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Sudden cardiac death and coronary artery anomalies in the athletes: A narrative review

ROBERTO BIANCO, GIADA ANNARUMMA , AMOS COSIMO COCOLA, FELICE SIRICO, VERONICA ROMANO

Department of Public Health, University Federico II of Naples, Italy

ABSTRACT

Sudden cardiac death (SCD) in the athletes is an unexpected dramatic event. The mechanism underneath SCD is often represented by a ventricular tachyarrhythmia arising as complication of a broad spectrum of cardiovascular diseases, with a silent clinical course. Therefore, SCD often represents the onset manifestation of an underlying heart disease. To prevent SCD in the athletes, several international guidelines proposed pre-participation screening protocols to identify high-risk subjects. Behind atherosclerotic diseases, other structural or functional conditions have been related to SCD, such as hypertrophic cardiomyopathy, QT-long syndrome, arrhythmogenic right ventricular dysplasia, and others. Among these, the coronary artery anomalies represent almost the 20% of all cases. The coronary artery anomalies can be classified into anomalies of origin, course and termination and can be isolated or associated with other congenital cardiac defects. Some of them are rarely symptomatic. Others could impair heart function and determine SCD. Some others determine secondary cardiovascular diseases such as increased risk of endocarditis, secondary aortic valve diseases, myocardial ischemia, and others. Innovative diagnostic and therapeutic options allowed to recognize the different coronary artery anomalies, preventing SCD in athletes. The aim of this review was to analyse coronary artery anomalies to understand their implications in SCD in athletes.

Keywords: Coronary artery; Sudden cardiac death; Athletes.

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Corresponding author. *Department of Public Health, University Federico II of Naples, Italy.*

E-mail: giada.annarumma@gmail.com

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INTRODUCTION

Sudden cardiac death (SCD) of a young athlete during sports is an event of high emotional impact, unexpected, dramatic and psychologically devastating for the entire community (Corrado et al., 2003). Sports SCD can be defined as "*a death that occurs within one hour of the onset of acute symptoms, in temporal coincidence with sports activity, and in the absence of external causes capable of causing it*" (Zeppilli, 1983).

The causes of cardiac arrest in young athletes have multiple anatomical substrates, the most represented being hypertrophic cardiomyopathy in the USA, followed by congenital anomalies of the coronary arteries, rupture of the aorta and coronary atherosclerosis (Maron et al. 1996). Hypertrophic cardiomyopathy is characterized by an abnormal extracellular matrix (ECM) turnover leading to myocardial fibrosis, an event accompanying most forms of myocardial diseases, suggesting that ECM changes could be involved in progression of the disease (Belviso et al., 2020a, 2020b; Castaldo et al., 2013). Arrhythmogenic right ventricular heart disease is the leading cause in Italy, followed by both acquired and congenital heart disease (Corrado et al., 1990), mitral valve prolapse, conduction tissue pathology and myocarditis. Among congenital diseases affecting the heart, post-mortem and retrospective studies historically reported a prevalence of 1-2% (Roberts, 1986) of congenital anomalies of the coronary arteries (Yamanaka and Hobbs, 1990). However, in recent studies, the prevalence of these anomalies is 0.44% (Angelini et al., 2018).

The congenital anomalies of the coronary arteries represent an heterogeneous groups of conditions, and some of them play a non-negligible role in SCD among athletes (Frescura et al., 1998; Maron et al., 2009) , increasing the risk of death during exertion of about 79 times (Corrado et al., 2003).

Two-thirds of athletes with congenital anomalies of the coronary arteries are asymptomatic (Basso et al., 2000), but some have syncope or SCD as the only manifestation (Van Hare et al., 2015).

The congenital anomalies of the coronary arteries cause SCD more frequently in young athletes (Harmon et al., 2015), and less commonly in individuals older than 40 years of age (Gräni et al., 2018).

This review aims to analyse the anomalies that have the greatest impact on SCD, classifying them for simplicity into anomalies of origin, course and termination.

NORMAL ANATOMY OF THE CORONARY ARTERY SYSTEM

Left coronary artery

The heart is supplied by the right and left coronary arteries, which originate from the ascending aorta, in particular from the anterior and left posterior Valsava sinuses. The arterial circulation has the shape of an inverted crown arranged obliquely along the cardiac axis, consisting of the intersections of the marginal arteries on the acute and obtuse margins, and the descending arteries at the apex.

The first section of the left coronary artery (LCA) is called the common trunk and runs in the epicardium between the pulmonary trunk and the left atrium. It originates from the left anterior aortic sinus of Valsalva and is usually 1-2 cm long. In two thirds of cases it divides below the left auricle into anterior descending (AD) artery and circumflex artery (CA), in one third of cases an intermediate artery arises thus forming a trifurcation that follows the path of a circumflex branch (Edwards et al., 2010).

The AD artery is one of the two main components of the LCA (Angelini et al., 1999). It supplies the anterolateral myocardium, apex, and interventricular septum, covering the 45-55% of the left ventricular mass and it is therefore considered the most critical vessel in terms of myocardial blood supply.

It passes to the left of the common trunk of the pulmonary artery and continues anteriorly in the anterior interventricular sulcus to the apex of the heart (Brown and Borger, 2019). The AD can be divided into a proximal segment (from the origin to the origin of the first septal perforator), a middle segment (from the first septal perforator origin halfway to the left ventricular apex) and a distal segment (from this halfway point to the apex itself). Its normal length is from 10 cm to 13 cm (Villa et al., 2016). The anterior descending artery gives rise to two groups of branches: the diagonal branches and the septal branches. The diagonal branches of the AD artery usually supply the anterior wall of the left ventricle. The number and course of the diagonal branches is variable; there is usually at least one diagonal branch. The septal branches arise perpendicularly from the ventral portion of the AD artery. They are smaller in size than the diagonal branches and provide vascularity to the anterior two-thirds of the interventricular septum (Brown and Borger, 2019). The terminal part of the AD artery surrounds the apex of the heart and supply the lower portion of the left ventricle. The AD terminates at the cardiac apex, or 1 to 2 cm before or after the apex (Angelini et al., 1999). In some subjects, the right coronary artery is larger, and its distal branches reach the apex of the heart.

Right coronary artery

The Right Coronary Artery (RCA), which can be principally considered the artery that supplies the right side of the heart, generally arises from an ostium located just below the sinotubular junction, in the middle of the right anterior sinus of Valsalva of the ascending aorta (Angelini et al., 1999).

It passes anteriorly and to the right between the right auricle and the pulmonary artery and then dips down almost vertically in the right atrioventricular sulcus. When the RCA reaches the acute margin of the heart, it continue posteriorly in the sulcus toward the junction of the atrial and ventricular septa, the so called crux cordis, often terminating in the circumflex branch of the left coronary artery (Villa et al., 2016).

The RCA, which usual length varies from 12 cm to 14 cm, provides branches to the right atrium and ventricle, the atrioventricular septum and portions of the left chambers.

It is divided into proximal, middle, and distal segments. The proximal segment goes from the origin halfway to the acute margin. The middle segment runs from this halfway point to the acute margin itself. The distal segment goes from the acute margin to the base of the heart at the junction of the atrial and ventricular septa (Macdonald et al., 2011). In 50–60% of individuals, a conus branch arises as the first branch of the RCA to supply the right ventricular outflow tract. The conus branch, sometimes defined "*third coronary artery*" can serve as an important source of collateral supply to the left anterior descending artery through the so-called "*circle of Vieussens*" (Angelini et al., 1999). The second branches usually consist of the sinoatrial node artery and several anterior branches that supply the free wall of the right ventricle (Kim et al., 2006). The sinus node artery originates from the right (66% of the cases) and passes in the groove between the right auricle and the ascending aorta surrounding the base of the superior vena cava to supply the sinus node and both atria (Villa et al., 2016).

The branch to the right ventricle at the junction of the middle and distal RCA is called the acute marginal branch (Kim et al., 2006). The right marginal branch arise as the RCA approaches the acute margin of the heart and continues along this border toward the cardiac apex and it supplies the right ventricle free wall (Kim et al., 2006).

In the majority (80%) of individuals, the RCA continues forwards from the crux along the posterior interventricular groove to become the posterior descending artery, running to the apex of the heart. This is by convention called RCA dominance (Geuns and Cademartiri, 2005). The atrioventricular nodal branch is a small branch to the atrioventricular node; the posterior interventricular branch is the final major branch, which lies in the posterior interventricular sulcus (Villa et al., 2016).

CORONARY ARTERY ANOMALIES ANOMALIES OF ORIGIN

High take-off

The origin of the RCA or LCA may be above the aortic cusps or above the sinotubular junction. Both ostia in 6% were found above the sinotubular junction (Edwards and Vlodaver, 1971) but the most affected is RCA (Frescura et al., 1998).

The cause of the high origin of the coronary arteries is due to malrotation of the aortic root in embryonic development which involves a deviation of the coronary artery with a reduction in diastolic flow important for the purpose of myocardial perfusion (Dotan et al., 2013).

Some patients have typical or atypical symptoms of angina with exercise, others may have SCD (Basso et al., 2000).

Coronary ostial atresia

It is defined as the absence of the left main ostium with the AD and CA connected but ending blindly and supplied by the right coronary artery (RCA) via collaterals. The common trunk may be normal, hypoplastic, or atretic. The clinical presentation is non-specific and widely variable depending on the degree of collateral circulation and myocardial perfusion. Some patients become symptomatic early in life, mostly with congestive heart failure and syncope, whereas others remain asymptomatic into late adulthood, before presenting mainly with angina. Sometimes the first presentation reported of this anomaly is a sudden cardiac death (SCD) (Alsalehi et al., 2019).

It is a rare anomaly, difficult to diagnose (goes into differential diagnosis with ALPACA). Non-conservative treatment is recommended in symptomatic patients, i.e. myocardial revascularization with coronary reconstruction osteoplasty (Alsalehi et al., 2019).

Ostial plication

Another condition associated with SCD is ostial plication, a stenosis of the coronary ostium attributable to a valve-like ridge as a consequence of a fold in the elastic tunica media of the aorta. Plication of the aortic wall leads to a "*valve-like*" ridge that can act as a door blocking inflow during diastolic filling. Consequent ischemia may produce a life-threatening arrhythmia (De-Giorgio and Arena, 2010). The surface area of the ridge must exceed 50% of the coronary ostial lumen to be related to sudden death (Virmani et al., 1984).

Single coronary artery

The origin of a single coronary artery is an extremely rare anomaly present in 0.0024-0.044% of the population (Desmet et al., 1992). The anomaly is defined as the origin of a single arterial coronary trunk from a single ostium which can be the left or right Valsalva sinus and then divides (Villa et al., 2016). It can also be classified according to the anatomical course: "*type I*" follows the normal course of the left or right coronary; "*type II*" has an abnormal origin from the proximal segment of the other coronary artery; "*type III*" is

characterized by a single artery originating from the right Valsalva sinus with descending-anterior and circumflex originating from the common trunk (Lipton et al., 1979).

Although the abnormalities are usually benign, if the course of the right coronary artery is between the pulmonary artery and the aorta it can cause myocardial ischemia and SCD (Yurtdas and Gülen, 2012).

The proximal stenosis at the origin of the single trunk is critical due to the impossibility of forming collateral circles (Nieman et al., 2001).

Anomalous origin of the coronary artery from the pulmonary artery

The anomalous origin of the coronary arteries can occur from the pulmonary artery at different levels: from the trunk or from the right or left main branches.

The possible anomalous origins are: i) left coronary artery from the main trunk of the pulmonary artery or from the main branches; ii) CA from the pulmonary trunk or main branches ; iii) left and right coronary artery from the pulmonary trunk.

The most common form of this type of anomaly is the origin of the left coronary artery from the pulmonary artery and the right coronary artery from the aorta which is known as Bland-White-Garland syndrome (Bland et al., 1933). The anomaly is estimated at 1 in 300,000 births (Dodge-Khatami et al., 2002).

In this syndrome, myocardial blood supply occurs by means of collateral circulation between the left and right coronary arteries with inversion of the flow towards the pulmonary artery.

The abnormal origin of the coronary artery from the pulmonary artery then generates a left-to-right shunt.

The shunt causes blood flow to the myocardium that becomes dependent on the coronary artery originating from the aorta.

If the collateral circulation does not allow a good myocardial circulation and the patients are not treated, they do not reach the first year of life and this event occurs in 90% of cases. Consequently, few patients have a well-developed collateral circulation that allows survival to adulthood (Wesselhoeft and Fawcett, 1968).

During foetal life, this anomalous origin is tolerated as pulmonary and systemic pressures are similar. At birth, there is a drop in pulmonary pressure and an increase in systemic pressures, consequently the blood coming from the left artery decreases and there is a reversal of the flow which can be the cause of myocardial ischemia.

The diagnostic suspicion is based on growth delays, pallor, dyspnoea. On auscultation there is a continuous murmur. Ischemic changes are present in the resting ECG. It is useful to complete diagnostic assessment with heart ultrasound and Doppler examination to evidence the coronary ostia and a continuous flow in the pulmonary artery (Swensonn et al., 1988).

These anomalies are usually asymptomatic with a high risk of SCD, chest pain or arrhythmias (Corrado et al., 2006).

Surgical treatment is always indicated and aims to re-create the double coronary circulation, through different approaches (ligation of the anomalous coronary artery, coronary reimplantation, Takeuchi procedure, direct reimplantation of the left coronary artery into the aorta) (Dodge-Khatami et al., 2002; Lange et al., 2007).

Origin of the coronary artery or branch from the opposite or noncoronary sinus and anomalous course

The prevalence of this anomaly is 0.9-0.11% in the general population, identified with traditional coronary angiography (Danias et al., 2001; Desmet et al., 1992).

There are four variants of anomalous origin from the opposite sinus:

1. the RCA originating from the left coronary sinus.
2. the LCA originating from the right coronary sinus.
3. the CA or DA originating from the right coronary sinus.
4. the LCA or the RCA (or a branch of an artery) originating from the non-coronary sinus.

A coronary artery that arises from the contralateral sinus of Valsalva can take five paths to its perfusion territory:

1) Pre-pulmonary: anterior to the right ventricular outflow tract; it is generally not haemodynamically significant and seldom associated with angina. This anomaly usually involves the LMCA and it is often found in tetralogy of Fallot;

2) Retro-aortic: Posterior to the aortic root. It passes posteriorly and into the space between the posterior sinus of Valsalva and the interatrial septum, where normally there are no vascular structures. This variant does not seem haemodynamically significant but may complicate surgery of the cardiac valves. This anomaly usually involves an artery arising from RCA or right sinus of Valsalva that supplies the distribution of LCA or CA artery;

3) Inter-arterial: Between the aorta and pulmonary artery. This course has been recognized as having serious prognostic implications associated with more severe prognosis and increased risk of SCD especially in young individuals. One hypothesis is based on the fact that exercise leads to expansion of the aortic root and pulmonary trunk and this may increase the existing angulation of the coronary artery, decreasing the luminal diameter. Moreover, the vessel is often hypoplastic with an aberrant course within the aortic wall and it is exposed to a lateral compression over the entire proximal intramural tract (intussusception into the aortic wall). However, in these patients, resting electrocardiograms are usually normal and stress tests are not always positive for inducible ischaemia (Angelini et al., 2002);

4) trans-septal: The coronary artery takes a subpulmonic course. The artery traverses anteriorly and inferiorly through the interventricular septum and takes an intramyocardial course, giving off septal branches and finally emerging at its normal epicardial position. The arteries most commonly involved are the AD or LCA.

This anomaly is characterized by the hammock sign, which refers to the "*downward dip*" that the coronary artery makes as it traverses below the level of pulmonic valve in the septal myocardium. With anomalous transseptal course, the coronary artery arises from the contralateral artery or cusp, courses downward and forward in the interventricular septum followed by an upward and leftward course as it emerges out in the anterior interventricular groove (Moore and Agarwal, 2014).

5) retro-cardiac: the path is in the posterior AV groove, behind mitral and tricuspid valves. The clinical relevance of this coronary anomaly lies in the fact that the atypical origin and course causes coronary arteries to develop atherosclerosis more easily.

In about 15% of patients with CAAs, myocardial ischemia can develop in the absence of atherosclerosis. In addition, some potential mechanisms have been proposed to explain ischemia and SCD: spasm of the anomalous coronary artery (possibly as a result of endothelial injury or ischemia caused by its long distance), acute angle of take-off of the anomalous vessel (which may become kinked and occluded during exercise) and the related slit-like orifice (Angelini et al., 2002).

ANOMALIES OF COURSE

Myocardial bridging

Normally, in human hearts, coronary arteries and their branches run in the loose connective tissue of the subepicardial space (Angelini et al., 1999). In myocardial bridging, a portion of epicardial coronary artery, known as a tunnelled segment, passes through the myocardium for a short part before re-entering the epicardial fat. The length of the myocardial bridge most often varies between 10-50 mm (Villa et al., 2016). It then branches normally and terminates within the myocardium (Angelini, 2007). This congenital coronary anomaly results in systolic compression and remains clinically silent in the majority of cases. Any epicardial artery can be affected but bridging of the middle segment of the left anterior descending is the most common; occasionally the circumflex, diagonals, and right coronary artery (RCA) are also involved (Corban et al., 2014). Since the myocardial bridging prevalence varies between 0.15%-25% angiographically and 15%-86% at autopsy, its frequency in the general population suggests that it should be considered a normal variant (Angelini et al., 1999; Angelini, 2007; Villa et al., 2016), rather than an anomaly (Ghosh et al., 1994).

However, the prevalence of myocardial bridges varies greatly based on the technique used, highlighting the importance of differentiating a significant functional finding from an anatomic finding. In incomplete myocardial bridging, the involved artery extends down to and touches the myocardium but does not completely enter before extending back up into the myocardium. Complete myocardial bridging is seen in up to 20% of asymptomatic patients and is a very rare cause of ischemia However, rare cases of myocardial bridging are related to ischemia and atypical angina or even death (Tio et al., 1997). Possible causes are endothelial dysfunction, a delay in diastolic reopening of the intramyocardial segment of the artery that was compressed during systole and a deeper intramyocardial course of the bridge, in contrast to the more benign superficial myocardial bridges (Ferreira et al., 1991; Kumari et al., 2011; Morales et al., 1993). In addition, there is a high prevalence (41%) of myocardial bridging in adults with hypertrophic cardiomyopathy (HCM) (Sorajja et al., 2003). In these patients, the myocardial bridge tends to be deep, but it does not appear to influence prognosis and the risk of sudden events death in adults (Basso et al., 2009; Olivotto et al., 2009). Therefore, in asymptomatic adults' patients with HCM, the myocardial bridge appears to be a benign condition that does not warrant any treatment.

However, the myocardial bridging has not been ruled out as a possible cause of ischemia and sudden death in younger individuals with HCM. Treatment with stent implantation, coronary artery bypass surgery or surgical unroofing via supra-arterial myotomy may improve quality of life in adult symptomatic patients with HCM and myocardial bridging, as well as reduce risk of SCD and alleviate symptoms in younger patients (Basso et al., 2009).

On the other hand, patients with coronary anomalies or myocardial bridging may be at increased risk of ischemia during exercise, when there is an increased oxygen demand and ischemia could also favour arrhythmic risk in such a context. Therefore, it is quite crucial to identify for each patient what is the level of exercise that could be beneficial and when the risk of adverse events could overcome the advantages. Athletes-patients with myocardial bridging requiring treatment, even beta-blockers only, should be excluded from participating in competitive sports and should be adequately informed about recreational activities (Castelletti and Crotti, 2020).

ANOMALIES OF TERMINATION

Coronary artery fistula

A coronary fistula (CAF) or coronary arteriovenous fistula is a congenital or acquired abnormal vascular communication of the coronary arteries with the pulmonary artery, coronary sinus, cardiac chamber, or the superior vena cava, without an interposed capillary bed. Fistulas which end in the right heart chambers represent about 60% of cases.

CAFs are uncommon coronary artery abnormalities (McNamara, 1969) and can be classified according to their origin or drainage site: RCA is the most common origin site of CAFs, being the 50%–55% of cases. AD represents about the 35%–40% of cases, and CA accounts the 5%–20% cases (Gowda et al., 2006). The prevalence of CAFs originating from both the RCA and the AD is reported to be as high as 59% in cases of coronary-pulmonary fistula (Kim et al., 2010).

The prevalence of CAFs observed on computed tomographic angiography is 0.9% of congenital heart disease, which is higher than the previously reported prevalence of 0.002% – 0.3% at invasive angiography (Vavuranakis et al., 1995).

The causes of CAFs are either congenital or acquired (Challoumas et al., 2014). During foetal development, sinusoids nourish the primitive myocardium, then in adulthood, sinusoids become obliterated into the thebesian vessels and capillaries. Sinusoids that don't regress may contribute to a fistulous communication between the coronary arteries and cardiac chambers, that is, a coronary cameral fistula (Challoumas et al., 2014; Rittenhouse et al., 1975). Therefore, a remnant connection between coronary arteries and other mediastinal vessels (bronchial, pericardial, or mediastinal arteries) or the superior vena cava may cause a coronary arteriovenous fistula (Baroldi et al., 1956).

The acquired forms of CAFs are rare, but the incidence is increasing; they result from iatrogenic events such as coronary stent placement, coronary bypass surgery, trauma, chest irradiation (Luo et al., 2006; Mangukia, 2012), coronary vasculitis and myocardial infarction (Yu et al., 1986).

Small size fistulas (especially those that drain into the main pulmonary artery and the left ventricle) are much more common and are asymptomatic; however, many coronary artery fistulae continue to enlarge over time and eventually cause ischemia, or the deprivation of oxygen-rich blood to the heart tissues, which may cause fatigue and/or dyspnoea during exertion (Latson, 2007).

CAFs with large intracardiac shunts are rare in adults, as are most detected and repaired in childhood. These patients with larger CAFs show an unexplained loud continuous heart murmur or abnormalities at ECG or at chest radiography (Latson, 2007).

The amplitude of the shunt is determined by the size of the fistula and the pressure difference between the coronary artery and the drainage zone (Qureshi, 2006).

CAFs pathophysiology is caused by resistance of the connection, on the site of fistulous termination. Since the blood bypasses the myocardium and the perfusion distal decreases, a coronary steal phenomenon occurs, provoking angina or myocardial ischemia, during exercise or other activities that increase the oxygen demand.

Moreover, it should be stenosis of side branches secondary to thrombus associated with fistulous tracts, ulcerations and atherosclerosis (Vitarelli et al., 2002).

With a left-to-right shunt, CAFs drains into the systemic circulation and blood volume increases in right heart structures, pulmonary vessels, and left heart structures, causing pulmonary hypertension and volume overload in both ventricles. Conversely, the CAFs drains into the left atrium or pulmonary vein, and the risk of left heart volume overload increases.

Patients may become symptomatic, usually in the 5th or 6th decade of life, depending on the severity of the left-to-right shunt. Various symptoms, including moderate dyspnoea, fatigue, angina, congestive heart failure, and myocardial infarction, have been reported (Shiga et al., 2008). CAFs are also associated with atrial fibrillation, ventricular tachyarrhythmia (Heart et al., 2010; Kugelmass et al., 1992), valvular regurgitation (Morgan et al., 1972). In the 3%–12% of CAFs patients' infective endocarditis may occur.

Symptomatic patients with large fistulae may develop arrhythmias and heart failure. In these cases, surgical closure of the fistulae at the drainage site is recommended. Closure of a coronary artery fistula may be achieved through surgery or with the use of a coil or occlusion device introduced through a catheterization procedure.

While there are no exercise restrictions for patients with small CAFs with negligible symptoms, they have to be monitored regularly by a cardiologist to avoid developing arrhythmias, ischemia or heart failure. Patients with CAFs have a slightly higher risk than healthy ones of ectopic beats or sudden death during extreme exertion, for example during athletic competitions. Therefore, they should undergo a comprehensive pre-participation screening before these activities (Castelletti and Crotti, 2020).

CONCLUSIONS

Athletes with congenital anomalies of coronary arteries could be asymptomatic or present with chest pain, dyspnoea, palpitations, syncope (Ricci et al., 2018), and develop ventricular fibrillation, myocardial infarction or even SCD, especially during exercise.

For several years, traditional angiography has been the gold standard for the study of coronary arteries, with excellent sensitivity in demonstrating the origin and course of coronary arteries. Non-invasive methods for the evaluation of coronary artery anomalies includes transoesophageal echocardiography, transthoracic echocardiography (Ricci et al., 2020), multilayer computed tomography and magnetic resonance.

Especially in the so-called "*athlete's heart*" (D'Andrea et al., 2020), the delay in diagnosis of silent coronary anomaly may be fatal. Therefore, early identification of patients with a coronary anomaly is crucial as they

can be saved by appropriate therapy and join a particular form of physical activity, that has several benefits in cardiovascular patients (Palermi et al., 2020).

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