6. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, et al. Truncating *FLNC* mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. J Am Coll Cardiol. 2016; 68(22):2440~-51. doi:10.1016/j.jacc.2016.09.927.
7. Bienengraeber M, Olson TM, Selivanov VA, Kathmann EC, O'Cochlain F, Gao F, et al. ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic KATP channel gating. Nat Genet. 2004; 36:382-7.
8. Richards S, Aziz N, Bale S, Beck D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17(5):405-24 doi:10.1038/gim.2015.30.
9. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016; 375(13):1221-30
10. Sociedade Brasileira de Cardiologia. Diretriz de Insuficiência Cardíaca. Diretriz de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018; 111:436-539.
11. Towbin JA, McKenna WJ, Abrams DJ. HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: executive summary. Heart Rhythm. 2019; 16(11):e373–e407. doi:10.1016/j.h

Life-Threatening Ventricular Arrhythmia Induced by Atrial Tachycardia in a Child with an SCN5A Mutation

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Introduction

Mutations in the SCN5A gene, encoding the cardiac Na+channel, can result in several life-threatening arrhythmias. These mutations have proven to be causative for inherited and primarily electrical diseases, including Brugada Syndrome (BrS), Long QT Syndrome, and other cardiac conduction disturbances.[1,2] BrS, the most reported condition in this group of disorders, has typically been described in adult populations and related to approximately 20% of all sudden deaths (SD) in patients with apparently normal hearts.[3-5] Therefore, few reports have shown significant arrhythmic events (AE) caused by this mutation in childhood.[6]

Atrial arrhythmias, as well as sick sinus syndrome (SSS), may be related to Na+channel abnormalities. In BrS, atrial arrhythmias are being diagnosed in up to 38% of patients and are related to worse prognosis.[7]

Case Report

A 2-year-old boy, with no cardiac structural anomalies detected in transthoracic echocardiogram and magnetic resonance imaging (MRI) exams, was admitted twice to the hospital with a typical pattern of atrial flutter (AFL), which was reverted by electrical cardioversion. After the last episode, he was discharged on 3 mg/Kg amiodarone daily. The 12-lead ECG showed a normal QT (390 – 410 ms) and QTc (413 – 440 ms) interval, slightly prolonged PR interval (200 ms) and negative T waves in right precordial leads (Figure 1).

A 24h-Holter obtained three months later, after amiodarone withdrawal, recorded a syncopal episode – agonal respiration, cyanosis, convulsive movements – while sleeping on his mother's lap. The ECG strap showed a wide RR variation with intermittent atrial tachycardia (AT) that became sustainable with a 1:1 atrioventricular (AV) conduction pattern with a progressive QRS complex enlargement, follow by polymorphic ventricular tachycardia (VT), ventricular fibrillation (VF), and 30 seconds of asystole; the sinus rhythm was spontaneously restored (Figure 2).

Keywords

Cardiac Arrhythmia; Brugada Syndrome; Syncope; Child.

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A wide QRS tachycardia recurred in the intensive unit when 1 mg of adenosine IV was administered, unmasking an AFL before a new electrical cardioversion.

An electrophysiological study (EPS) was performed under deep intravenous sedation (ketamine 0.2 mg/kg and continuous propofol infusion) with two 5F multipolar catheters. An increased HV interval (63 ms) was detected and cavo-tricuspid isthmus (CTI) dependent AFL was induced by programmed atrial pacing. Linear radiofrequency (RF) catheter ablation was performed to achieve a bidirectional CTI conduction block. Programmed stimulation (2 cycles and 2 extra-stimulus) did not induce ventricular arrhythmias.

A heterozygous pathogenic SCN5A gene mutation - c.362G>A p. (Arg121Gln) variant in exon 3 of the SCN5A (NM_198056) gene, compatible with BrS, was identified by genetic tests.

The patient is an only child, with no family history of arrhythmias, syncope, or SD. His 30-year old mother had a normal ECG and negative genetic panel. His father, an asymptomatic 34-year old man, showed a first-degree AV block (PR = 220 ms) and typical Type I BrS-pattern on ECG (Figure 1), an abnormal HV interval (73 ms) without inducible ventricular arrhythmias, and the same SCN5A mutation.

After an 18-month follow-up without symptoms or AE, a new syncopal episode occurred, triggered by fever. No new electrocardiographic changes were observed, neither in rest ECG or Holter monitoring. At this time, a transvenous single chamber implantable cardioverter defibrillator (ICD) was implanted. In a 6-month follow-up, no device related complications, AE, or therapies were observed.

Discussion

The present study described a case of a 2-year old boy with an apparently normal heart with life-threatening AE triggered by a sustained AT. This uncommon event leads us to suspect of a possible channelopathy. SCN5A mutation was detected in the infant and in his father, who presented a Type-I ECG BrS pattern.

Since the initial description of the disease in 1992, which includes three children,[3] the published data on the BrS pediatric population is very limited. The typical ECG pattern of BrS (type I - ST coved elevation in right precordial leads) and clinical manifestations are not usually seen in young children. The age of onset symptoms and AE range from 40 to 50 years of age is rare in pediatrics or the elderly.[5] In SABRUS (Survey on Arrhythmic Events in Brugada Syndrome), which includes 678 BrS-patients, the vast majority (94.2%) of the patients were 16-70 years of age at the time of first AE,

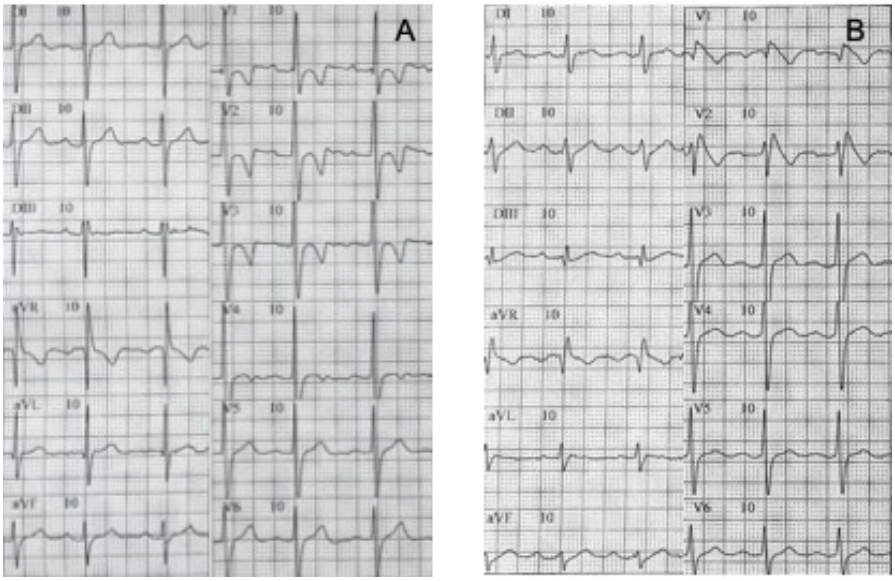

Figure 1 – *Spontaneous 12-lead ECG: (A) – Child; (B) – Father.*

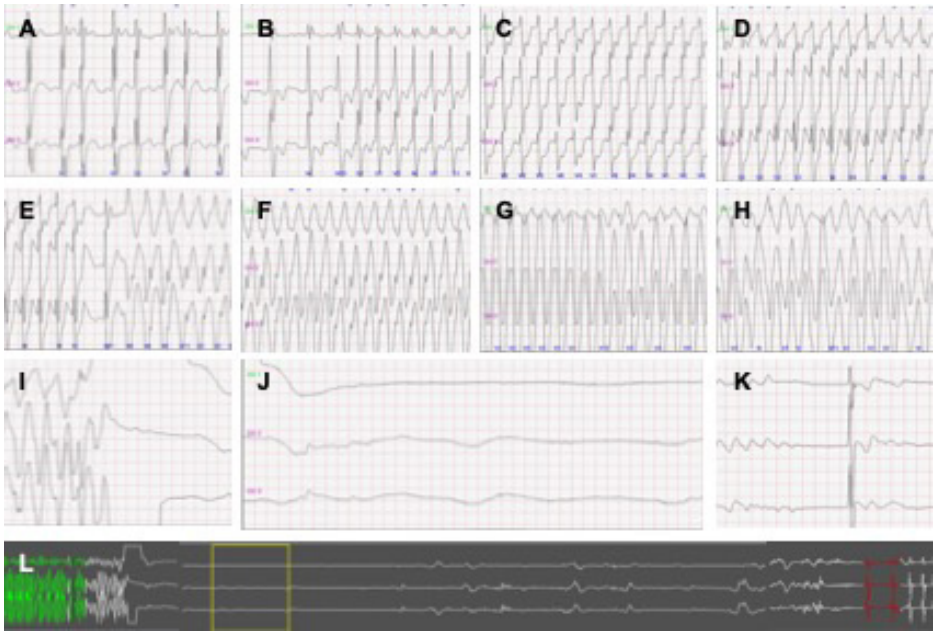

Figure 2 – *Syncopal event recorded by 24-Holter. A, B – variable AV conduction AT/AFL, with a narrow QRS; C, D – The AV conduction became 1:1 with progressive QRS enlargement; E, F, G, H – sustained wide polymorphic VT and VF; I, J, K – the VF is followed by 30 seconds of asystole, with spontaneous sinus rhythm recovery; L – long strap of total asystole.*

while pediatric (<16 years) and elderly patients (>70 years) comprised 4.3% and 1.5%, respectively.[8] Syncope is usually the first clinical manifestation in 14% to 21% and SD in 5% to 7% in pediatric BrS-patients, but the majority are asymptomatic.[9,10] The significant male predominance observed in adults is not reported in prepubertal children, possibly due to hormonal influences, particularly testosterone levels.[5,11]

The AE occurred during sleep in our patient, as is often described in BrS-patients, suggesting an association with bradycardia and possibly vagal modulation. In the present case, the syncopal arrhythmic event registered on a 24h-Holter – VT/VF – was triggered by an AT with a fast AV conduction during sleep, suggesting some vagal influence. Fever is also known to be a common arrhythmic trigger (and may unmask the typical ECG pattern),[6,12] and was seen in our patient's second syncopal event. There are a few reports in the literature regarding life-threatening arrhythmias and SD in very young BrS-child patients, but none clearly document a direct participation of an AT on VT/VF induction.

Risk stratification in young patients remains challenging. Type I ECG pattern, syncope, SD, sinus node dysfunction, atrial arrhythmias, conduction abnormalities, and ventricular arrhythmias induced on EPS have been described as predictors of life-threatening events.[9,10]

The presence of an SCN5A mutation has not been proven to be risk marker in any large study. However, SCN5A compound mutations seem to lead to more severe phenotypes.[13]

Although this child, since the index event, has already met indication criteria for ICD, the potential risks of an ICD in a very young child (inappropriate therapies and lead complications) were taken into account to extend the implant. Moreover, the possibility to ablate the VF-trigger (AFL) led us to believe in a lower chance of early recurrence.

Conclusion

The presented case demonstrates a severe presentation of an AE in a toddler, who was diagnosed with a SCN5A gene mutation. The VT/VF trigger circuit (AFL) was ablated, resulting in symptom relief over a long period of time, but an ICD was implanted due to syncope recurrence, highlighting how complex a presentation and evolution of some channelopathies can be in a pediatric population.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Silva MA; Acquisition of data: Silva MA, Elias Neto J, Futuro GMC, Merçon ES, Vasconcelos D, Kuniyoshi R; Writing of the manuscript: Silva MA, Elias Neto J; Critical revision of the manuscript for intellectual content: Silva MA, Elias Neto J, Futuro GMC, Merçon ES.

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References

1. Zaklyazminskaya E, Dzemeshkevich S. The Role of Mutations in the SCN5A Gene in Cardiomyopathies. Biochim Biophys Acta. 2016;1863(7 Pt B):1799-805. doi: 10.1016/j.bbamcr.2016.02.014.
2. Remme CA. Cardiac Sodium Channelopathy Associated with SCN5A Mutations: Electrophysiological, Molecular and Genetic Aspects. J Physiol. 2013;591(17):4099-116. doi: 10.1113/jphysiol.2013.256461.
3. Brugada P, Brugada J. Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome. A Multicenter Report. J Am Coll Cardiol. 1992;20(6):1391-6. doi: 10.1016/0735-1097(92)90253-j.
4. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(9):1046-1059. doi: 10.1016/j.jacc.2018.06.037.
5. Brugada P. Brugada syndrome: More than 20 Years of Scientific Excitement. J Cardiol. 2016;67(3):215-20. doi: 10.1016/j.jjcc.2015.08.009.
6. Chockalingam P, Rammeloo LA, Postema PG, Hruda J, Clur SA, Blom NA, et al. Fever-induced Life-threatening Arrhythmias in Children Harboring an SCN5A Mutation. Pediatrics. 2011;127(1):e239-44. doi: 10.1542/peds.2010-1688.
7. Francis J, Antzelevitch C. Atrial Fibrillation and Brugada Syndrome. J Am Coll Cardiol. 2008;51(12):1149-53. doi: 10.1016/j.jacc.2007.10.062.
8. Milman A, Andorin A, Gourraud JB, Sacher F, Mabo P, Kim SH, et al. Age of First Arrhythmic Event in Brugada Syndrome: Data From the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 Patients. Circ Arrhythm Electrophysiol. 2017;10(12):e005222. doi: 10.1161/CIRCEP.117.005222.
9. Corcia MCG, Sieira J, Pappaert G, Asmundis C, Chierchia GB, Sarkozy A, et al. A Clinical Score Model to Predict Lethal Events in Young Patients (≤19 Years) With the Brugada Syndrome. Am J Cardiol. 2017;120(5):797-802. doi: 10.1016/j.amjcard.2017.05.056.
10. Andorin A, Behr ER, Denjoy I, Crotti L, Dagradi F, Jesel L, et al. Impact of Clinical and Genetic Findings on the Management of Young Patients with Brugada Syndrome. Heart Rhythm. 2016;13(6):1274-82. doi: 10.1016/j.hrthm.2016.02.013.
11. Mariani S, Musumeci B, Basciani S, Fiore D, Francia P, Persichetti A, et al. Lack of Influence of the Androgen Receptor Gene CAG-Repeat Polymorphism on Clinical and Electrocardiographic Manifestations of the Brugada Syndrome in Man. Clin Med Insights Cardiol. 2012;6:145-52. doi: 10.4137/CMC.S10553.
12. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, et al. Ionic Mechanisms Responsible for the Electrocardiographic Phenotype of the Brugada Syndrome are Temperature Dependent. Circ Res. 1999;85(9):803-9. doi: 10.1161/01.res.85.9.803.
13. Sacilotto L, Epifanio HB, Darrieux FC, Wulkan F, Oliveira TG, Hachul DT, et al. Compound Heterozygous SCN5A Mutations in a Toddler - Are they Associated with a More Severe Phenotype? Arq Bras Cardiol. 2017;108(1):70-73. doi: 10.5935/abc.20170006.

The Effect of Respiratory Protective Surgical Mask on Physiological Markers of Endurance Performance in a Recreational Runner

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Introduction

The advent of the Coronavirus 19 (COVID-19) pandemic, which has quickly spread worldwide, has raised the attention regarding the use of respiratory protective face masks (PFM) not only by healthcare personnel, but also the general population.[1] In this context, wearing a PFM during physical exercise in an external environment can reduce COVID-19 infection risks. On the other hand, the use of PFM can increase the subjective perception of breathing difficulty through the formation of microclimates inside the face mask (i.e., temperature and humidity) and airflow restriction.[2]

In recent years, the number of amateur runners has significantly increased among many populations around the world, as running can be performed with minimal equipment, and by a broad variety of people.[3] Interestingly, during endurance exercise, the adaptability of the cardiorespiratory system is of paramount importance, as it increases both convective and diffusive oxygen transport, thus enabling the body to meet the demands for oxygen, substrate delivery, and carbon dioxide removal.[4] Moreover, the so-called physiological markers of endurance performance, such as ventilatory anaerobic threshold, respiratory compensation point, running economy, and maximal oxygen uptake, also seem to be important in determining absolute exercise intensity (i.e., pace, power output).[5]

In this light, it is important to have a clear understanding of whether or not the use of a PFM affects physiological markers of endurance performance during running. Therefore, our case-study evaluated the effect of wearing a PFM on 1) physiological markers of endurance performance and 2) cardiorespiratory response during exercise in a recreational runner.

Keywords

Coronavirus-19; Pandemics; Facial Mask; Respiratory Protective Devices; Resistance Performance; Physical Activity; Population Education; Exercise; Oxygen Consumption; Coronavirus-19 Infection.

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Case Report

The volunteer who participated in this case study was a healthy 28-year-old male runner with 10 years of half-marathon running experience. In the last three months, he ran an average of 35 kilometers per week with a frequency of 3-4 weekly sessions. The participant had no experience with the practice of aerobic exercise while wearing a protective face mask. The study was carried out after informed consent from the participant. The study was approved by the Research Ethics Committee of the Federal University of Piauí, Teresina, Brazil under protocol number 4.429.909.

Laboratory Assessment

This investigation was carried out in one week and consisted of 2 phases. In the first phase, the volunteer performed the running tests while wearing a PFM and no mask (NM) in the second phase. The tests were performed at the same time of day, and with an interval of at least 48 hours between the tests. The runner underwent 1) a pulmonary function test (PFT),[6] 2) a cardiorespiratory exercise test (CPET) to assess ventilatory thresholds and maximal oxygen consumption,[7] and 3) a progressive square-wave test (PSWT) to evaluate both cardiorespiratory demands and running economy.[8]

The spirometer mask was placed over the PFM and fixed with head straps in a leak-proof manner (Figure 1). The fitting was thoroughly checked for the absence of leakage by the investigators and the volunteer. The correct fitting and leak tightness were confirmed before each test was started.

PFM. In this study, a disposable non-woven COVID-19 type II surgical mask was used. Its structure comprises a non-woven fabric layer, filter material (melt-blown fabric), nose clip, and mask belt. The mask is rectangular in shape and contains three layers.[9]

PFT. The pulmonary function test measurement was carried out before the CPET, according to American Thoracic Society recommendations.[10]

CPET. The cardiorespiratory exercise test was conducted using a programmable treadmill (Inbramed model ATL, Brazil) in order to determine maximal oxygen consumption (VO_2 max), ventilatory anaerobic threshold (VAT), and the respiratory compensation point (RCP).[7] The exercise workload (speed) was increased every one minute to complete the incremental part of the exercise test, which lasted between 8 and 15 minutes. The starting speed in the graded exercise test was 7 km/h. Gas exchange and ventilatory variables were measured continuously breath-by-breath during the gas exchange test,

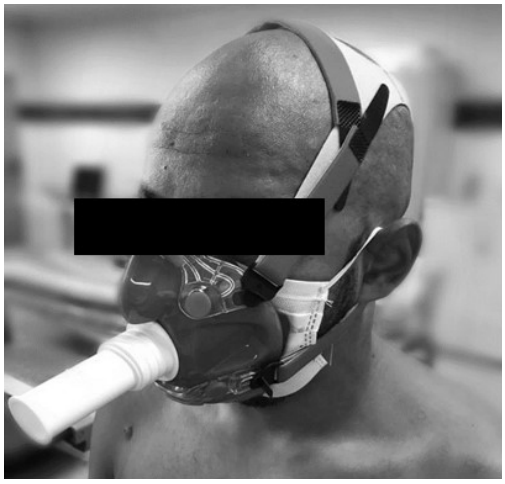

Figure 1 – *Fitting of the spirometer mask to the protective face mask.*

using a metabolic analyzer system (Ergoestik Geratherm®, Germany). The following criteria were used to define maximal effort: 1) participant demonstrated subjective evidence of exhaustion (perceived exertion, i.e., Borg scale above 17); and either 2) peak heart rate (HR) ≥90% age-predicted maximum or 3) maximal respiratory exchange ratio (RER) ≥1.10.[11]

PSWT. 24 hours after the CPET, the runner underwent a PSWT to determine both the running economy (RE) and cardiorespiratory response in steady-state condition at three exercise domains: 1) at 80% VAT, 2) at VAT, and 3) at RCP.[8] Each intensity domain lasted five minutes. The RE was calculated in terms of oxygen cost to cover a given distance using the proposed equation: RE (ml O_2.kg^{-1}.km^{-1}) = VO_2 (ml .kg^{-1}.h^{-1}) x 60 / speed (Km. h^{-1}).[12] The rating of perceived exertion (RPE) was used in both CPET and PSWT with the 15-point (6-20) Borg scale.[13]

Results

PFT. The runner showed similar values for lung volumes and airflow resistance (Table 1) in both PFM and NM conditions. However, the recreational runner demonstrated lower values of peak expiratory flow rate (PEFR) while wearing the PFM when compared to NM (Δ%=-25.0; Table 1).

CPET. For both conditions, our data showed similar values for VO_2 max, peak HR, and O_2 pulse. However, the recreational runner presented lower VVO_2 max, pulmonary ventilation (VE), and respiratory rate (RR) while wearing the PFM (Δ%=-10.5, -17.6, and -24.0, respectively; Table 1). On the other hand, our results showed higher volume tidal (VT) values with face mask use (Δ%=-10.0, Table 1).

Regarding ventilatory thresholds, the volunteer demonstrated similar speed values for both conditions. However, our results showed differences in VO_2 (mL.kg^{1}. min^{1}and L.min^{1}) and HR values (Table 1).

The cardiorespiratory response during CPET is shown in Figure 2. With respect to VE/VO_2, the runner demonstrated lower values while wearing PFM when compared to NM. (Figure 2A). A similar finding was observed for the RR/VT ratio (Figure 2B). By contrast, the volunteer demonstrated higher HR response while wearing the PFM compared to NM (figure 2C). Moreover, a similar response was observed in O_2 pulse for both conditions (Figure 2D).

PSWT. The recreational runner showed greater values for RE, VO_2 and HR while wearing the PFM (Figures 3A, B, and D, respectively). However, our data demonstrated lower values of VE while wearing the PFM compared to NM (Figure 3C).

RPE. Our results showed that RPE during the CEPT was greater while wearing the PFM when compared to the control condition (Δ=1 point; at speeds= 9,10,13,14,15,16, and 17 km/h; Figure 4A). Likewise, during PSWT, the participant showed higher RPE levels while wearing the PFM for both VAT (Δ=2 points) and RCP (Δ=2 points).

Discussion

Our data suggest that the use of a protective face mask affected the exercise tolerance and running economy in a recreational runner. It has already been reported that both cardiopulmonary exercise capacity and comfort are reduced by surgical masks and highly impaired by FFP2/N95 face masks in healthy subjects.[14] Moreover, it has been observed that wearing a surgical mask does not affect cardiopulmonary function capacity during pedaling exercise.[15] However, to the best of our knowledge, this is the first case study to specifically evaluate the effect of a protective face mask on physiological markers of endurance performance in a recreational runner.

Interestingly, a self-paced running intensity is dependent on both psychological and physiological markers of endurance exercise.[5,16] In the present case study, our results showed a similar response to both VO_2 max and ventilatory thresholds when wearing a face mask. On the other hand, the recreational runner showed lower speed at VO_2 max while wearing the PFM. Importantly, our findings suggest that, although the ability of oxygen transport and use is preserved, the runner presented lower exercise tolerance. It is important to note that the participant also demonstrated a worsening in RE while wearing PFM, which suggests greater oxygen demands during running when compared to the NM condition.

Another interesting point is how the ventilatory response adapts to the use of a protective face mask during CPET and PSWT. During physical exercise, there is an increase in metabolic rate and, consequently, in ventilatory demands. It is also worth noting that the runner demonstrated lower ventilatory response during exercise with the use of PFM. More specifically, our results demonstrated lower values for the VE/VO_2 ratio, suggesting greater ventilatory efficiency with PFM use. However, despite the improvement in the ventilatory efficiency, the volunteer showed greater respiratory discomfort wearing PFM.

Based on the above findings, the following question emerges: what physiological mechanisms underlie respiratory discomfort with wearing PFM? In fact, we suggest that factors associated with an increase in airflow impedance may be related. In this context, our results demonstrated lower levels of PEFR and VE at the peak of the exercise. Furthermore,

Table 1 – Physical and Cardiorespiratory parameters

Physical measurements			
Age (years)	28.0		
Weight (kg)	81.0		
Height (cm)	175.0		
Pulmonary Function Test	**PFM**	**NM**	**Δ%**
FVC (L)	4.3	4.4	**0.0**
FEV_1 (L)	4.0	4.1	**0.0**
FEV_1 /FVC (%)	92.3	92.3	**0.0**
PEFR (L/s)	6.9	9.2	**25.0**
Cardiorespiratory Exercise Test			
VO_2 max (mL.kg¹.min¹)	45.5	45.6	**0.0**
VO_2 max (L.min¹)	3.69	3.71	**0.0**
VVO_2 max (km/h)	17.0	19.0	**10.5**
Peak RER (Units)	1.21	1.18	**0.02**
Peak HR (bpm)	184	185	**0.0**
Peak O_2 pulse (ml/bpm)	20.3	20.1	**0.0**
VE max (L.min¹)	116.2	141.1	**17.6**
RR (b.min¹)	57	75	**24.0**
TV (L.min¹)	2.1	1.9	**10.0**
Ventilatory anaerobic threshold			
VO_2 (mL.kg¹.min¹)	30.5	28.5	**0.07**
VO_2 (L.min¹)	2.45	2.31	**0.06**
Speed (km/h)	11.0	11.0	**0.0**
HR (bpm)	163	154	**0.06**
Respiratory compensation point			
VO_2 (mL.kg¹.min¹)	34.9	32.7	**0.06**
VO_2 (L.min¹)	2.82	2.65	**0.06**
Speed (km/h)	13.0	13.0	**0.0**
HR (bpm)	174	165	**0.05**

Symbols and abbreviations: PFM: protective face mask; NM: no mask; FVC: functional vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_1/FVC: forced expiratory volume in 1 second to functional vital capacity ratio; PEFR: peak expiratory flow rate; VO_2 max: maximal oxygen uptake; VVO_2: the speed at maximal oxygen uptake; RER: respiratory exchange ratio; HR: heart rate; VE: pulmonary ventilation; RR: respiratory rate; TV: tidal volume; L: liters; L/s: liters per seconds; km/h: kilometers per hour; bpm: beats per minute.

regarding breathing patterns, the runner showed a lower RR/VT ratio when wearing a face mask. Importantly, the RR/VT ratio is used to indirectly evaluate mechanical/ventilatory interactions during exercise.[17] In this sense, for a given ventilatory output, the runner increased the tidal volume more sharply than the respiratory rate, consequently increasing the inspiratory muscle effort and, therefore, the sense of respiratory effort.

Finally, our data suggested an association between inspiratory muscle effort and increased both oxygen demands and heart rate response during exercise with face mask use. In this context, Harms et al.[18] demonstrated that inspiratory muscle unloading during aerobic exercise was associated with reduced VO_2 and dyspnea ratings. For instance, there is evidence that greater inspiratory effort during exercise is related to increased activation inspiratory muscle metaboreflex and, thus, sympathetic outflow.[19] Notably, in the same study,[19] the authors observed that five weeks of inspiratory muscle training was capable of increasing inspiratory muscle strength and attenuating the rise in heart rate during exercise.

Practical Applications

The present case study indicates that both exercise tolerance and running economy are worsened when the recreational runner wore a protective face mask. Additionally, our findings suggest a possible association

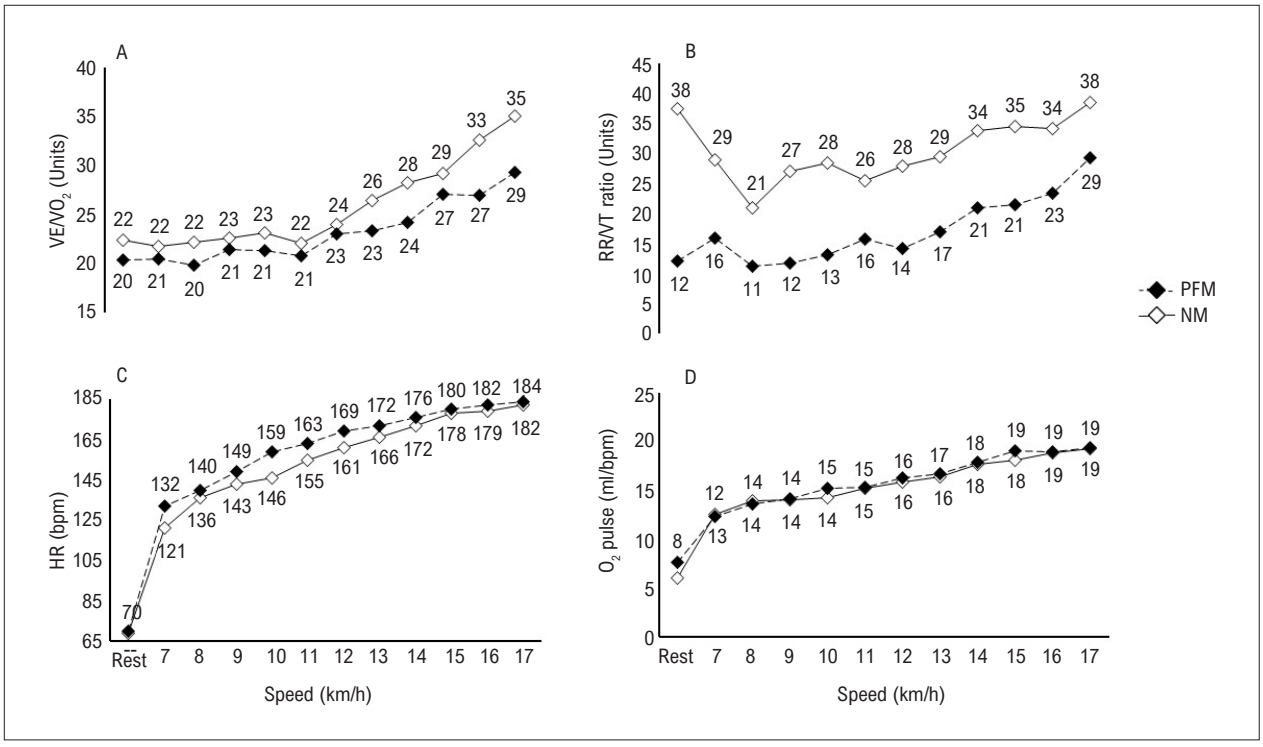

Figure 2 – *Cardiorespiratory response during CPET in a recreational runner with and without PFM use. Panel A= VE/VO$_2$; Panel B= RR/VT ratio; Panel C= HR; Panel D= O$_2$ pulse. PFM: protective face mask; NM: no mask; CPET: cardiorespiratory exercise test; VE/VO$_2$: ventilatory equivalent for oxygen; RR/VT ratio: respiratory rate to volume tidal ratio; HR: heart rate.*

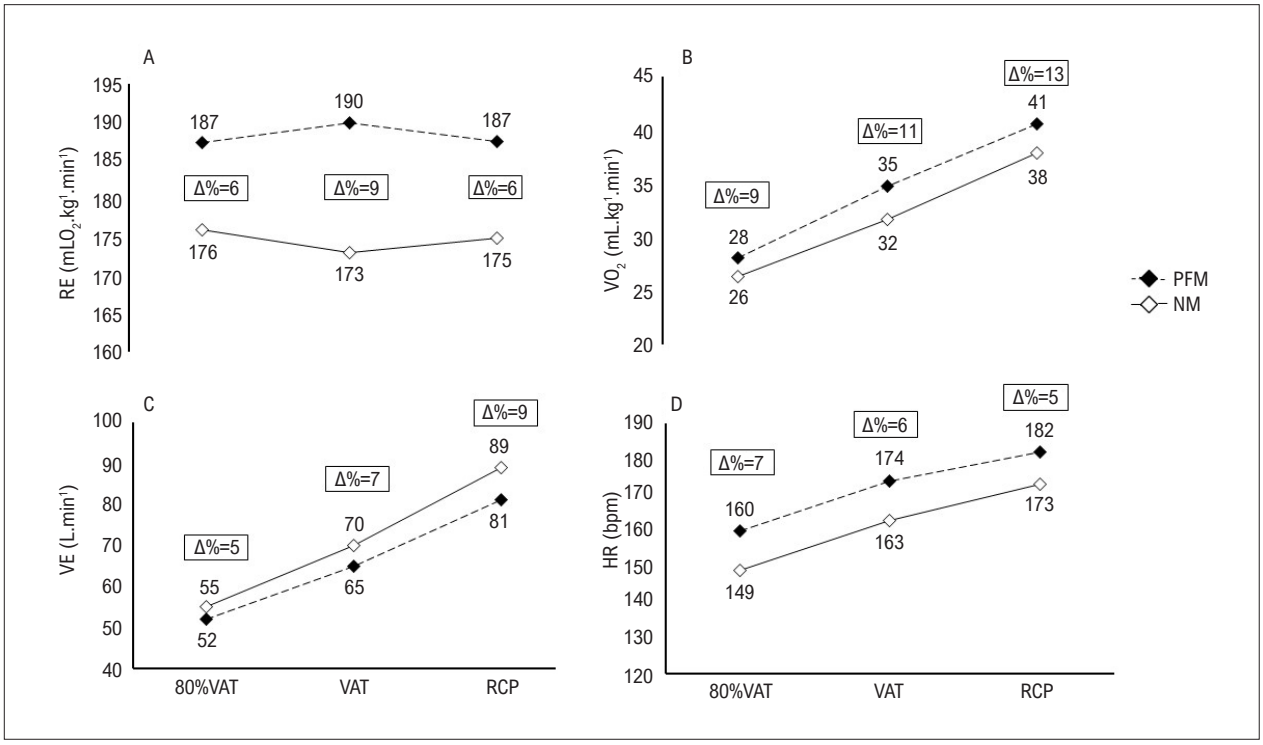

Figure 3 – *Cardiorespiratory response during PSWT in a recreational runner with and without PFM use. Panel A= RE; Panel B= VO$_2$; Panel C= VE; Panel D= HR. PFM: protective face mask; NM: no mask; PSWT: progressive square wave test; RE: running economy; VE: pulmonary ventilation; HR: heart rate.*

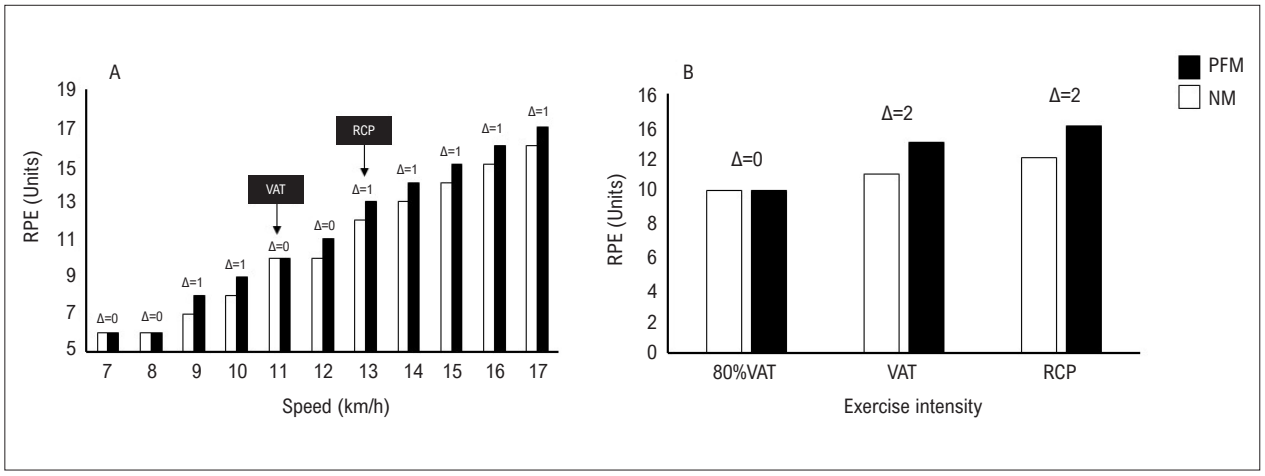

Figure 4 – *Rating of perceived exertion during CPET (panel A) and PSWT (panel B) in a recreational runner with and without PFM use. PFM: protective face mask; NM: no mask; RPE: rating of perceived exertion; VAT: ventilatory anaerobic threshold; RCP: respiratory compensation point.*

between increased airflow impedance, greater inspiratory muscle mechanical overload, and higher cardiovascular demands during endurance exercise. It is important to point out that each test lasted less than 20 minutes, which helped maintain the condition and functioning of the mask.

Thus, based on the findings of the present case study, we suggest the following strategies to minimize respiratory discomfort during aerobic exercise when wearing a PFM: 1) inspiratory muscle training inclusion in the endurance training program; 2) prescription of aerobic exercise intensity based on percentages of heart rate reserve (HRR) (i.e., Karvonen method) or ventilatory thresholds (i.e., VAT and RCP); 3) prescription of the aerobic exercise intensity into three zones, i.e., Zone 1 - easy (<VAT); Zone 2 - moderate (between VAT and RCP); and Zone 3 - high intensity (> RCP); and 4) For both sedentary individuals and patients with chronic diseases, we suggest that, in the early stages of the endurance training program, the aerobic exercise may be of low intensity (i.e., < VAT or 30- 40% HRR).

Conclusions

In conclusion, our results suggest that the recreational runner, while wearing a PFM, showed: first, decreased exercise tolerance despite similar response to both VO_2 max and ventilatory thresholds; second, a worsening of the running economy; third, an increase in cardiovascular demand regarding heart rate response; fourth, despite the lower ventilatory demand, the breathing pattern adopted during exercise increased the burden on the respiratory muscles; and last, an increase in rating of perceived exertion and respiratory discomfort.

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Authors' Contributions

Conception and design of the research: Prado DML, Santos MAP. Analysis and interpretation of the data: Prado DML; Acquisition of data: Silvino VO, Vieira EG, Rosa BV, Santos MAP; Statistical analysis: Prado DML, Silvino VO; Writing of the manuscript: Prado DML, Silvino VO, Santos MAP, Silva ASV; Critical revision of the manuscript for intellectual content: Prado DML, Silva ASV, Santos MAP.

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

The study was approved by the Research Ethics Committee of the Federal University of Piauí, Teresina, Brazil under protocol number 4.429.909. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from the participant included in the study.

References

1. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet.2020;6736(10242):1973-87.
2. Li Y, Tokura H, Guo YP, Wong ASW, Wong T, Chung J, et al. Effects of wearing N95 and surgical facemasks on heart rate, thermal stress and subjective sensations. Int Arch Occup Environ Health. 2005;78(6):501–9.
3. Videbæk S, Bueno AM, Nielsen RO, Rasmussen S. Incidence of Running-Related Injuries Per 1000 h of running in Different Types of Runners: A Systematic Review and Meta-Analysis. Sport Med. 2015;45(7):1017–26.
4. Richardson RS. Oxygen transport and utilization: An integration of the muscle systems. Am J Physiol - Adv Physiol Educ. 2003;27(1–4):183–91.
5. Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. J Physiol. 2008;586(1):35–44.
6. Ponce MC, Sharma S. Pulmonary function tests. In: Stat Pearls [Internet] [Internet]. Treasure Island: StatPearls Publishing; 2020. p. 653–64.[Cited in 2020 Feb 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482339/?report=classic
7. Herdy AH, Ritt LEF, Stein R, de Araújo CGS, Milani M, Meneghelo RS, et al. Cardiopulmonary exercise test: Background, applicability and interpretation. Arq Bras Cardiol. 2016;107(5):467–81.
8. Barner KR, Kilding AE. Running economy: measurement, norms, and determing factors. Sports Medicine. 2015;1:8.
9. World Health Organization. Advice on the use of masks in the context of COVID-19. Interim Guid [Internet]. 2020;1–5.[Cited in 2020 Dec 12]. Available from: https://www.who.int/docs/default-
10. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8):E70–88.
11. Howley ET, Bassett DR, Welch HG. Criteria for maximal oxygen uptake: review and commentary. Med Sci Sport Exerc. 1995;27(9):1292–301.
12. di Prampero PE. Energy Cost of Human Locomotion on Land and in Water. Int J Sports Med. 1986;7(2):55–72.
13. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sport Exerc. 1982;14(5):377–81.
14. Fikenzer S, Lavall TUD, Falz URR, Hepp MBP. Effects of surgical and FFP2/N95 face masks on cardiopulmonary exercise capacity. Clin Res Cardiol [Internet]. 2020;1–9. Available from: https://doi.org/10.1007/s00392-020-01704-y
15. Otsuka A, Komagata J, Sakamoto Y. Wearing a surgical mask does not affect the anaerobic threshold during pedaling exercise. J Hum Sport Exerc. 2020;17(1):1–7.
16. Scherr J, Wolfarth B, Christle JW, Pressler A, Wagenpfeil S, Halle M. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. Eur J Appl Physiol. 2013;113(1):147–55.
17. Neder JA, Dal Corso S, Malaguti C, Reis S, De Fuccio MB, Schmidt H, et al. The pattern and timing of breathing during incremental exercise: A normative study. Eur Respir J. 2003;21(3):530–8.
18. Harms CA, Wetter TJ, St Croix CM, Pegelow DF, Dempsey JA. Effects of respiratory muscle work on exercise performance. J Appl Physiol. 2000; jul; 89(1):131-8.
19. Witt JD, Guenette JA, Rupert JL, Mckenzie DC, Sheel AW. Inspiratory muscle training attenuates the human respiratory muscle metaboreflex. J Physiol. 2007;584(3):1019–28.

Novel Mutation in *DSP* Gene – A Case of Arrhythmogenic Cardiomyopathy with Isolated Left Ventricular Phenotype and High Risk of Sudden Cardiac Death

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Introduction

Sudden cardiac death (SCD) in young adults (18–35 years) most commonly results from previously undiagnosed inherited cardiomyopathies. The most common causes of sudden cardiac death are hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy (ACM), followed by congenital anomalies of coronary arteries, myocarditis, aortic rupture in Marfan's syndrome, conduction defects, and valve diseases.[1]

ACM accounts for up to 20% of sudden cardiac death in individuals under 35 years of age.[2] In a series of 86 victims of SCD at a young age, ACM accounted for 10.3% of the cases, being the second major cause of SCD.[3] Dilated cardiomyopathy (DCM) is a less frequent cause of SCD in young individuals, accounting for nearly 2% of cases in athletes.[4]

ACM is an inherited heart muscle disorder that results from fibrofatty infiltration of the ventricular myocardium.[5]

ACM is a genetically determined cardiomyopathy caused by mutations in genes encoding proteins of desmosomes, which are specialized intercellular structures.[6]

The current classification of ACM includes the classic arrhythmogenic right ventricular cardiomyopathy, biventricular disease variants, predominant left ventricular (LV) involvement, and the LV phenotype characterized by isolated LV involvement.[7]

The diagnosis of ACM is based on the modified Task Force Criteria (TFC) from 2010.[8] However, these modified TFC lack sensitivity in the diagnosis of ACM with isolated or predominant LV involvement. Furthermore, differential diagnosis of ACM from other entities, such as DCM, sarcoidosis or myocarditis, may be challenging.

Clinical case

A 49-year-old man, with a history of mild to moderate alcohol consumption, was followed up in a cardiology consultation for 12 years with the diagnosis of DCM, presumably due to alcohol consumption. Transthoracic echocardiogram showed mild dilatation of four chambers and mild left ventricular systolic dysfunction with global hypokinesia (Figure 1A). The electrocardiogram revealed sinus rhythm with a poor progression of the R wave in V1-V3 and negative T wave in leads I, II, III, aVF, aVL, and V4-V6 (Figure 1B). Myocardial perfusion scintigraphy was negative for ischemia. A 24h-Holter monitoring showed a sinus rhythm, nearly 6,000 multifocal ventricular ectopic beats, and one non-sustained VT with seven complexes and incomplete right bundle branch block (RBBB) (Figure 1C). The exercise stress test showed frequent ventricular ectopy, mostly with LV origin (Figure 1D).

After 12 years of follow-up, the patient suffered a pre-syncope while at work, and was immediately taken to the hospital by the emergency medical team. Upon arrival at the hospital, the patient developed ventricular fibrillation and, despite the advanced life support measures, eventually died.

Two weeks after his death, his 16-year-old son, with no known pathological history, was found inanimate by his mother in his bed where he was sleeping. Advanced life support was initiated at the arrival of the emergency medical services, but it was unsuccessful and the teenager died.

Spouse, daughter, and seven siblings of the index case were submitted to screening with ECG, echocardiogram, and 24h-Holter, all of whom had normal results.

The autopsy of the index case showed an enlarged heart weighing 600g and discrete coronary atherosclerosis. No acute or chronic ischemic lesions were found on the macroscopic examination. Based on these findings, the autopsy report concluded that an arrhythmic cause of death could not be excluded. The autopsy of the son of the index case also showed an enlarged heart weighing 535g. The autopsy report described that the external third of the LV circumferential wall appeared to be detached, in all its longitudinal length, from the two inner thirds of the LV wall. Unfortunately, the histological reports were not made available for siblings or their physicians.

Post-mortem genetic study revealed, in both cases, the variant in heterozygosity c.1080G>A (p.Trp360*) in the *DSP* gene, classified as probably pathogenic, and the variant c.3010G>T (p.Ala1004Ser) in the *MYH6* gene, classified as a genetic variant of uncertain significance (GVUS).

So far, no relatives were found carrying the *DSP* variant. Figure 2 shows the family pedigree with the genetic findings.

Discussion

The diagnosis of ACM is challenging because of the absence of specific unique diagnostic criteria, its variable expressivity,

Keywords

Cardiac Sudden Death; Cardiovascular Diseases.

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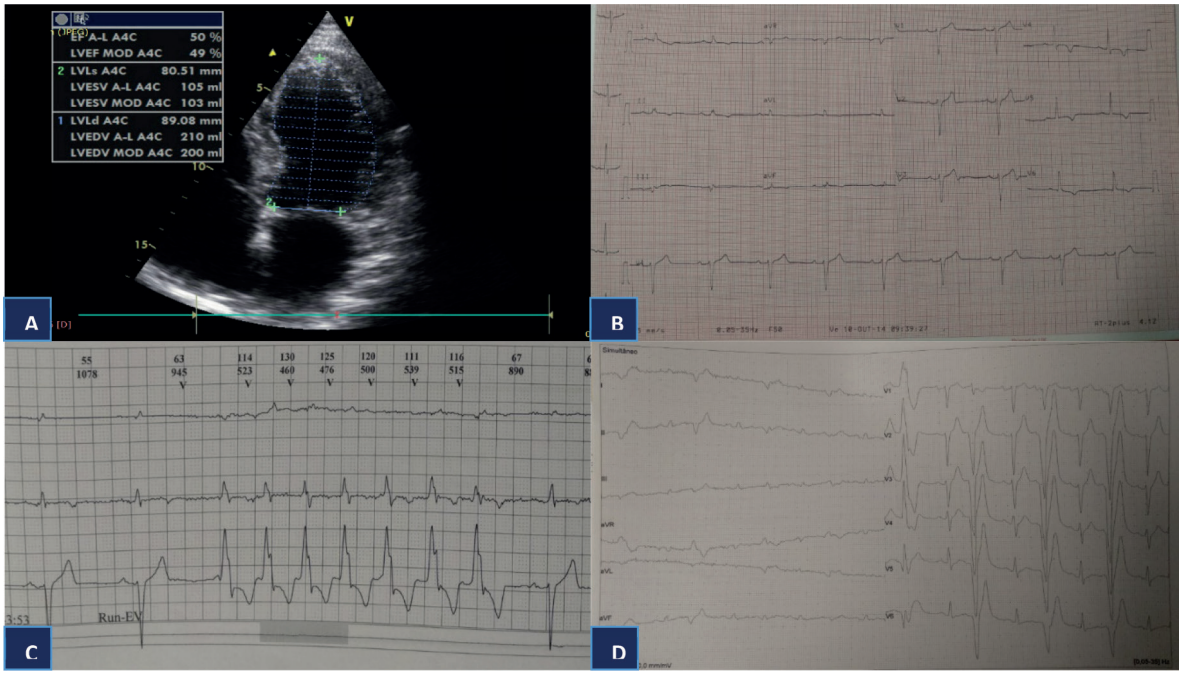

Figure 1 – *A) Transthoracic echocardiogram (apical four-chamber view) showing mild left ventricular dysfunction and dilatation. B) ECG showing sinus rhythm with poor progression of R wave in V1-V3 and negative T waves in leads I, II, III, aVF, aVL, and V4-V6. C) 24h-Holter monitoring revealing non-sustained VT with seven complexes and incomplete right bundle branch block. D) Exercise stress test, showing frequent ventricular ectopy, mostly with LV origin.*

and its incomplete penetrance in relatives.[9] ACM, which was initially described as an isolated or predominant RV disease, exhibits frequent LV involvement, which may be present or even predominant at early stages in some mutation carriers, expanding the clinical spectrum of the disease.[9]

According to the modified TFC of 2010, the index case presented a major criterion (identification of pathogenic mutation categorized as associated or probably associated with ACM) and two minor criteria (inverted T waves in V4-V6 and > 500 ventricular premature beats on 24h-Holter monitoring), which enabled the definitive diagnosis of ACM.[8]

Nevertheless, as the modified TFC lacked sensitivity in the diagnosis of ACM with isolated or predominant LV involvement, Corrado et al. recently presented an International Expert Consensus document proposing the "Padua criteria", which constitutes an upgrade of the diagnostic criteria of ACM aiming for the diagnosis of the entire spectrum of the phenotypic variants of ACM.[10]

In this recent consensus, new criteria have been added that reflect LV involvement, namely: (i) LV systolic dysfunction has been proposed as a minor criterion for diagnosing "biventricular" or "dominant-left" disease variants; (ii) LV myocardial LGE/fibrosis in the form of a stretch mark (or band) pattern affecting ≥1 segment of the LV free wall, septum, or both has been proposed as a major criterion; (iii) Repolarization abnormalities with inverted T waves in left precordial leads (V4-V6) (in the absence of complete LBBB) has been proposed as a minor criterion; (iv) Depolarization abnormalities with low QRS voltages in the limb leads (in the absence of obesity, emphysema, or pericardial effusion) has been proposed as a minor criterion, based on the notion that the decrease of LV myocardial mass by fibro-fatty replacement may lead to low QRS voltages; v) Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia with an RBBB morphology (excluding the fascicular pattern) has been proposed as a minor criterion; and (vi) Demonstration of a pathogenic mutation in ACM-related genes has been considered a necessary criterion for the diagnosis in patients with left-dominant ACM and no clinically detectable RV involvement, because it is the most specific finding linking the LV phenotypic features to ACM.[10]

Indeed, all the aforementioned criteria are fulfilled in the index case of our report (except changes in the MRI because it was not performed during follow-up), thereby confirming the diagnosis of left-dominant ACM.

DCM is particularly difficult to distinguish from non-classic forms of ACM. These two entities can significantly overlap, which may result in a mislabeling of the diagnosis, as it probably occurred in our index case. Desmosomal gene mutations are relatively common in patients with a clinical diagnosis of DCM, and *DSP* mutations are found in 3% of patients with DCM.[11]

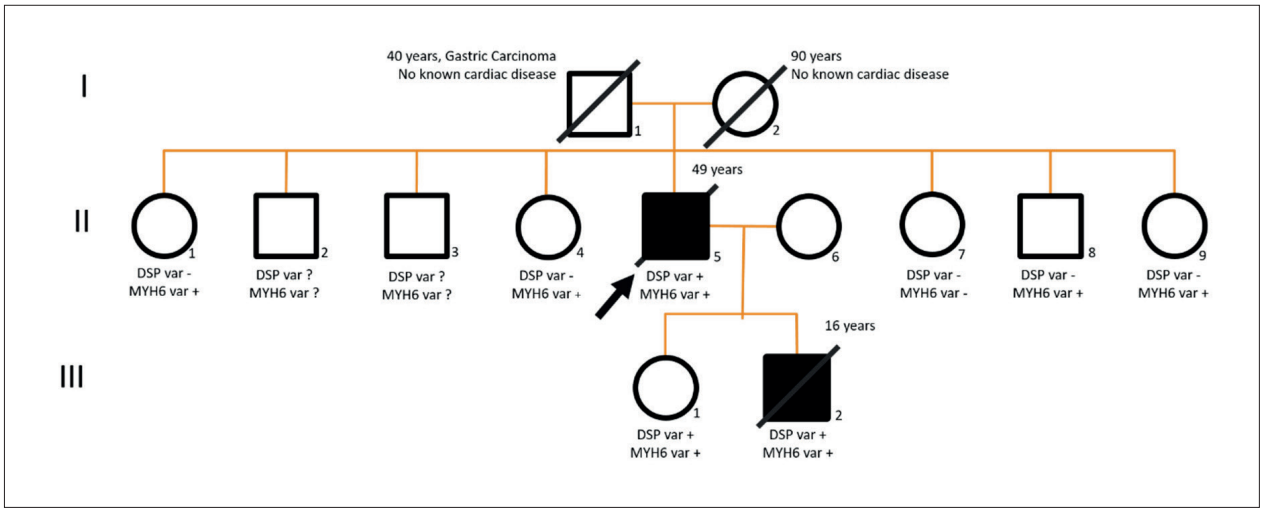

Figure 2 – *Family pedigree showing affected individuals with ACM (dark symbols) and non-affected individuals (white symbols). The arrow indicates the proband. The DSP variant is present (+) in affected individuals, being absent (-) in non-affected ones. The MYH6 variant is present (+) in affected patients, but also in some non-affected relatives. DSP var: variant in heterozygosity c.1080G>A (p.Trp360*) in the DSP gene, classified as probably pathogenic; MYH6 var: variant c.3010G>T (p.Ala1004Ser) in the MYH6 gene, classified as a genetic variant of uncertain significance.*

Left-dominant ACM may present over a wide range of ages typically with palpitations and impaired consciousness. Ventricular arrhythmia (VA) with RBBB morphology is characteristic and often out of proportion to the degree of LV dysfunction.

Palpitations, (pre)syncope, and VA are present at an early stage of ACM, often in the absence of gross structural abnormalities, as observed in both the index case and his son.

Genotype/phenotype studies have suggested that *DSP* mutations are associated with a severe phenotype with a higher risk of VA and SCD, and a high level of LV involvement, particularly in patients with truncating mutations, as observed in our patients. In addition, in line with our case, *DSP* mutations may be associated with T wave inversion in leads V4 to V6.[12]

In our case, the variant p.Trp360* was found in the *DSP* gene. Although it has never been described in the literature or genetic databases, this mutation results in a truncated protein, which may relate to a more aggressive phenotype, as seen in our family. Furthermore, pedigree analysis showed a positive congregation pattern, as the *DSP* mutation was found only in affected patients, but not in negative-phenotype patients, including the older ones.

This case shows the importance of *post-mortem* genetic study in patients with DCM/ACM phenotype, who suffered SCD before the genetic testing was performed.

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Author Contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Leite PVH, Azevedo O; Statistical analysis and Writing of the manuscript: Leite PVH; Critical revision of the manuscript for intellectual content: Leite PVH, Azevedo O, Dias G, Cardoso F, Pereira T, Lourenço A.

Potential Conflict of Interest

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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.

References

1. Corrado D, Zorzi A. Sudden Death in Athletes. Int J Cardiol. 2017;237:67-70. doi: 10.1016/j.ijcard.2017.03.034.
2. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in Sudden Cardiovascular Death in Young Competitive Athletes after Implementation of a Preparticipation Screening Program. JAMA. 2006;296(13):1593-601. doi: 10.1001/jama.296.13.1593.
3. Zhao YH, Li FH, Jiang HG, Luo BT, Chen XY. Clinicopathological Analysis of Autopsy of 86 Cases with Sudden death. J Guod Med Coll.2009;27:624-8.
4. Harmon KG, Drezner JA, Maleszewski JJ, Lopez-Anderson M, Owens D, Prutkin JM, et al. Pathogeneses of Sudden Cardiac Death in National Collegiate Athletic Association Athletes. Circ Arrhythm Electrophysiol. 2014;7(2):198-204. doi: 10.1161/CIRCEP.113.001376.
5. Bennett RG, Haqqani HM, Berruezo A, Della Bella P, Marchlinski FE, Hsu CJ, et al. Arrhythmogenic Cardiomyopathy in 2018-2019: ARVC/ALVC or Both? Heart Lung Circ. 2019;28(1):164-77. doi: 10.1016/j.hlc.2018.10.013.
6. Ohno S. The Genetic Background of Arrhythmogenic Right Ventricular Cardiomyopathy. J Arrhythm. 2016;32(5):398-403. doi: 10.1016/j.joa.2016.01.006.
7. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, et al. Arrhythmogenic Right Ventricular Cardiomyopathy: Evaluation of the Current Diagnostic Criteria and Differential Diagnosis. Eur Heart J. 2020;41(14):1414-29. doi: 10.1093/eurheartj/ehz669.
8. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task Force Criteria. Eur Heart J. 2010;31(7):806-14. doi: 10.1093/eurheartj/ehq025.
9. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical Diagnosis, Imaging, and Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: JACC State-of-the-Art review. J Am Coll Cardiol. 2018;72(7):784-804. doi: 10.1016/j.jacc.2018.05.065.
10. Corrado D, Marra MP, Zorzi A, Beffagna G, Cipriani A, Lazzari M, et al. Diagnosis of Arrhythmogenic Cardiomyopathy: The Padua Criteria. Int J Cardiol. 2020;319:106-14. doi: 10.1016/j.ijcard.2020.06.005.
11. Haas J, Frese KS, Peil B, Kloos W, Keller A, Nietsch R, et al. Atlas of the Clinical Genetics of Human Dilated Cardiomyopathy. Eur Heart J. 2015;36(18):1123-35. doi: 10.1093/eurheartj/ehu301.
12. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD, et al. Impact of Genotype on Clinical Course in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy-associated Mutation Carriers. Eur Heart J. 2015;36(14):847-55. doi: 10.1093/eurheartj/ehu509.

Transcatheter Aortic Valve Implantation Assisted by Extracorporeal Membrane Oxygenation for the Treatment of Aortic Stenosis with Cardiogenic Shock

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Introduction

Aortic stenosis is a common heart valve disease, mostly caused by degenerative aortic valve disease in the elderly.[1] Aortic stenosis obstructs the forward flow of the left ventricle to the aorta, leading to a pressure differential between the left ventricle and the aorta and increased left ventricular pressure secondary to left ventricular hypertrophy. As the disease progresses, it leads to left ventricular systolic and diastolic dysfunction and myocardial ischemia due to decreased coronary blood flow. However, cardiogenic shock secondary to aortic stenosis is one of the most serious complications and has a high mortality rate due to its limited therapeutic effect.[2] Since its inception in 2002, transcatheter aortic valve implantation (TAVI) has become the first choice of treatment for elderly patients with severe aortic stenosis and high surgical risk due to its advantages of minimally invasive, non-extracorporeal circulation, and good medium-long term efficacy.[3-5] With the development of device technology and low-resistance transmission systems, TAVI has recently been shown to be no less effective than traditional surgery, even in medium-risk patients.[6] However, for patients with a long medical history, significantly reduced cardiac ejection fraction (EF), cardiogenic shock, decompensated aortic valve disease, and severe complications such as intraoperative hemodynamic breakdown and malignant arrhythmia, still exist during TAVI surgery, greatly increasing the risk of TAVI. The present study reports a case of severe aortic stenosis complicated by cardiogenic shock that was successfully treated with TAVI assisted by extracorporeal membrane oxygenation.

Case Report

A 64-year-old female patient was hospitalized due to "repeated chest tightness and fatigue for more than 2 months and aggravation for 3 days". She had a previous history of cholecystectomy for 10 years. The physical examination upon admission indicated a temperature of 36.8°C, 18 breaths/min, a pulse of 46 beats/min, and blood pressure 136/92 mmHg. The patient had an orthopnoea. The breathing sounds of both lungs were coarse, and a moist rhonchus could be heard. Systolic blowing murmur could be heard in the aortic valve auscultation, and there was slight pitting edema over both legs. Laboratory examination showed N-terminal pro-brain natriuretic peptide (NT-proBNP)>25000 pg/mL, Troponin I(TnI) 0.12 μg/L. The indexes of liver and kidney function also increased significantly. Echocardiography suggested severe aortic stenosis with mild insufficiency, the maximum systolic pressure gradient was 130mmHg, and the left ventricle was significantly enlarged (LVIDd:58.3mm) with systolic diastolic dysfunction. The EF was measured as 23.5% by biplane method (Figure 1). Chest CT showed double pneumonia exudate, pulmonary interstitial edema, encapsulated effusion of both lungs with pulmonary insufficiency. A 24h dynamic ECG suggested a sinus rhythm with frequent atrial and ventricular premature beats. The results of ambutral blood pressure examination showed that the blood pressure was 96/64mmhg throughout the day, 98/65mmhg during the day, and 93/62mmhg at night. TAVI imaging evaluation of the patients was conducted, and the results showed typical aortic stenosis with bicuspid malformation (type 0) and moderate calcification (Figure 2). The diagnoses were aortic stenosis and cardiogenic shock with a heart function classification of NYHA IV. The patient was given cardiotonics, diuretics, non-invasive ventilator adjuvant treatment, but the heart failure and respiratory symptoms did not improve. Considering that the patient was at high risk of cardiogenic shock and heart failure caused by aortic stenosis, there were no conditions for routine open-heart surgery, and the risk of TAVI surgery was also very high. Thus, after a multidisciplinary consultation, we proposed the treatment plan for ECMO-assisted TAVI surgery. Tracheal intubation was inserted under general anesthesia. The 6F sheath tube was indwelling in the right jugular vein, and then the temporary pacemaker was inserted into the right ventricle through the sheath tube. The right femoral artery was punctured with a 4F micropuncture needle, and the sheath of 6F and 11F was used to expand, and 2 Perclose Proglide closure devices (Abbott Vascular, Minneapolis, MN) were inserted for standby application, and then the 18F sheath tube was inserted. Then venoarterial extracorporeal membrane oxygenation (VA-ECMO) was performed by inserting 16F arterial cannula and 22F venous cannula into the left femoral artery and femoral vein respectively. The circulation assisted flow was 2.7L/min, and the blood pressure was maintained at about 120mmHg. During the operation, it is necessary to ensure that the position of the artery and vein cannula is in good condition to prevent pulling, bending, displacement, and prolapse. It is also important to observe the blood color

Keywords

Extracorporeal Membrane Oxygenation; Aortic Valve Stenosis; Cardiogenic Shock.

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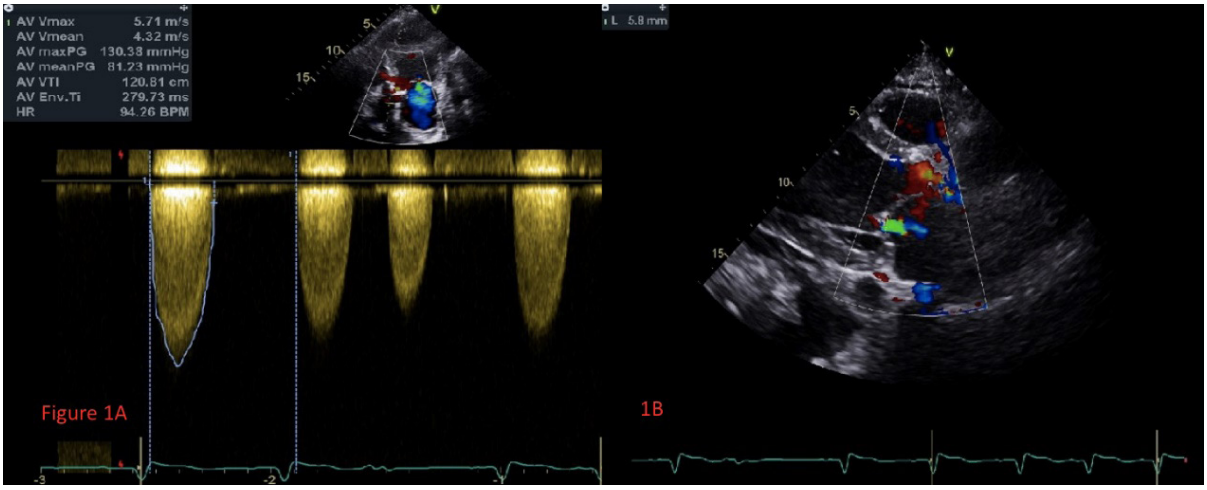

Figure 1 – *A and B) Preoperative echocardiography indicated that aortic valve velocity and pressure gradient increased, aortic valve lobe calcified, and severe aortic stenosis occurred.*

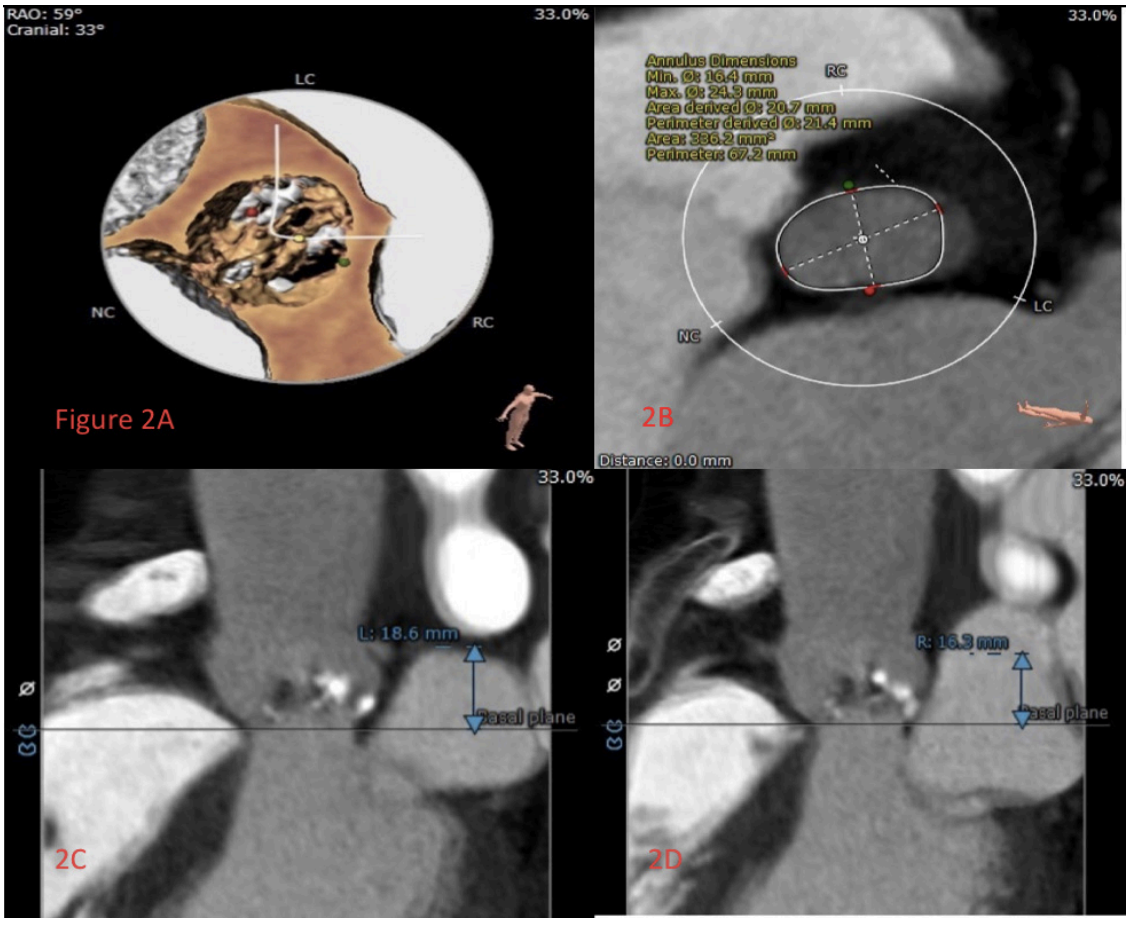

Figure 2 – *Three-dimensional reconstruction of the aortic valve (2A), the aortic annular diameter (2B), height of the left coronary ostium (2C), and the right coronary ostium (2D).*

and tension of the lumen, whether the lumen is quivering, whether there is blood clot, and whether the hemodynamics is stable during the period of circulation assistance. A left ventricular catheter was placed via the left radial artery sheath and showed an LV pressure of 167/25mmHg and aortic blood pressure of 100/77 mmHg. The guide wire was sent into the left ventricle through the 18F sheath tube and then put into the 18mm Numed balloon and expanded after setting the temporary pacing rate to 180 beats/min. Based on measured data of the CT reconstruction, we selected the 23mm Venus A-Valve (Venus MedTech, Hangzhou, China). The valve was released under precise positioning and temporary pacing rate of 160 beats/min. The results indicated that the valve shape and position were good, and the angiography indicated a small amount of perivalvular leakage (Figure 3).

After the procedure, the patient, reliant on full ECMO support and vasoactive drugs to maintain hemodynamics, was transferred to the intensive care unit (CCU). The hemodynamics of the patient was stable and ECMO was removed 20 hours after surgery. Due to preoperative atelectasis and pulmonary edema, tracheal intubation was extracted three days after the operation. Postoperative symptoms and signs of the patient were significantly improved, NT-proBNP, TnI and liver and kidney function indexes were significantly decreased. The postoperative echocardiography indicated a normal valve function accompanied by a small amount of perivalvular leakage. The valve orifice velocity and pressure gradient were significantly reduced compared with those before surgery and the EF increased to 66% (Figure 4). Due to the patient's severe condition before surgery, long postoperative bed time, malnutrition, and the influence of drugs, the postoperative symptoms such as consciousness disorder, pulmonary infection and bilateral intermuscular vein thrombosis of the lower extremities occurred. Through the improvement of internal environment balance, nutritional nerve, anti-infection, and rehabilitation function exercise after surgery, the patient was finally discharged successfully.

Discussion

TAVI is a new technology for the treatment of aortic disease. After more than a decade of development, TAVI has emerged as an attractive, less invasive treatment option for severe aortic stenosis, and is superior to drug therapy for patients who cannot undergo conventional surgery.[7,8] With modern advances in equipment, TAVI has proven to be no less effective than traditional surgery in patients with intermediate risk.[6] However, in clinical practice, some patients were associated with low EF, small left ventricle, cardiogenic shock and other symptoms before surgery, which undoubtedly increased the risk of TAVI surgery. Finding a safe and effective treatment for these very high risk patients is always a challenge

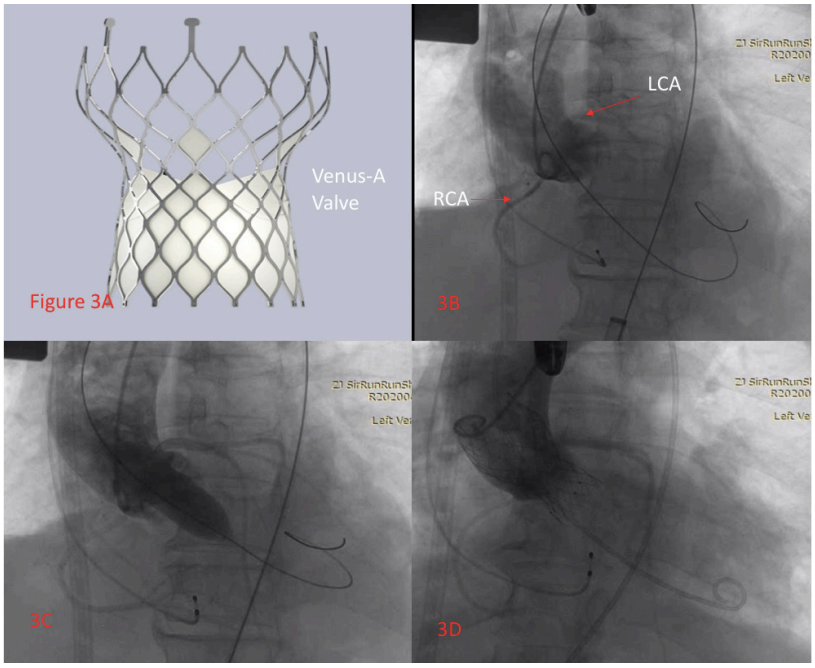

Figure 3 – *A) The valve used was from China; B) Aortography before the balloon dilatation indicated that the coronary arteries were well developed and a severe stenosis of the aortic valve; C) Aortography with the balloon fully inflated showing the patency of both the left and right coronary arteries; D) The final aortography after valve deployment and dilation showed a good position of the valve and a small amount of perivalvular leakage.*

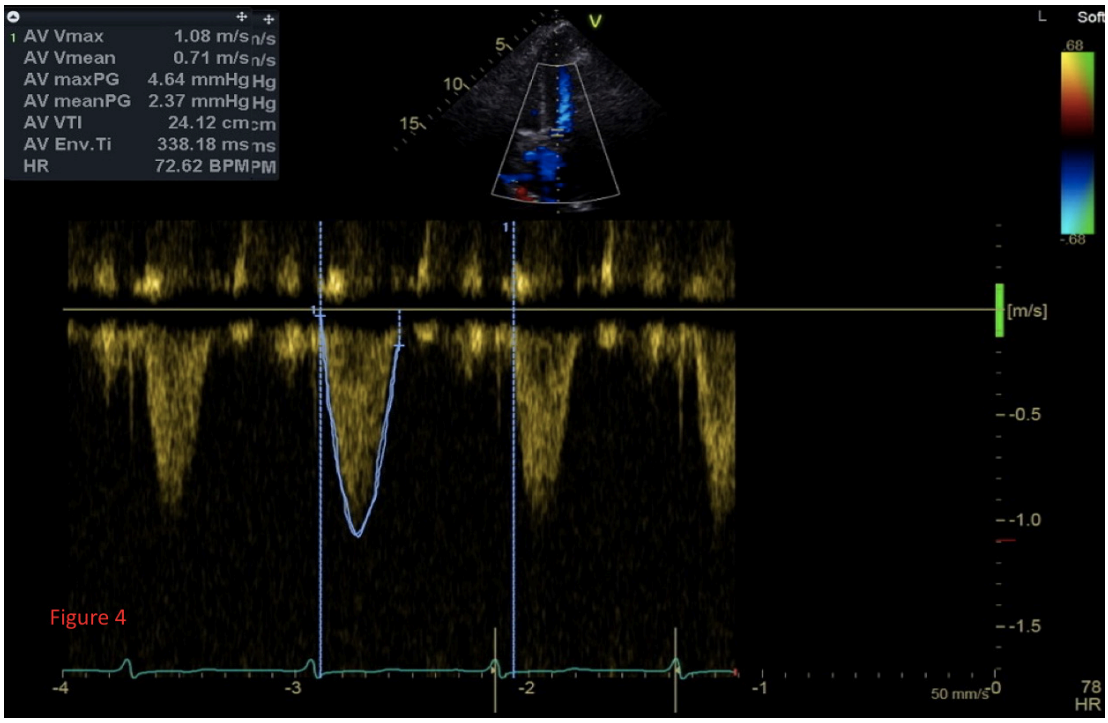

Figure 4 – *Postoperative echocardiography indicated that aortic valve velocity and pressure gradient improved significantly.*

for cardiologists. ECMO is a mechanical circulatory support device, which has been used in the rescue adjuvant therapy of cardiogenic shock and cardiopulmonary resuscitation due to various reasons in recent years.[9] For patients with hemodynamic instability, ECMO can provide stable blood flow and oxygen supply, thus effectively treating reversible heart failure.[10] However, for high-risk aortic stenosis patients with cardiogenic shock, the experience of ECMO in TAVI is limited. An observational study[11] examined the results of transapical TAVI in patients with cardiogenic shock, and found that the presence of cardiogenic shock significantly increased the mortality at 30 days after TAVI (19% cardiogenic shock vs. 5% non-cardiogenic shock; p = 0.02). However, the mortality rate of TAVI in the cardiogenic shock group was still lower than that after emergency routine aortic valve replacement (19% vs 26%), suggesting that TAVI may be a viable treatment option for cardiogenic shock. Our patient presented severe cardiogenic shock symptoms after admission, such as hypotension and orthopnoea, and was at high risk, with an STS score of 30.06. Traditional SVAR surgery carries a very high risk. However, TAVI surgery at this time also undoubtedly increases the risk of intraoperative hemodynamic instability, malignant arrhythmia, and even sudden death. In addition, conservative treatments, such as cardiotonics, diuretics, and non-invasive ventilator assisted ventilation failed to improve the patient's symptoms, the final result may also be death. Therefore if circulatory collapse occurs or the patient seems to be intolerable of TAVI, we should not hesitate to use ECMO. According to our practical experience, the intraoperative use of ECMO effectively guarantees stable hemodynamics, enables the repeated expansion of a diseased aortic valve with no malignant arrhythmias, such as supraventricular tachycardia and ventricular fibrillation appeared, greatly reduces the risk of TAVI procedures, significantly reduces possible intraoperative heart irritability in key surgical stages, such as balloon expansion of the aortic valve and the release of the intervening valve, and effectively guarantees the surgical safety of high-risk patients. At the same time, for patients with severe aortic stenosis, blood pressure was improved to different degrees after balloon dilation assisted by ECMO, avoiding the risk of circulatory collapse caused by balloon dilation in the unprotected state of such patients, so that the patients could benefit to the maximum extent.

However, the incidence of ECMO-related complications (such as lower limb ischemia, stroke, vascular injury, acute kidney injury, bleeding, and infection) is so high that it is critical for effective and rational use of ECMO by an experienced heart team.[12] By contrast, after the successful removal of ECMO, more attention should be paid to postoperative management in order to improve postoperative outcomes, such as the use of medication for heart failure, comprehensive intervention for comorbidities, prolonged cardiac rehabilitation, and close outpatient follow-up. Our patient presented postoperative consciousness disorder, and CT showed no signs of cerebral infarction or cerebral hemorrhage, which may well be caused by an excessive use of sedatives. Therefore, we decided to discontinue sedatives and give neurotrophic therapy. Early transfer out of intensive care unit can reduce the incidence

of cross-infection and iatrogenic infection after operation. In addition, early postoperative rehabilitation exercises, such as getting out of bed, lung vibration, and sputum drainage can also prevent pulmonary infection and lower limb venous thrombosis.

In conclusion, our experience can provide a solution for such patients. However, studies conducted with large samples are still needed to find the best treatment.

Conclusion

TAVI assisted by ECMO may be a reasonable choice for patients with preoperative severe aortic stenosis complicated with low EF, heart failure, or even cardiogenic shock. Meanwhile, reasonable postoperative management can effectively prevent ECMO-related complications and improve the prognosis of patients.

Author Contributions

Conception and design of the research: Zhang W, He F; Acquisition of data and Analysis and interpretation of the data: Chen H; Statistical analysis: Huang G; Obtaining financing: Chen H, Zhang W; Writing of the manuscript: Huang G; Critical revision of the manuscript for intellectual content: He F.

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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.

References

1. Ross J Jr, Braunwald E. Aortic Stenosis. Circulation. 1968;38(1 Suppl):61-7. doi: 10.1161/01.cir.38.1s5.v-61.
2. Caetano F, Almeida I, Seca L, Botelho A, Mota P, Marques AL. Severe Aortic Stenosis and Cardiogenic Shock: A Therapeutic Challenge. Rev Port Cardiol. 2013;32(9):701-6. doi: 10.1016/j.repc.2012.12.011.
3. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the Management of Valvular Heart Disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42(4):1-44. doi: 10.1093/ejcts/ezs455.
4. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in pAtients who Cannot Undergo Surgery. N Engl J Med. 2010;363(17):1597-607. doi: 10.1056/NEJMoa1008232.
5. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med. 2011;364(23):2187-98. doi: 10.1056/NEJMoa1103510.
6. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20. doi: 10.1056/NEJMoa1514616.
7. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J. 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391.
8. Huang J, Chen P, Hu X, Tang J, Fang Z. Aortic Stenosis Complicated by Cardiogenic Shock Treated by Transcatheter Aortic Valve Replacement With Extracorporeal Membrane Oxygenation: A Case Report. Medicine. 2018;97(33):e11900. doi: 10.1097/MD.0000000000011900.
9. Abrams D, Combes A, Brodie D. Extracorporeal Membrane Oxygenation in Cardiopulmonary Disease In Adults. J Am Coll Cardiol. 2014;63(25 Pt A):2769-78. doi: 10.1016/j.jacc.2014.03.046.
10. Annabi MS, Clisson M, Clavel MA, Pibarot P. Workup and Management of Patients with Paradoxical Low-Flow, Low-Gradient Aortic Stenosis. Curr Treat Options Cardiovasc Med. 2018;20(6):49. doi: 10.1007/s11936-018-0642-y.
11. D'Ancona G, Pasic M, Buz S, Drews T, Dreysse S, Kukucka M, et al. Transapical Transcatheter Aortic Valve Replacement in Patients With Cardiogenic Shock. Interact Cardiovasc Thorac Surg. 2012;14(4):426-30. doi: 10.1093/icvts/ivr095.
12. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of Extracorporeal Membrane Oxygenation for Treatment of Cardiogenic Shock and Cardiac Arrest: A Meta-Analysis of 1,866 Adult Patients. Ann Thorac Surg. 2014;97(2):610-6. doi: 10.1016/j.athoracsur.2013.09.008.