

Coexistence of anomalous right coronary artery and non-obstructive hypertrophic cardiomyopathy in two deaths under dissimilar circumstances

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ABSTRACT

A previously healthy 39-year-old man had collapsed while playing football and was pronounced dead on arrival to a local hospital. A post-mortem examination revealed a rare combination of two uncommon congenital diseases of the heart; an anomalous origin of the right coronary artery and borderline non-obstructive hypertrophic cardiomyopathy, each with a propensity to cause sudden death during physical exertion. Few months later a 51-year-old man who died following injuries sustained in a road accident also showed identical anomalies of the heart. Aetiology of sudden cardiac death (SCD) during sports is discussed with special emphasis on congenital coronary artery anomalies (CCAA) and hypertrophic cardiomyopathy (HCM).

Keywords: Cardiomyopathy, anomalous coronary artery, sudden cardiac death, arrhythmias

INTRODUCTION

Sudden death of a healthy young athlete in sports is uncommon and victims include both competitive athletes and non-athletes. Sudden death in apparently fit person while taking part in a sporting event draws the attention of concerned officials and the general public. Death can be due to a direct result of the sporting activity such as injuries sustained during sports or due to an indirect

cause aggravating a pre-existing natural disease. A proper investigation including a post-mortem examination is essential to dispel any suspicion on the circumstances of the death and also in taking appropriate measures to prevent such deaths.

Retrospective studies on sudden deaths in young athletes have shown that cardiovascular diseases are the major cause of deaths.¹⁻³ Atherosclerotic coronary artery disease is responsible for the majority (80%) of sudden cardiac deaths (SCD) among athletes over 35 years.⁴ A study by the Ameri-

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can Heart Association on SCD in young athletes (<35 years) reported that HCM (36%) and CCAA (19%) were the two leading causes. Other causes included myocarditis (6%), ruptured aortic aneurysm (5%), tunnelled left anterior descending artery (5%), aortic valve stenosis (4%), dilated cardiomyopathy (3%) and arrhythmogenic right ventricular dysplasia (2%).⁵ Such occurrence has prompted sports authorities to implement pre-participation screening programmes for the competitive athletes in order to detect any cardiac disease with a potential to cause morbidity or mortality.

We report two rare cases of the coexistence of anomalous right coronary artery (RCA) and non-obstructive hypertrophic cardiomyopathy (HCM) in two patients with SCD deaths under dissimilar circumstances. Aetiology of SCD during sports is discussed with special emphasis on CCAA and HCM.

CASE REPORTS

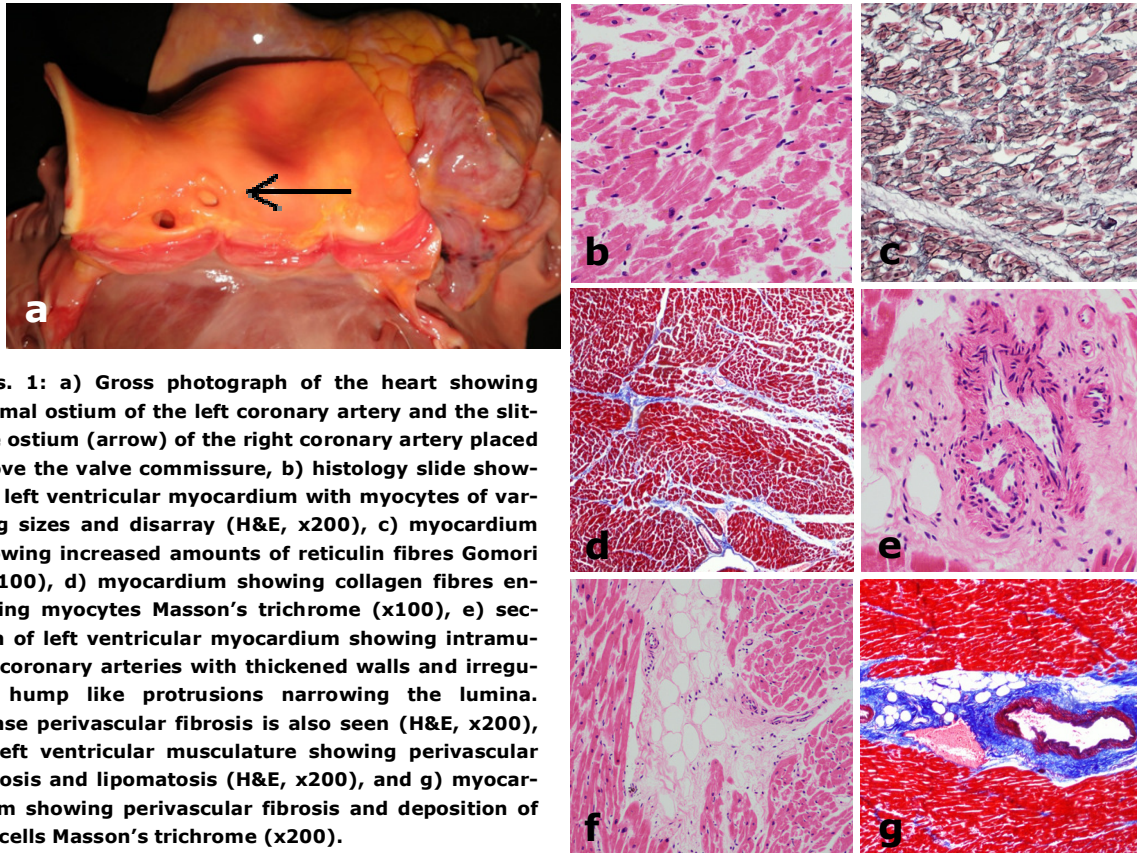
CASE 1: The was a previously fit and healthy 39-year-old man who had been playing football on a regular basis. On the day he died, he had collapsed 40 minutes into uninterrupted playing and struck his head on the wooden floor of the indoor stadium. Cardiopulmonary resuscitation was provided at the site and he was rushed to the local hospital where he was pronounced dead on arrival. There was no history of any illnesses or any complaints or distress while engaged in strenuous physical activities. There was no family history of any cardiac disease.

A post-mortem examination conducted the following day revealed a well-built, 87kg young male. There were three abrasions

0.2 x 0.1cm, 0.1 x 0.1cm and 0.5 x 0.3 cm on the mid-forehead with underlying contusion 4.5 x 5cm due to the fall.

Examination of the cardiovascular system revealed a marginally hypertrophied heart (420gm). The measured thicknesses of the left and right ventricles were 15mm and 3mm respectively. The left ventricular wall including the inter-ventricular septum was of uniform thickness. The valves, papillary muscles, chordae tendinae and chambers were unremarkable. The myocardium was unremarkable macroscopically. The left coronary artery (LCA) had its origin from the centre of the left sinus of Valsalva while the circumflex and anterior descending branches were fully patent. The ostium of the LCA was patent and circular in shape. The RCA was found to be arising from the right margin of the left sinus of Valsalva placed 3mm above the sinotubular junction along the valve commissure. The RCA was seen to emerge from the aorta at an acute angle and was directed sharply downwards between the right border of aorta and pulmonary artery. The ostium of the RCA was slit like in shape (Figure 1a). The right RCA was patent throughout its passage up to the posterior inter-ventricular septum where it continued as the posterior inter-ventricular artery.

The thoracic and abdominal segments of the aorta were free of atheromatous changes except at the root of the aorta where there was minimal degree of atheromatous plaques. The mucosa of the tracheo-bronchial passage was congested with some inhaled particulate food matter in the lower passages. Left lung weighed 620 gm and right lung was 530 gm and both were oedematous. The



Figs. 1: a) Gross photograph of the heart showing normal ostium of the left coronary artery and the slit-like ostium of the right coronary artery placed above the valve commissure, b) histology slide showing left ventricular myocardium with myocytes of varying sizes and disarray (H&E, x200), c) myocardium showing increased amounts of reticulin fibres Gomori (x100), d) myocardium showing collagen fibres encasing myocytes Masson's trichrome (x100), e) section of left ventricular myocardium showing intramural coronary arteries with thickened walls and irregular hump like protrusions narrowing the lumina. Dense perivascular fibrosis is also seen (H&E, x200), f) left ventricular musculature showing perivascular fibrosis and lipomatosis (H&E, x200), and g) myocardium showing perivascular fibrosis and deposition of fat cells Masson's trichrome (x200).

brain, liver, gastrointestinal tract and kidneys were all unremarkable. Blood and urine samples were negative for alcohol and drugs.

Most of the myocytes were of uniform size and contained regular nuclei. However, focal areas with myocytes of varying sizes and disarray were observed (Figure 1b). Occasional myocyte atrophy, degeneration and infiltration by histiocytes were also observed. These features were suggestive of focal hypertrophic cardiomyopathy changes. The second abnormality seen in the heart was in the connective tissue. There was an increase in reticulin fibres (Figure 1c) and fibrosis in the interstitium (Figure 1d). The third abnormality was in relation to the microvasculature. The small vessel walls (intramural coronary

arteries) showed thickening of the media and intima. Some of the vessels showed irregular hump like thickening of the wall protruding into the lumina causing partial obstruction of small vessels (Figure 1e). In addition there was perivascular deposition of mature fat cells (seen along with fibrosis) in the interstitium (Figures 1f and 1g). The changes seen could be categorised into three groups; focal myocardial fibre hypertrophy and disarray suggestive of cardiomyopathy, changes in the interstitium with increase in reticulin, fibrosis and lipocytes and small vessel disease; hypertrophy of the media with partial obliteration of the lumina.

CASE 2: Refer to Supplementary Text for details of case.

DISCUSSION

There are numerous studies reported on SCD in athletes. It is estimated that 80% of SCD occur during and 20% immediately after the events.⁶ Physical exercise leads to adjustments in the cardio-vascular system to meet the increased metabolic demand and this can trigger fatal arrhythmias athletes with compromised cardiac blood supply due to undiagnosed cardiac disease such as CCAA or HCM.

The most common CCAA encountered in SCD in fit individuals are coronary arteries originating from the wrong sinus of Valsalva. However, in majority of cases of CCAA there is no or minimal cardiac symptoms. The incidence of CCAA has been based coronary angiographic studies on patients referred for the assessment of cardiac functions and is reported to be between 0.6% and 1.3%.⁷⁻⁹ The commonest CCAA is the origin of the left circumflex branch from the right sinus of Valsalva.¹⁰ Anomalous origin of the LCA from the right sinus of Valsalva carries a greater risk of SCD than the anomalous origin of the RCA from the left sinus of Valsalva since bulk of the left ventricular myocardium is supplied by the LCA. In both our cases the RCAs originated from the left sinus of Valsalva.

Several mechanisms have been hypothesised as being responsible for the reduction in the blood supply to the myocardium during exertion in individuals with anomalous RCA originating from the left sinus of Valsalva. Firstly, when the anomalous RCA leaves the aortic sinus of Valsalva at an acute angle as in these two cases, it produces a slit like orifice restricting the amount of blood entering the coronary artery. The angulations were more pronounced in these two cases as

the RCA was taking off from a higher position in the aorta (3mm above the sino-tubular junction). Due to the same anatomical anomaly (seen in these two cases), a second mechanism has been described in which the ridge like lower border of the RCA ostium is pushed against the outer wall of the coronary artery. This movement further constricts the lumen during dilation of the aortic root in systole which would become more pronounced during exertion.¹¹ Furthermore, a valve like ridge with a surface area exceeding 50% of the coronary ostial surface area is said to further enhance the occurrence of SCD.¹⁰ However there was not present in our cases. The third mechanism is based on the positioning of the RCA between the root of the aorta and the pulmonary trunk which was observed in these two cases. It has been suggested that the RCA undergoes compression as it emerges between the pulmonary trunk and the aorta.⁹ It has also been suggested that the proximal part of the anomalous RCA is prone to undergo spasm as it lies between the pulmonary artery and the aorta.¹² Additionally, when the angle of take-off of the coronary artery is acute the proximal part of the coronary artery tends to have an intramural course in the aorta which in-turn will lead to added constriction of the coronary artery during dilation of the aorta.¹³ It has been shown that the acute take-off of the coronary artery by itself can cause SCD even in absence of anomalous origins.¹¹

A study on the clinical profile of young competitive athletes with anomalous origin of the coronary artery from the wrong sinus reported no clinical manifestations in 55% and in the remaining 45%, the only clinical manifestations were syncope and chest

pain.¹⁴ However, one study reported that SCD was the first manifestation of the illness in 50% of subjects. The only signs and symptoms indicative of a cardiac disease were palpitations, syncope and ventricular arrhythmias.¹⁵ One study reported that 70% of the patients with anomalous origin of the RCA from the left sinus of Valsalva were symptomless and the other 30% died suddenly.¹⁶ Among competitive athletes who died suddenly, cardiovascular disease was diagnosed or suspected only in about 25% prior to the participation in the event.¹⁷ Thus the paucity of clinical signs and symptoms prior to the episode causing the death is one of the main reasons for non-identification of young athletes at risk of SCD. A study conducted on siblings of children diagnosed with anomalous coronary arteries has found five families with a second child afflicted with a coronary artery anomaly and the researchers suggested a possible genetic basis for CCAA.¹⁸

HCM is a familial autosomal dominant disorder and is due to mutations in any one of the 12 or more genes that encode cardiac sarcomere proteins. HCM heart characteristically weighs over 600gm with gross hypertrophy of the left ventricle. These were absent in the two cases under discussion. However, in both cases the microscopic examination revealed the spectrum of histopathological changes typically described in HCM; myocytes of varying sizes with hypertrophy and disarray, interstitial and perivascular fibrosis and narrowing of the lumina of small vessels (intramural coronary arteries) due to hyperplasia of media and intima.¹⁹

Myocyte disarray in HCM is associated with disorganisation of the intercellular junc-

tions in the affected zones of the heart. These structural variations in the intercellular junctions involve both desmosomes and the gap junctions that are responsible for mechanical coupling and electrical coupling respectively. It has been shown that the disorganisation of the gap junctions between myocytes can be a substrate for arrhythmia generation and propagation.²⁰

In both our cases, small vessels with narrowed lumen were seen in association with areas of fibrosis in the myocardium. Myocardial fibrosis in HCM is said to be closely linked with diminished myocardial blood supply due to narrowing of lumen of small vessels consequent to thickened media and intima.²¹ It has been shown that the degree of intramural coronary artery dysfunction in HCM is a strong predictor of the progress of the disease.²² Finding of thickening of walls and narrowing of lumen of intramural coronary arteries in HCM has led to the belief that HCM is a disease involving abnormalities in both sarcomere and connective tissue elements. A study on HCM patients with mild or no symptoms had shown that the presence of myocardial fibrosis was associated with increase in the frequency of ventricular tachyarrhythmia.²³ Therefore it is evident that areas of myocardial fibrosis and myocyte disarray can serve as foci of electrical instability.

Our second case had thickening and ballooning of the mitral valve leaflets and thickened chordae tendinae. Floppy mitral valve and mitral chordae tendinae pathology have been described as associated abnormalities in HCM.²⁴ Due to the genetic heterogeneity of the population, the clinical and morphological features in HCM can be diverse.

Cardiac dimensions of a highly trained athlete may fall within the 'grey zone' shared with borderline cases of HCM causing a diagnostic dilemma to the clinicians and pathologists.²⁵ It has also been shown that the appearance of the characteristic morphological features of HCM may be delayed up to adulthood. Hence some researchers have advocated carrying out screening tests to detect HCM beyond 18-21 years.²⁶

We report that the two deceased were suffering from two congenital cardiac diseases; CCAA and borderline HCM each of which by itself could have led to SCD during physical exertion. Both CCAA and HCM are two conditions, which may remain dormant without causing many symptoms until SCD. These two cases portray the well-recognised extremes of the clinical spectrum of HCM and anomalous origin of coronary artery; the young male in Case 1 had a SCD during exertion and the male in Case 2 lived up to 51 years and died due to multiple injuries sustained during a road accident. A previous case has been reported in the literature where a 20-year-old man died during a football training session and he was found to have multiple coronary anomalies (including anomalous origin of RCA) and borderline HCM.¹³

As a means of preventing SCD among the competitive athletes, pre-participation screening have been advocated and tried out in many countries. A nation-wide screening programme of competitive athletes launched in Italy in 1982 had led to the reduction of SCD from 3.6 to 0.4/100,000 per year. It was mainly due to the diagnosis and disqualification of athletes with cardiomyopathy from

participating in competitive sports.²⁷ However, there is much controversy on the cost benefit of a comprehensive pre-participation cardiovascular screening programme at national level, as more invasive and costlier investigations are needed to diagnose lesions such as CCAA.²⁸

In conclusion, our cases reiterate the benefits of a thorough dissection of the coronary arteries during a post-mortem examination and the contribution of the histopathological examination in arriving at a comprehensive mechanism of death. It also highlights the value of implementing a pre-participation screening programme for competitive athletes, which could be carried out without much cost in a country with a relatively small population as in Brunei.

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CASE 2: A 51-year-old male with no previous history of any medical condition was admitted to hospital after being knocked down by a vehicle while riding a motor cycle. He died six hours after admission.

A post-mortem examination was conducted on the following day on the refrigerated body. The body was that of a thinly built adult male, weighing 54 kg. There were multiple abrasions, contusions and lacerations on the head, face, trunk and lower limbs. He had skull fractures associated with sub-arachnoid and subdural haemorrhages, contre-coup cerebral contusions, a large peri-renal haematoma, burst fracture of the third cervical vertebra and multiple fractures of the right lower limb. Other internal organs including the heart were free from any traumatic injuries. The lungs were oedematous.

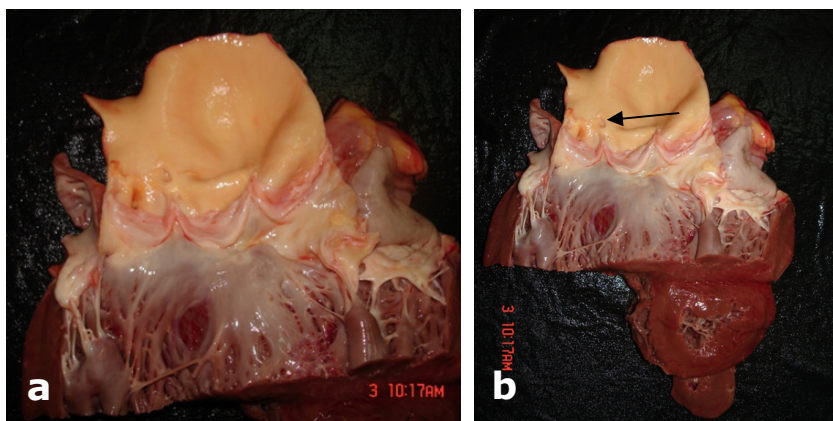
Furthermore, very interestingly examination of the heart revealed macroscopic and microscopic pathological features in the myocardium and RCA although they didn't play a role in the cause of death.

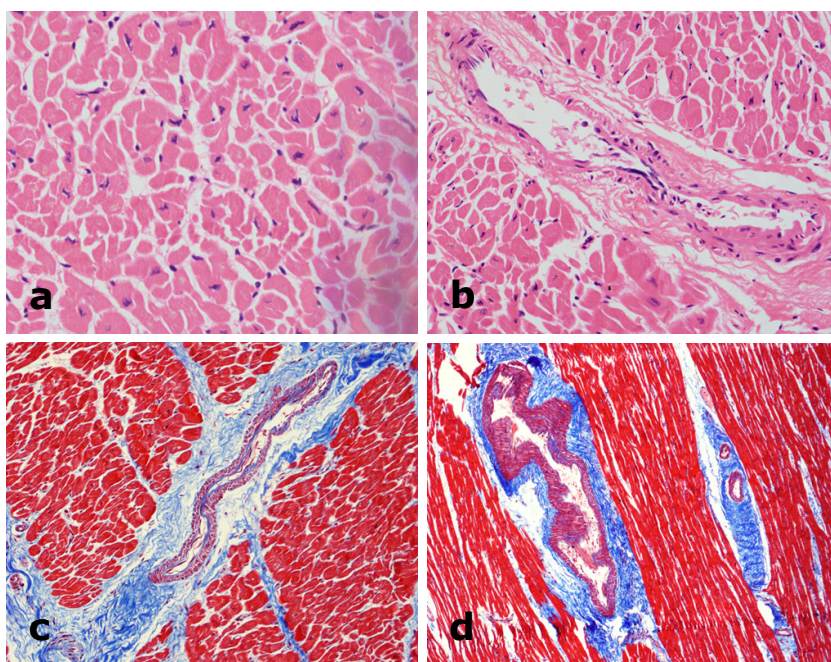
The heart weighed 320 gm, myocardium showed sub-endocardial whitish discolouration due to fibrosis in the left ventricular

wall. The mitral valve leaflets were enlarged, thickened and were ballooning upwards. The chordae tendinae of the mitral valve leaflets were thickened and shortened (Figure 2a). The left ventricular wall including the inter-ventricular septum was of uniform thickness and measured 14 mm. The right ventricular wall measured 3 mm. The LCA originated from the centre of the left sinus of Valsalva and the ostium was circular shaped. The anterior descending and circumflex branches showed 10-20% narrowing due to atherosclerotic changes. The RCA originated from the right margin of the left sinus of Valsalva 0.3cm above the valve commissure and had an acute take-off from the aorta with a slit-like ostium (Figure 2b). The RCA was seen to emerge between the aorta and pulmonary artery and coursed along the right atrio-ventricular groove. The RCA lumen was 20-30% narrowed due to atherosclerotic changes. Toxicological examination of blood and urine showed no alcohol or drugs. The cause of death was determined as multiple injuries following the road accident.

The samples taken from the inter-ventricular septum and free wall of the left ventricle were subjected to the same staining procedure described in Case 1.

Figs. 2: Gross photograph of the heart showing thickening of the mitral valve cusps, short chordae and subendocardial fibrosis, and b) showing slit like ostium (arrow) of the right coronary artery originating above the valve commissure and the normal ostium of the left coronary artery.





Figs. 3: a) Histology of the left ventricular myocardium showing myocytes of different sizes in disarray (H&E, x200), b) showing myocytes of different sizes and thickening of the intramural coronary arteries (H&E, x200), c) showing intra-myocardial, perivascular and septal fibrosis (Masson's trichrome, x100), and e) showing intramural coronary artery wall thickening with hump like projections, perivascular and focal fibrosis (Masson's trichrome, x100).

The microscopic features were very much similar to those observed in case 1 which showed three groups of histopathological features. The myocytes were of different sizes with some showing hypertrophy and myocyte disarray (Figure 3a). The microvas-

culature showed thickening of the media with protrusion of the intima causing obstruction of the lumina of the small vessels (Figure 3b). There was also intra-myocardial, perivascular and septal fibrosis (Figures 3c and 3d).