Research paper

Chronicle of a death foretold. It is time for echocardiographic screening in young athletes

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ABSTRACT

Background: The novel "*Chronicle of a death foretold*" by Gabriel Garcia Marquez is a story of a sudden death which could have been prevented. In 1976, within the University of Maryland basketball program and only 8 weeks apart, two athletes died suddenly during physical exertion. They were affected by hypertrophic cardiomyopathy and Marfan syndrome and in both cases an echocardiogram would have prevented the tragic epilogue. This coincidence drew everyone's attention and experts' interest on sudden death in sports.
Methods and results: Even in recent Italian history, unexpected deaths continue to affect athletes but surprisingly any real knowledge regarding the numbers and the impact of those tragedies must take medical literature and non-medical press into consideration. Herein we report the clinical case of a 13-year-old patient with a bicuspid aortic valve, whose mother was alarmed by the news of a young boy who died because of an anomalous origin of coronary artery (AOCA) which had not been diagnosed at transthoracic echocardiography (TTE). Her obstinacy induced the physicians to repeat TTE and led to the same diagnosis in her son: actually, his right coronary artery originated from the opposite sinus of Valsalva. The suspicion was confirmed by coronary CT scan and, thanks to appropriate therapy, the boy now fares well.
Conclusions: AOCA is the second most common cause of sudden death in young athletes. Although AOCA is often undetectable at ECG, TTE increases sensitivity of preparticipation screening. It could therefore allow us to avoid such coincidences and prevent sudden juvenile death.

1. Chronicle of a death foretold. It is time for echocardiographic screening in young people

In the novel "*Chronicle of a death foretold*" by Gabriel Garcia Marquez, Santiago Nasar and his mother are the only ones in a small Colombian town who do not know that Santiago will be killed a few hours after attending the wedding of his killers' sister. Actually, due to superstition, envy, prejudice or ignorance, everyone knows but no one acts to save Santiago, a 21-year-old young man who had lost his father three years earlier owing to sudden death. Marquez's book is an autopsy that investigates family and social connections, essentially an apologue on communication between human beings, the *social connexome* that links, transmits and even kills.

A recent clinical case embarrasses us and asks us whether in the small but globalized world of cardiology we are at risk of becoming like the characters of Marquez's novel. A woman brought her 13-year-old son for

a transthoracic echocardiography (TTE) three months after a follow-up check for a bicuspid aortic valve. Surprised, we asked the mother why she came back so early as her son had an uncomplicated disease, which usually required a biennial follow-up. The mother replied that she had heard on TV of a boy who died because of a coronary malformation and wanted to make sure that her son did not have the same condition. Actually, the national press had extensively covered the news of a 14-year-old boy who two weeks earlier had died while playing football in a small Italian town: the autopsy revealed an anomalous origin of coronary artery (AOCA) with a left coronary artery (LCA) which originated from the right sinus of Valsalva and had an interarterial course.

We told the anxious mother that we were the same doctors who had performed her son's previous TTE and we would use the same echograph of three months before making a second examination redundant. She insisted, saying that, five months before his death, the TTE of the boy of the news was reported as normal. She wanted us to only look for that
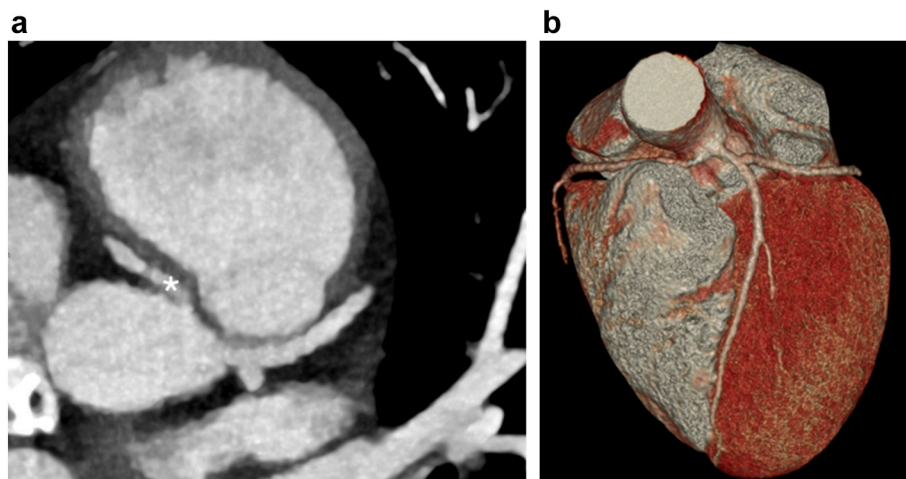
Fig. 1. CT scan (a) and 3D-reconstruction (b) of RCA (*) arising from the opposite sinus of Valsalva with interarterial course.

particular anomaly, because her son needed to play football safely.

During the examination it was impossible to find the right coronary artery (RCA) clearly arising from the ipsilateral sinus of Valsalva. Indeed, it appeared to come from the left sinus. That suspicion was explained to the mother and then confirmed by the coronary CT scan (Fig. 1). The effort electrocardiography (ECG) was negative, while the stress scintigraphy was positive for apical ischemia. The boy was suspended from sport and put on beta blocker therapy.

This case demonstrates that a mother's obstinacy allowed a diagnosis and perhaps saved her son's life; sudden death in AOCA is not always due to massive infarction, but sometimes to malignant ventricular arrhythmias secondary to limited ischemias during exertion, even in patients who had a negative maximal stress test before dying.

If the boy with the "simple" bicuspid aortic valve had died within a short distance of time after the death of the 14-year-old who had alarmed his mother, we would have been faced with a coincidence like the one that happened in the USA 45 years ago. In 1976, within the University of Maryland 1st-division basketball program and only 8 weeks apart, two athletes died suddenly during physical exertion [1].

The first one was Owen Brown, 23 years of age, who died during an informal basketball game: the autopsy revealed that he was affected by hypertrophic cardiomyopathy (HCM). Actually, the athlete had been previously tested due to extrasystoles, but the diagnosis remained unresolved even after cardiac catheterization. Of note, HCM was subsequently recognized as the most common cause of sudden death (SD) in American athletes aged <35 years [2], but Owen Brown's diagnosis was the first one of HCM in a competitive athlete.

Only 2 months later, Chris Patton, aged 21 years, collapsed all of a sudden because of aortic rupture. Indeed, he had an unrecognized Marfan syndrome, clearly suggested by his phenotype, but no cardiac disease that would place him at death risk had been suspected. A few years earlier (1972–73) M-mode echocardiography had been introduced into clinical practice and, thanks to this imaging tool, left ventricular hypertrophy and aortic root enlargement could have been detected without difficulty.

Every tragic event affecting professional athletes is considered counterintuitive and absurd: their healthy lifestyle, mythologized invulnerability and physical achievements supposedly rule out any possibility of a potentially fatal disease. Nevertheless, misfortunes of this kind continue to occur, they shock the local community and have a huge impact on physicians too. Prior to these two tragic deaths, the issue of SD in athletes had not achieved wide public recognition, but understandably the media interest around unexpected tragedies in sport increased after the Maryland deaths. Hence, in the U.S., public and nationwide reporting of such events was established in order to describe the
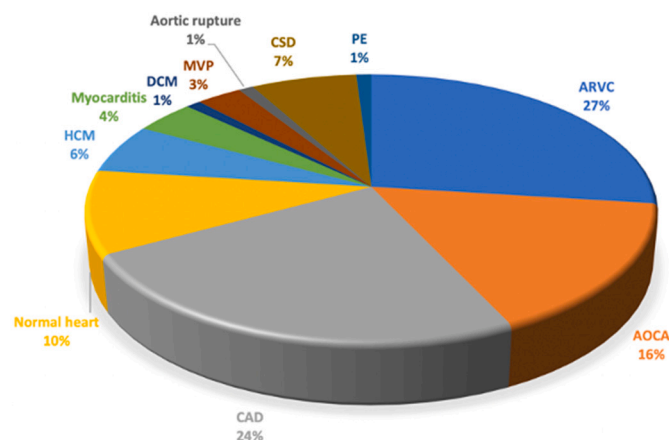

Fig. 2. Causes of sudden cardiac death in athletes aged <35 years in the Veneto region of Italy (modified from Corrado et al. [10]). ARVC: arrhythmogenic right ventricular cardiomyopathy, AOCA: anomalous origin of coronary artery, CAD: coronary artery disease (of atherosclerotic nature), HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, MVP: mitral valve prolapse, CSD: conduction system disease, PE: pulmonary embolism.

epidemiology, causes and incidence of SD in athletes [3].

The reported incidence of cardiac SD is 1 in 200,000 athletes per year [4] and variables like sex, race and type of sport influence this rate: for instance, male black basketball players have an even higher incidence of 1:7000 [5]. The main mechanism of cardiac arrest is ventricular fibrillation due to an underlying cardiovascular disease, the culprit lesions are often clinically silent and the patient is rarely symptomatic [6].

Atherosclerotic coronary artery disease is the most common cause of SD in adults aged >35 years, whereas a wider spectrum of cardiovascular conditions can explain SD in younger people [7] (Fig. 2). Cardiomyopathies are usually reported as the principal cause of SD in young athletes: HCM accounts for more than one third of cases in the U.S. and arrhythmogenic right ventricular cardiomyopathy represents approximately one fourth of cases in the Italian Veneto region [8].

The most important strategies aiming at creating a safer athletic environment are preparticipation screening and eligibility or disqualification standards to prohibit sick athletes from competing in sport and thereby reduce their mortality risk [9]. A preparticipation evaluation is encouraged by multiple societies, in order to identify or raise the suspicion of cardiovascular abnormalities that could potentially result in SD [10,11,12]. The addition of ECG to the standard evaluation based only on medical history and physical examination has been recommended by

the European Society of Cardiology [10] and the International Olympic Committee [13]. Data suggest that the sensitivity of ECG in detecting cardiovascular abnormalities associated with a risk of SD is equal to 80% and it is superior to that of mere clinical evaluation [14].

In Italy, a mandatory national program has been adopted since 1982 to screen all competitive athletes with medical history, physical examination and a 12-lead ECG [15]. This policy gained considerable visibility thanks to an observational study coming from the North-Western Italian region of Veneto, that showed a considerably reduced incidence of SD in athletes, from 3.6 to 0.4/100,000 person-years ($p < 0.001$) after 20 years of screening [16]. According to the authors, the mortality reduction was predominantly due to a lower incidence of unexpected deaths from cardiomyopathies, which represented the most common diseases diagnosed at preparticipation screening.

Italy is the only country where the law prescribes that every young subject >12 years old engaged in competitive sports must undergo ECG before entering agonistic physical activity. 12-lead ECG offers the potential to detect several lethal conditions other than cardiomyopathies, for example long QT, Brugada and Wolff-Parkinson-White syndromes [7]. However, some cardiac structural diseases, such as coronary anomalies and incipient forms of cardiomyopathies, can be missed on physical examination and ECG, but they may be easily identified by TTE [17].

AOCA from the wrong coronary sinus is a congenital malformation with a silent clinical course, which represents the second most common cause of SD in the young, accounting for 17% of unexpected deaths among athletes [18]. Through echocardiographic screening, its estimated prevalence is around 0.1–0.2% in the general population [19]; however, thanks to magnetic resonance imaging (MRI), the prevalence rate is higher (0.7% between 11 and 15 years old) [20]. The most frequent anatomic finding is represented by an RCA arising from the opposite sinus of Valsalva, but the origin of the LCA from the right sinus is the anomaly that most commonly leads to SD [21]. In fact, the calculated cumulative risk of SD over a 20-year period in individuals <35 years old participating in competitive sports is 6.3% for an anomalous LCA and 0.2% for an anomalous RCA [22]. Among athletes dying because of AOCA, only 31% have symptoms before death [23]: these include exertional syncope, dyspnea and chest pain.

In the presence of AOCA, the anomalous vessel leaves the aorta assuming an acute angle with the aortic wall and is characterized by a slit-like ostial orifice. If the coronary artery courses between the aorta and the pulmonary artery, SD may occur during or shortly after vigorous exercise. In addition, it may contain a narrow intramural segment which runs inside the aortic wall and this is probably the most threatening feature of AOCA [24]. Thus, during physical effort, an increased oxygen demand, decreased blood supply to the myocardium and a shorter diastolic period may result in cardiac ischemia, ventricular arrhythmias and SD. Surprisingly, even high-sensitivity stress tests do not provoke ischemic alterations, regardless of the presence of symptoms [25].

The pathophysiology of AOCA is more complex than a simple coronary stenosis. Factors like vasospasm, arterial resistance and autonomic balance come into play, to the extent that in the ergometry laboratory it is difficult to reproduce the signs and symptoms that fatally occur on the playing field. It is also possible that micro-ischemias repeated over the years prepare a substrate which is already predisposed to electrical SD. For that to happen, complete obstruction of the anomalous coronary artery and a massive infarction are not necessary, but even a limited ischemia is sufficient to destabilize a predisposed substrate.

It is no coincidence that, in the case of AOCA, the age of presentation of symptoms is usually after 10 years, partly because effort becomes greater after that age, but partly because time is needed for the development of an arrhythmogenic substrate [37].

As a consequence, congenital coronary anomalies are most often undetectable at ECG screening, but they should be suspected in young individuals or athletes who present with effort-induced chest pain or syncope. Unfortunately, for some, the first presentation is SD or cardiac arrest [26].

AOCA associated with an intramural and/or interarterial course is typically identified thanks to TTE as an incidental finding; nevertheless, definitive diagnosis relies on further tests, such as cardiac MRI or CT-coronary angiography, which accurately reveal the pathological vessel. Cardiac MRI offers 3D-imaging at high spatial resolution, without radiation exposure and makes it possible to acquire further relevant information including valvular and ventricular function, regional contractility and myocardial viability [27].

Given the fact that ECG screening is a life-saving strategy [28], we tend to affirm that TTE provides higher sensitivity to the pre-participation evaluation, especially in competitive athletes [29]. Performing a simple TTE in the parasternal short axis projection in the plane of the aortic root may distinguish the two coronary ostia and even identify the initial course of coronary arteries [17]: Wyman et al. conducted an echocardiographic study on 395 young athletes, visualizing the ostium and the proximal portion of the LCA in 99% of cases and the RCA in 96% [30]. One of the first articles focused on the importance of correct coronary imaging as part of the routine echocardiographic evaluation of competitive athletes was published in 1991 [31], but there are currently only few data regarding the cost-effectiveness of adding a TTE to the standard screening protocol [32]. Although TTE is not currently recommended in the screening of athletes and the systematic assessment of AOCA is not yet universally performed, many centers conduct echocardiographic studies to assess the SD risk in young sportspeople [33]. As coronary anomalies are one of the most common etiologies of SD of a cardiac nature and proximal coronary anatomy may be readily and reliably observed, we believe that coronary artery evaluation should always be included in the echocardiographic screening of athletes. Moreover, visualization of these vessels by TTE is easier in athletes because of their favorable chest conformation, the prolonged diastolic time due to bradycardia and a real increase in coronary size due to training [34].

On the other hand, the arguments against echocardiographic screening are limited human resources and the large financial investment in performing TTE. A recent cost-benefit analysis of pre-participation echocardiographic screening compared the cost of screening to the dollar value of a statistical life saved and showed that if screening saves 10 lives, its estimated benefit is between 67 and 83 million dollars, thereby favoring screening even from an economic point of view [35].

TTE might therefore be a useful, accessible and non-invasive tool to increase the sensitivity of clinical and ECG screening and, together with the standard evaluation, identify the majority of common anomalies that lead to SD in athletes. Recommendations for multimodality imaging of AOCA have been recently published, supporting the use of echocardiography as first-line imaging modality [36].

In Italy, in the last 5 years, at least 10 young people between 10 and 20 years old have suffered cardiac arrest due to an AOCA, according to reports that appeared in newspapers and on TV. The non-medical press is fundamental in becoming aware of these cases: curiously, these statistics are based on news that appeared in these media forms. Even in our clinical case, without the news of the boy who had died suddenly due to AOCA, the mother would not have been alarmed and the same diagnosis could not have been made in her son.

In Marquez's novel, the mother was the only person who would have been able to save her son, if she had known the risk he was running.

In our case, the mother was able to save her child thanks to her obstinacy, teaching us many things. First, mothers do their utmost to save their children, especially if they find allies among physicians.

Second, we find what we seek and we seek what we know. The insistence of that mother allowed the same cardiologists with the same TTE machine to discover a serious pathology that three months earlier, with the same tools, they had missed. AOCA is not an easy diagnosis, but it is certainly helpful for cardiologists to perform TTE thinking that a *visionary* mother is looking over their shoulder. The coronary arteries
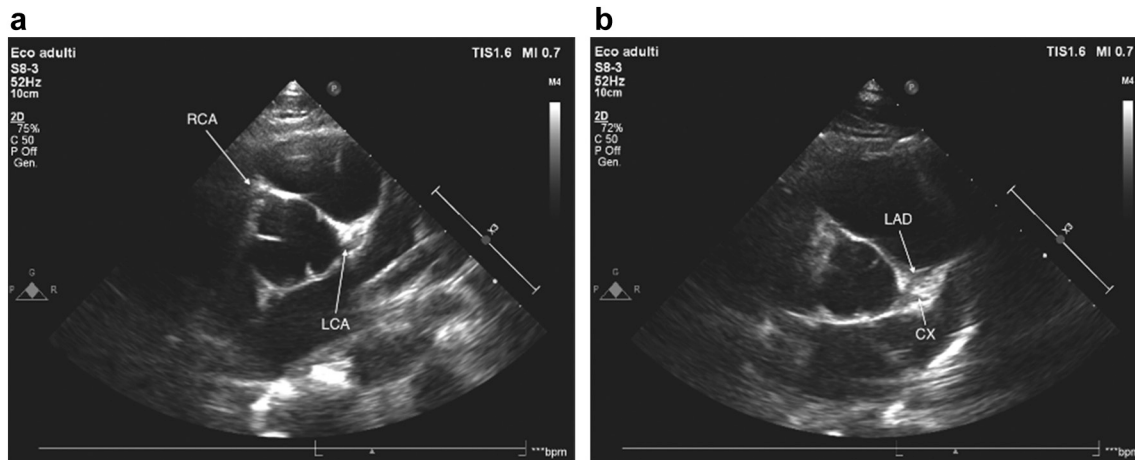
Fig. 3. TTE of normal coronary arteries (parasternal short axis projection). Coronary ostia (a) and LCA bifurcation (b). CX: circumflex coronary artery, LAD: left anterior descending artery, LCA: left coronary artery, RCA: right coronary artery.

that appear in Fig. 3 were not chosen among the best ones, but represent the average that can be obtained in the TTE lab any morning, relying on a young chest and on modern instrumentation. Even if no abnormal coronary arteries are found, this attitude will make it easier to identify pathologies such as cardiomyopathies or aortic diseases.

Third, we do not have to wait for coincidences. Already in 1976, at the time of the newborn M-mode, the almost simultaneous death of two athletes had made public opinion ask whether it was necessary for all athletes to undergo echocardiographic screening. Half a century later, in the era of 3D-echocardiography, we must seriously ask ourselves if time has come to screen not only athletes, but all young people over 10 years old. If the media and mothers are already doing so much to prevent juvenile SD, cardiologists must prove they are up to it.

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