Non-atherosclerotic coronary artery disease and sudden death in the young

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Abstract

Objective—To assess prevalence and type of non-atherosclerotic coronary artery disease in young people (≤35 years) who died suddenly.

Design—A necropsy study of 150 consecutive cases of sudden death (that is, within 6 h of the onset of symptoms).

Results—Death was attributed to coronary artery disease in 48 cases: in 16 (33%) of them the disease was non-atherosclerotic. Twelve subjects (eight males and four females, age range 2–35 years, mean 24 ± 2) had congenital anomalies: a deep intramyocardial course in six, origin from the wrong sinus in three, and ostial obstructions in three. Sudden death was the first manifestation of disease in six cases. The other six had a history of palpitation or syncope or both. An electrocardiogram was available in five cases and showed ventricular arrhythmias in four; none had angina pectoris. Stress testing was available in two cases: neither showed any effort-dependent ST-T abnormalities. In six cases sudden death was related to physical exercise. Acquired non-atherosclerotic coronary artery disease was found in four cases: spontaneous coronary dissection in three previously symptom free patients and Kawasaki coronary arteritis in one child who had had acute myocardial infarction.

Conclusion—One third of the cases of fatal coronary artery disease were non-atherosclerotic with coronary artery anomalies being the most frequent form. Coronary artery anomalies should be suspected in young patients who have symptoms of ventricular arrhythmias without any overt signs and symptoms of ischaemia.

Clinical and pathological studies have shown that atherosclerotic coronary artery disease, often complicated by acute thrombosis, is the most common cause of sudden death in adults.1,4 The few studies of sudden death in young people showed that in this subgroup ischaemic cardiac arrest was often triggered by non-atherosclerotic coronary artery disease.4 The incidence, clinical significance, mechanism of ischaemia, and possibility of early diagnosis of non-atherosclerotic disease have not been studied, however.

We report here the clinical and pathological findings in a group of young people who died suddenly of non-atherosclerotic coronary artery disease since 1979 in the Veneto region (northeast) of Italy.

Patients and methods

The Veneto region covers an area of 18 368 km². In the 1985 census it had a population of 4 370 533. The residents are white and the population is ethnically homogeneous. Italian law does not require postmortem examination of all persons who die suddenly so fatal cases were reported to pathologists or medical examiners only at the specific request of the General Attorney. All sudden deaths reported during this period were included in this study, but we do not know how many cases were not referred for postmortem examination. After necropsy the hearts were forwarded to the Institute of Pathological Anatomy of the University of Padua for detailed morphological study.

From 1 January 1979 to 30 September 1991 we collected 150 consecutive cases of juvenile sudden death, which was defined as an unexpected natural fatal outcome within 6 h of the initial symptoms in people aged 35 or less; cases of infant sudden death syndrome were excluded. The methods of investigation have been reported in detail elsewhere.8

There were 126 sudden fatal cardiovascular events and death was attributed to coronary artery disease in 48 cases: 32 had obstructive atherosclerotic coronary artery disease and 16 (33%) had non-atherosclerotic coronary artery disease.

Sudden death was deemed to be coronary in origin in the absence of other cardiac pathology and in the presence of ischaemic damage in the myocardial territory supplied by the affected coronary artery.

Results

The table shows the main clinical and pathological findings.

Twelve individuals (8 male and 4 female, aged 2–35 years (mean 21.6) had congenital coronary anomalies. In six the fatal event occurred at rest and in six it was related to physical exercise (during effort in five and after effort in one). In six sudden death was the first manifestation of the disease. The other six had a history of palpitation or syncope or both; a resting electrocardiogram was available in five and had showed isolated ventricular extrasystoles in four (fig 1A and B). Ambulatory Holter monitoring was available in two. It showed complex ventricular arrhythmias consisting of ventricular couplings in patient 5 and non-sus-
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Sudden death in the young caused by non-atherosclerotic coronary artery disease: main clinical and pathologic findings in 16 subjects

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age, sex</th>
<th>History</th>
<th>Previous ECG findings</th>
<th>Circumstances of death</th>
<th>Main pathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22, M</td>
<td>Athlete, palpitation</td>
<td>Ventricular extrasystoles</td>
<td>During effort</td>
<td>RCA from left coronary sinus</td>
</tr>
<tr>
<td>2</td>
<td>29, M</td>
<td>Athlete, palpitation</td>
<td>Ventricular extrasystoles, normal</td>
<td>During effort</td>
<td>RCA from left coronary sinus.</td>
</tr>
<tr>
<td>3</td>
<td>11, F</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>During effort</td>
<td>Left atrioventricular block.</td>
</tr>
<tr>
<td>4</td>
<td>19, F</td>
<td>Family history of sudden death; symptom free</td>
<td>Normal standard ECG</td>
<td>During sleep</td>
<td>Intramyocardial course of LAD</td>
</tr>
<tr>
<td>5</td>
<td>30, F</td>
<td>Palpitation</td>
<td>Multiform extrasystoles, ventricular couplets</td>
<td>At rest</td>
<td>Intramyocardial course of LAD</td>
</tr>
<tr>
<td>6</td>
<td>27, M</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>At rest</td>
<td>Intramyocardial course of LAD.</td>
</tr>
<tr>
<td>7</td>
<td>35, M</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>After meal</td>
<td>Slit-like lumen of left coronary artery.</td>
</tr>
<tr>
<td>8</td>
<td>14, M</td>
<td>Athlete, effort-induced syncope</td>
<td>Ventricular extrasystoles and unsustained ventricular tachycardia, normal stress testing</td>
<td>At rest</td>
<td>Intramyocardial course of LAD.</td>
</tr>
<tr>
<td>9</td>
<td>29, M</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>After meal</td>
<td>Valve-like ridge of right coronary artery.</td>
</tr>
<tr>
<td>10</td>
<td>2, M</td>
<td>Recurrent syncope</td>
<td>Not performed</td>
<td>After meal</td>
<td>Valve-like ridge of right coronary ostium.</td>
</tr>
<tr>
<td>11</td>
<td>7, F</td>
<td>Recurrent syncope</td>
<td>Normal standard ECG</td>
<td>After effort</td>
<td>Valve-like ridge of right coronary ostium.</td>
</tr>
<tr>
<td>12</td>
<td>35, M</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>After meal</td>
<td>Valve-like ridge of right coronary artery.</td>
</tr>
<tr>
<td>13</td>
<td>34, F</td>
<td>Asymptomatic</td>
<td>Not performed</td>
<td>During sleep</td>
<td>Spontaneous LAD dissection.</td>
</tr>
<tr>
<td>14</td>
<td>28, F</td>
<td>Pregnancy, Marfan; symptom free</td>
<td>Not available</td>
<td>At rest</td>
<td>Spontaneous LAD dissection.</td>
</tr>
<tr>
<td>15</td>
<td>23, M</td>
<td>Symptom free</td>
<td>Not performed</td>
<td>At rest</td>
<td>Kawasaki coronary arteritis.</td>
</tr>
<tr>
<td>16</td>
<td>6, M</td>
<td>Previous myocardial infarction</td>
<td>Not available</td>
<td>At rest</td>
<td>Kawasaki coronary arteritis.</td>
</tr>
</tbody>
</table>

RCA, right coronary artery; LAD, left anterior descending coronary artery; LM, left main coronary artery.

tained ventricular tachycardia in patient 8, in whom neither conduction disturbances nor ventricular tachycardia had been induced during electrophysiological study with programmed ventricular stimulation.

No patient had angina pectoris, and electrocardiographic stress testing in two patients (cases 2 and 8) had not shown any effort-dependent ST-T abnormalities.

Postmortem examination in six cases showed that a subepicardial coronary artery (the proximal tract of the left anterior descending branch in five (fig 2) and the intermediate branch of the left coronary artery in one (fig 3)) followed a deep intramyocardial course. The length of the intramyocardial course ranged from 10 to 25 mm and the depth from 4 to 8 mm. Histological examination showed that the intramyocardial coronary segments were separated from the subepicardial fat by a myocardial bridge and were also encircled by a muscular "sheath" that compressed and deformed the coronary lumen; moreover, we found myocardial disarray around the intramural segment in four cases (fig 4). In every case the myocardial tributary of the intramural coronary artery showed histological features of ischaemic injury, consisting of an acute myocardial infarction of the left ventricular lateral wall (case 8) (fig 3B), a post-infarction scar in the interventricular septum (case 5), and signs of "hyperacute" myocardial damage such as contraction band necrosis (fig 2B) and wavy fibres in the anteroseptal wall of the left ventricle in the four other cases.

A coronary artery originated from the wrong aortic coronary sinus in three cases. In two (cases 1 and 2) both the right and left coronary arteries arose from the left coronary sinus (fig 1C) and the proximal tract of the right coronary artery ran between the aorta and the pulmonary infundibulum, following an intramural course in the aortic tunica media and with a slit-like lumen. We found scattered foci of contraction band necrosis in the posterosingal wall of the left ventricle in both cases and an extensive healed posterior myocardial infarction in one (case 2). In case 3 the left coronary artery had an anomalous origin from the right coronary sinus and ran between the aorta and pulmonary artery and partially within the wall of the aorta (fig 5); a large anterior subacute myocardial infarction was also seen.

Isolated malformations that obstructed the ostial lumen were found in three cases. In two (cases 11 and 12) the right ostium was obstructed by a valve-like ridge produced by a fold in the elastic tunica media of the aorta (fig 6). In the third (case 10) the left ostium had a slit-like lumen caused by stenosis (fig 7).

There was evidence of acquired non-atherosclerotic coronary artery disease in four cases (two male and two female, aged 6-34 years (mean 22.7 years)). In three previously symptom free subjects sudden death was caused by spontaneous coronary dissection: in one patient (case 14) with Marfan's syndrome who was pregnant, the left main stem was affected. In the other two (cases 13 and 15), who had no risk factors, the dissection affected the left descending coronary artery. Cystic medial necrosis was seen only in the case with Marfan's syndrome.

Case 16 died suddenly three years after a myocardial infarction. The postmortem examination showed Kawasaki coronary arteritis causing atheromas and thrombosis of all the proximal subepicardial coronary arterial trunks, leading to severe ischaemic cardiomyopathy.

Discussion

Postmortem examinations after sudden cardiac death in adults have shown extensive coronary atherosclerosis. Unlike these older populations, 33% of cases of fatal coronary artery disease in our juvenile series were caused by non-atherosclerotic dis-
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coronary artery disease as the cause of 5–35% of the cases of sudden cardiac death in young people. However, in contrast to previously published series in which the most common coronary anomaly was an origin from the “wrong” coronary sinus, we found a wider range of abnormalities including coronary ostial malformations and the coronary trunks following an intramyocardial course. This latter condition has long been regarded as a normal anatomical variant; however, recent clinical and pathological studies showed that myocardial bridging of the coronary arteries can lead to myocardial ischaemia manifested as angina, myocardial infarction, and sudden death. Faruqui et al reported a significant clinical improvement in ischaemic symptoms after surgical debridging of the coronary artery.

The role of intramyocardial coronary arteries in precipitating fatal myocardial ischaemia during strenuous exercise was confirmed by Morales et al in a pathological study. They found ischaemic damage at various stages of healing in the myocardial territory supplied by the intramural coronary artery. Nonetheless, the pathophysiology of myocardial ischaemia caused by gross epicardial coronary trunks taking an intramyocardial course is still unknown. Effort-induced ischaemia has been attributed to tachycardia which increases the myocardial oxygen requirement and reduces the coronary flow during diastole. Ischaemia at rest, however, could be caused by vasospasm in the intramural coronary segment and the transient formation of platelet aggregates provoked by mechanical trauma of the vessel wall. The importance of myocardial bridging in patients who died suddenly is uncertain because this feature is not uncommon in healthy individuals. Ferreira et al examined a series of hearts at necropsy. They found that myocardial bridging was common but that only a deep and long intramyocardial course caused myocardial ischaemia. We too found that when a coronary artery followed a particularly deep and long intramyocardial course it could cause ischaemic cardiac arrest. We often found signs of hyperacute, recent or healed ischaemic injury in the myocardial territory supplied by a tributary of the intramural coronary artery. Case 14 is paradigmatic in that, to the best of our knowledge, it is the first reported necropsy case of effort-induced regional acute myocardial infarction with a corresponding intramural coronary arterial trunk.

Where a coronary artery followed a long and deep intramyocardial course we found the distinctive histological feature of ventricular myocardium organised to form a “sheath” encircling the intramural coronary segment with myocardial disarray and fibrosis. Could this myocardial ring have caused paradoxical obstruction of the intramural coronary segment by inducing “extrinsic” prolonged constriction? At angiography this mechanism can be indistinguishable from an “intrinsic” coronary vasospasm. Alternatively, the myocardial disarray and fibrosis surrounding the

Figure 1 Electrocardiograms (ECG) and cardiac morphology in a 29 year old male athlete (case 2) who died suddenly during effort. (A) Resting ECG showing isolated ventricular extrasystoles. (B) The ECG during effort did not show any ischaemic ST-T changes or arrhythmias. (C) Gross view of the aortic root showing that both coronary ostia originated from the left coronary sinus (arrow).
intramural vessel might have acted as a "restrictive" perivascular tissue to limit the diastolic flow in the coronary segment.

Case 14 had complained of syncope and had electrocardiographic evidence of ventricular arrhythmias but did not show any ST-T abnormalities in a maximal exercise test. A non-diagnostic electrocardiographic stress test was also obtained in one patient (case 2) who had an anomalous origin of the right coronary artery from the left coronary sinus and isolated extrasystoles on a resting electrocardiogram. Others have attributed fatal myocardial ischaemia in such cases to aortic root expansion, which increases the acute angulation of the coronary take-off, and compresses the vessel against the pulmonary trunk.\(^{27-30}\) Our histological findings suggest that the intramural course of the anomalous coronary artery in the aortic tunica media may be crucial because it produces a slit-like lumen.\(^{31}\) Thus in the absence of a fixed atherosclerotic coronary obstruction, the pathophysiological determinants of myocardial ischaemia are not readily reproducible, and this hinders the diagnosis of these congenital coronary anomalies that predispose to life-threatening arrhythmias.

None of our patients had had typical angina attacks and in half of them sudden death was the first manifestation of the coronary anomaly. Prodromal symptoms in the remaining subjects consisted of palpitation or syncopal episodes or both; electrocardiograms, when available, generally showed ventricular arrhythmias, such as isolated extrasystoles and unsustained ventricular tachycardia, in the absence of ST-T abnormalities. Therefore, in young patients with alarming symptoms of ventricular arrhythmia, an "ischaemic substrate" should be suspected even if exercise testing is normal and there is no chest pain. The origin and course of the coronary arteries should be investigated by a detailed echocardiographic study of the aortic root and, in selected cases, by coronary angiography.\(^{32-33}\)
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Figure 4  Histological examination of the heart of a 29 year old man who died suddenly at rest (case 9). (A) The anterior interventricular groove showing the intramyocardial course of the left anterior descending coronary artery. (Azan stain, original magnification, ×8). (B) Increased magnification of (A) (×18) showing the myocardial sheath encircling the coronary segment and dysplasia of the myocardium producing disarray.

Figure 5  Cardiac morphology and histology in an 11 year old girl who died suddenly during effort (case 3). (A) Gross view of the aortic root showing that both coronary ostia arise from the right coronary sinus (arrows). (B) Histological examination of the first segment of the left coronary artery showed that it ran in between the aorta and pulmonary artery. (Weigert-van Gieson, original magnification, ×6).

Congenital malformations of the coronary ostium such as a valve-like ridge or slit shaped lumen, that cause ostial stenosis, have been found only at necropsy, usually in association with anomalous origin of the coronary artery from the wrong coronary sinus or in combination with severe atherosclerotic coronary artery disease. In our cases, however, the malformation was isolated and was also seen in children. Virmani et al. postulated that ostial valve-like ridges may act as occlusion valves in the ostium, and thus predispose to sudden myocardial ischaemia. In our cases the fatal event occurred after eating (cases 10 and 11) or after effort (case 11), when a transient neurovagally mediated episode of hypotension could have been responsible for a sudden drop in aortic pressure, thus compromising the perfusion of the narrowed coronary ostium. Case 10 had had previous syncopal episodes that were interpreted as epileptic attacks.

The most common acquired non-atherosclerotic coronary artery disease in our series was spontaneous coronary artery dissection. This condition is usually an unrecognised cause of acute myocardial infarction or sudden death in young patients, especially peripartum women. Its aetiology is uncertain. Coronary artery dissection was idiopathic in two of our cases and related to pregnancy in
Figure 6  Cardiac morphology and histology in a 7 year old girl who died suddenly after effort (case 7). (A) A valve-like ridge (arrow) obscured the right coronary ostium. (B) Histological examination showed that the ridge was an aortic wall plication. (Weigert-van Gieson, original magnification, ×8).

Figure 7  Cardiac morphology and histology in a 2 year old child who died suddenly soon after eating (case 10). (A) Gross view of the left ventricular outflow tract showing the slit-like left coronary ostium (arrow). (B) Histological examination showing a narrowing of the coronary ostium (compare with the diameter of the main left coronary trunk). (Weigert-van Gieson; original magnification, ×8).

the patient with Marfan's syndrome who died suddenly during the third trimester.

This study suggests that non-atherosclerotic coronary artery disease is an important cause of fatal cardiac arrest in the young. It was present in one third of the cases of juvenile sudden coronary death that we studied. Congenital coronary diseases, consisting of apparent minor abnormalities of the ostium and of the origin and course of the coronary arteries, were the most frequent form of non-atherosclerotic coronary artery disease and were responsible for nearly 10% of juvenile sudden cardiac deaths in our series of necropsy cases. Angina or ischaemic electrocardiographic patterns were never seen, whereas half these cases had had arrhythmical symptoms (palpitation or syncope or both) and electrocardiographic signs (ventricular arrhythmias).

Addendum
Since the submission of the paper, we have studied 23 additional cases of juvenile sudden death. We found evidence of non-atherosclerotic coronary artery disease in two of them. An 11 year old boy who died suddenly while playing soccer had an anomalous origin of the left coronary artery from the right aortic coronary sinus. A 14 year old girl who died suddenly at school had Takayasu arteritis that also affected the coronary ostia.