Myocardial bridging, a frequent component of the hypertrophic cardiomyopathy phenotype, lacks systematic association with sudden cardiac death

Cristina Basso, Gaetano Thieme, Shannon Mackey-Bojack, Anna Chiara Frigo, Domenico Corrado, and Barry J. Maron

1Department of Medico-Diagnostic Sciences, Pathological Anatomy, University of Padua Medical School, Padova, Italy; 2Jesse E. Edwards Registry of Cardiovascular Diseases, St Paul, MN, USA; 3Department of Environmental Medicine and Public Health, University of Padua Medical School, Padova, Italy; 4Department of Cardiac, Thoracic, and Vascular Sciences, University of Padua Medical School, Padova, Italy; and 5Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, MN, USA

Received 17 August 2008; revised 4 March 2009; accepted 10 March 2009; online publish-ahead-of-print 30 April 2009

See page 1549 for the editorial comment on this article (doi:10.1093/eurheartj/ehp216)

Aims
The clinical significance attributable to myocardial bridging of left anterior descending coronary artery in hypertrophic cardiomyopathy (HCM) remains controversial.

Methods and results
Prevalence and depth of coronary artery bridges (CBs) were assessed in 255 hearts, including 115 with HCM (median age 29, range 5–90; 75% male), and 140 controls. Coronary artery bridges were more common in HCM (47/115; 41%) than in patients who died of a variety of non-HCM-related causes (21/100; 21%; P = 0.002), or in patients with congenital aortic stenosis and left ventricular (LV) hypertrophy (5/40; 12%; P = 0.001). Among the HCM hearts, CBs were present in 33 of 77 patients (43%) with sudden death, in 10 of 27 (37%) with heart failure death (or heart transplantation), and in 4 of 11 (36%) with other modes of death (P = 0.826). Deeply embedded CBs (>2 mm) occurred with similar frequency in HCM patients with sudden death (21 of 77; 27%) or heart failure death (5 of 27; 13%; P = 0.191). In sudden death patients, the presence of CB was unrelated to gender (33% in women and 45% in men, P = 0.406) and age (41% <18 years vs. 44% ≥18 years; P = 0.827).

Conclusion
In this morphological analysis of more than 250 hearts, CBs are a frequent component of phenotypically expressed HCM, and more common than in other disorders with or without LV hypertrophy. Although no systematic association with HCM-related sudden death is evident, our findings do not exclude the possibility that CB could contribute to increased risk in some individual patients, potentially impacting management decision-making on a case-by-case basis.

Keywords
Hypertrophic cardiomyopathy • Myocardial bridge • Congenital coronary anomalies • Sudden death

Introduction
Sudden cardiac death is a devastating and often unpredictable complication of hypertrophic cardiomyopathy (HCM). Considerable effort has been directed towards identifying clinical risk markers and the patient subset within the broad HCM disease spectrum most susceptible to lethal ventricular tachyarrhythmias. Efforts at segregating such high-risk patients from the general population of HCM patients have recently achieved even higher priority, given the demonstrated efficacy of the implantable cardioverter-defibrillator for the primary prevention of sudden death in this disease. Although the risk stratification algorithm currently used in HCM has proved to be an effective guide to defibrillator implantation, there is nevertheless the need for identification of additional markers of unacceptably high-risk status.

A disease feature that has previously been incriminated in the cardiac arrest of young HCM patients, although controversial, are short segments of left anterior descending coronary artery (LAD) embedded within (and completely surrounded by) myocardium, known as intramural coronary arteries or coronary artery bridging (CB). In order to add a measure of clarity to this important debate, in the present study we have re-visited this
issue concerning the significance of CBs by assessing its prevalence in HCM vs. non-HCM patients, and in different subsets of HCM patients, with a detailed morphological analysis in a large series of more than 250 hearts.

Methods

Patient selection

The archives of the Cardiovascular Registry, Institute of Pathological Anatomy, University of Padua (Padua, Italy) and the Jesse E. Edwards Registry of Cardiovascular Disease (John N. Nasseff Heart Hospital, St Paul, MN, USA) were accessed for retrospectively diagnosed cases of HCM and other diseases as controls.

Control categories were chosen based upon the following criteria: (i) non-HCM hearts, aortic stenosis due to bicuspid aortic valve with secondary left ventricular (LV) hypertrophy; (ii) non-HCM hearts, coming from autopsies for death due to cardiac and non-cardiac causes. The latter control group is a consecutive routine autopsy series (with the exclusion of HCM and congenital aortic stenosis with LV hypertrophy), to look for the prevalence of CB in an unselected ‘general’ population.

Availability of the entire formalin-fixed heart with major coronary arterial tree intact was required for inclusion in this analysis. Among the initial number of 280 hearts, a total of 255 comprised the study group, since 25 were deemed ineligible due to an extensive, non-conservative, sampling of the heart specimen.

Definitions

Hypertrophic cardiomyopathy was defined as a hypertrophied and non-dilated LV, in the absence of other cardiac or systemic diseases capable of the observed magnitude of hypertrophy (e.g. aortic stenosis or systemic hypertension).

The gross anatomic diagnosis was validated by histopathological evidence of widespread cardiac muscle cell disorganization (disarray) in the ventricular septum, involving an estimated >5% of transverse tissue sections.

Mode of death was assigned as either due to heart failure or sudden and unexpected. Heart failure death occurred in the context of cardiac decompensation and progressive disease course prior to death, including patients treated with heart transplantation.20 Sudden death was defined as an unexpected sudden collapse occurring <1 h from onset of symptoms in patients who had previously experienced a relatively stable and uneventful clinical course.

Morphological examination

Gross

Hearts were fixed in 10% phosphate buffered formaldehyde. Heart weight was assessed after removal of pericardium, post-mortem clots, and severing of the great arteries (2 cm above the semilunar valve), inferior and superior vena cava, as well as pulmonary veins at their junctions with the atria. Measurements were made of the maximum thickness of ventricular septum and LV-free wall, in cross-section, excluding papillary muscles and trabeculae.

The major epicardial coronary arteries (left main trunk, LAD, left circumflex branches, and right coronary artery) were visually inspected with respect to their origin and course, and cut transversely at 2 mm intervals to examine for obstructive atherosclerotic CAD, i.e. cross-sectional narrowing of the luminal diameter ≥75% in one or more extramural arteries. In particular, the LAD branch was carefully inspected for areas in which a segment was completely surrounded by myocardium. Such intramural (bridged) coronary artery segments were assessed grossly (as well as in histological sections) with respect to their length and linear depth of submersion within LV myocardium.

Histopathology

Full-thickness tissue blocks were obtained in the transverse plane from the ventricular septum, consisting of myocardium supplied by the LAD, and also from the LV free wall at the same level. In addition, large tissue blocks (2.5–5 cm long and 0.5–1.0 cm wide and thick), containing the intramural portion of LAD, were removed from each heart in which a CB was identified. Tissue blocks with arterial segments were dehydrated in a series of graded alcohols and cleared with xylene. All tissue specimens were embedded in paraffin, sectioned at 4 or 6 μm, thickness and stained with haematoxylin–eosin, azan-Heidenhain trichrome, and Weigert van Gieson techniques.

Statistical analysis

Categorical variables were summarized as count and percentages, and quantitative variables as medians and ranges. The comparisons of interests were: HCM vs. controls, cardiac and non-cardiac; HCM vs. controls, congenital aortic stenosis with secondary LV hypertrophy, HCM sudden death vs. HCM non-sudden death, HCM sudden death <18 years vs. HCM sudden death ≥18 years. The univariate relationships between the patients demographic and pathological characteristics and the groups defined as above were analysed with χ² or Fisher’s exact test when the predictor was categorical and with Wilcoxon rank-sum test when the predictor was quantitative. Logistic regression analysis was used to determine the effect of CB adjusted for sex, age, heart weight, and LV thickness.

The relationship between heart weight, LV thickness, CB length, and CB depth (<2 vs. ≥2 mm) in the HCM group was assessed with the Wilcoxon rank sum or Kruskal–Wallis test. All statistical tests were two-sided and conducted at the 0.05 significance level. No adjustment was performed to account for the inflation of the experiment wise Type I error and the individual P-values were reported. The results of the logistic regression were presented as odds ratios and 95% confidence intervals. All analyses were conducted with SAS 9.1.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Hypertrophic cardiomyopathy

Of 115 hearts with HCM (72 from the Cardiovascular Registry, University of Padua and 43 from the Jesse E. Edwards Registry, St Paul, MN, USA), 77 (67%) were from patients who had died suddenly, 27 (23%) represented heart failure patients, including 15 explants at transplantation, and 11 (10%) were due to other causes of death, i.e. early post-operative (septal myectomy) in 2, infective endocarditis in 1, and non-cardiac causes in 8 (i.e. pulmonary embolism in 2, trauma in 2, cerebral haemorrhage in 2, and cancer in 2). Median age was 29 years (range 5–90); 86 (75%) were male (Table 1).

Controls

A total of 140 hearts were retrospectively selected as controls including: (i) 40 consecutive specimens in the Cardiovascular Registry, University of Padua (no. 32) and Jesse E. Edwards Registry (no. 8) (1980–2000), from patients (35 male, 5 female, median age 50 years, range 15–77) who died suddenly of aortic stenosis due to congenital bicuspid aortic valve with LV hypertrophy;
100 consecutive hearts (2001) in the Cardiovascular Registry, University of Padua, from patients (57 male, 43 female, median age 69 years, range 14–91) who died of cardiac or non-cardiac causes (HCM or aortic valve stenosis excluded) with coronary artery disease (CAD, \(n = 40\), including acute myocardial infarction in 23, heart failure in 9, sudden death in 8), cancer (\(n = 8\)), pulmonary embolism (\(n = 6\)), aortic dissection (\(n = 6\)), ruptured atherosclerotic aortic aneurysm (\(n = 6\)), cerebral arterial haemorrhage (\(n = 6\)), blunt trauma (\(n = 4\)), mitral valve disease including prolapse (\(n = 6\)), dilated cardiomyopathy (\(n = 3\)), as well as bronchopneumonia, liver cirrhosis, cardiac amyloidosis, infective endocarditis, intravascular coagulation, pulmonary hypertension, bowel infarct (each \(n = 2\)), and myocarditis (\(n = 1\)). Overall, sudden death was the mode of death in 15 (15%) of controls.

### Characteristics of coronary artery bridges

#### Prevalence

Coronary artery bridges were more common in HCM hearts (47/115; 41%) than in aortic stenosis with LV hypertrophy (4/40; 12%; \(P = 0.001\)) or in cardiac and non-cardiac control hearts (21/100; 21%; \(P = 0.002\)) (Figure 1). Among HCM patients, CBs were present in 33 of 77 (43%) who died suddenly, compared with 10 of 27 (37%) who died of heart failure, and 4 of 11 (36%) dying of other causes (\(P = 0.826\)).

#### Table 1

Demographic and pathological findings in patients with hypertrophic cardiomyopathy and controls with aortic stenosis and left ventricle hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>HCM total ((n = 115))</th>
<th>Controls: AS with LVH ((n = 40))</th>
<th>HCM vs. controls AS with LVH (P-value)</th>
<th>HCM-SD ((n = 77))</th>
<th>HCM-HF death ((n = 27))</th>
<th>HCM-other mode of death ((n = 11))</th>
<th>HCM-SD vs. HCM-HF vs. HCM-other mode of death (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>29 (5–90)</td>
<td>50 (15–77)</td>
<td>&lt;0.001</td>
<td>22 (5–53)</td>
<td>54 (9–67)</td>
<td>67 (42–90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>86/29</td>
<td>35/5</td>
<td>0.094</td>
<td>62/15</td>
<td>17/10</td>
<td>7/4</td>
<td>0.131</td>
</tr>
<tr>
<td>Gender M (%)</td>
<td>75</td>
<td>88</td>
<td></td>
<td>81</td>
<td>63</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Heart weight (g), median (range)</td>
<td>475 (120–1000)</td>
<td>540 (300–900)</td>
<td>0.192</td>
<td>450 (120–1000)</td>
<td>520 (170–950)</td>
<td>600 (390–1000)</td>
<td>0.017</td>
</tr>
<tr>
<td>LV thickness (mm), median (range)</td>
<td>18 (8–35)</td>
<td>14 (11–22)</td>
<td>&lt;0.001</td>
<td>18 (8–35)</td>
<td>18 (12–30)</td>
<td>21 (13–70)</td>
<td>0.351</td>
</tr>
<tr>
<td>Associated CAD, no. (%)</td>
<td>15 (13)^a</td>
<td>10 (25)</td>
<td>0.077</td>
<td>2 (3)</td>
<td>8 (30)</td>
<td>5 (45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal fibrous scar, no. (%)</td>
<td>13 (13)^a</td>
<td>—</td>
<td></td>
<td>11 (15)^a</td>
<td>1 (5)^a</td>
<td>1 (17)^a</td>
<td>0.547</td>
</tr>
<tr>
<td>CB, no. (%)</td>
<td>47 (41)</td>
<td>5 (13)</td>
<td>0.001</td>
<td>33 (43)</td>
<td>10 (37)</td>
<td>4 (36)</td>
<td>0.826</td>
</tr>
<tr>
<td>Deep CB ≥ 2 mm, no. (%)</td>
<td>26 (23)</td>
<td>1 (3)</td>
<td>0.003</td>
<td>21 (27)</td>
<td>5 (19)</td>
<td>0 (0)</td>
<td>0.189</td>
</tr>
<tr>
<td>CB depth (mm), median (range)</td>
<td>2.0 (0.5–7.5)</td>
<td>1.0 (0.8–2.0)</td>
<td>0.044</td>
<td>2.0 (0.5–7.5)</td>
<td>1.7 (0.5–6.0)</td>
<td>1.25 (1.0–1.5)</td>
<td>0.213</td>
</tr>
<tr>
<td>CB length (mm), median (range)</td>
<td>15.0 (5.0–30.0)</td>
<td>5.0 (5.0–5.0)</td>
<td>0.010</td>
<td>15.0 (5.0–30.0)</td>
<td>16.5 (5.0–25.0)</td>
<td>10.0 (10.0–12.0)</td>
<td>0.273</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; CAD, atherosclerotic coronary artery disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricle; LVH, left ventricular hypertrophy; SD, sudden death.

^a Fifteen patients with associated obstructive CAD involving the LAD are excluded from this analysis.
Among the 100 controls coming from consecutive autopsies, CBs were found in 3 of 15 with sudden death (20%) and in 18 of 85 without sudden death (21%). Among the 40 cases who died due to CAD, 10 (25%) had CBs: of them, 2 died suddenly (25%), 6 suffered an acute myocardial infarction (26%), and 2 died due to heart failure (22%).

**Length and depth**

In HCM, CBs were most common in the middle segment (63%), less frequent in the proximal segment (23%), and rare in the distal segment (4%) of the LAD. Coronary artery bridges were 15 ± 7 mm in length (median 15, range 5–35) and 2.0 ± 1.5 mm deep within LV myocardium (median 2.0, range 0.5–8). When comparing CBs <2 mm and ≥2 mm in depth, no difference was found with respect to LV wall thickness (median 18 mm, range 10–33 vs. 20.5 mm, range 13–35; *P* = 0.135) and heart weight (470 g, range 130–1000 vs. 475 g, range 120–1000; *P* = 0.894) or ventricular septal thickness (median 20.5 mm, range 13–35 vs. 18 mm, range 8–33; *P* = 0.193).

**Atherosclerotic coronary artery disease**

Obstructive atherosclerotic CAD, involving one or more epicardial coronary arteries, was present in 15 HCM patients (13%), less commonly than in control patients (75/140; 53%). Among the 47 bridged coronary arterial segments, three showed mild stenosis due to non-obstructive atherosclerotic plaques.

**Hypertrophic cardiomyopathy and left ventricular myocardial scars**

On gross and/or histological examination, myocardial scars 1–14 mm (median 3.5) in maximum transverse diameter, either single or multiple and confined to the territory of LAD distribution (i.e. ventricular septum and apex), were identified in 13 out of 100 HCM hearts without atherosclerotic CAD (13%). These included 7 of 40 (17%) with CBs and 6 of 60 (10%) without CBs (*P* = 0.275) (Figures 4 and 5). Of the 13, 10 died suddenly, 2 of heart failure, and 1 of a non-cardiac cause.

**Hypertrophic cardiomyopathy and sudden death with respect to age**

The subgroup of HCM patients who died suddenly aged less than 18 years consisted of 22 cases (18 male, age range 5–17 years, median 14.5 years). When compared with the 55 HCM patients with sudden death ≥18 years (44 male; age range 18–53 years, median 28), the median heart weight was 410 vs. 475 g (*P* = 0.003), and the median LV wall thickness was 140 vs. 475 g (*P* = 0.003), and the median LV wall thickness was 17 vs. 19 mm (*P* = 0.099). CBs were present in 9 of 22 (41%) vs. 24 of 55 (44%) (*P* = 0.827), deep CBs were found in 6 of 22 (27%) vs. 15 of 55 (27%) (*P* = 1.000), the median CB depth was 2.0 mm (range

**Table 2** Logistic regression model evaluating the predictive role of coronary bridging adjusted for sex, age, heart weight, and left ventricular thickness

<table>
<thead>
<tr>
<th></th>
<th>P-value</th>
<th>OR</th>
<th>95% Confidence interval</th>
<th>Hosmer and Lemeshow goodness-of-fit test</th>
<th>Degrees of freedom</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM vs. controls, AS with LVH</td>
<td>0.029</td>
<td>4.191</td>
<td>1.160, 15.140</td>
<td>9.294</td>
<td>8</td>
<td>0.318</td>
</tr>
<tr>
<td>HCM-SD vs. HCM non-SD</td>
<td>0.533</td>
<td>1.448</td>
<td>0.453, 4.629</td>
<td>9.501</td>
<td>8</td>
<td>0.302</td>
</tr>
<tr>
<td>HCM-SD &lt;18 years vs. HCM-SD ≥18 years</td>
<td>0.694</td>
<td>0.804</td>
<td>0.271, 2.385</td>
<td>9.152</td>
<td>8</td>
<td>0.330</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; OR, odds ratio; SD, sudden death.
0.9–5.0) vs. 2.0 mm (range 0.5–7.5) (P = 0.724), the median CB length was 15 mm (range 6–25) vs. 15 mm (range 5–30) (P = 0.566). A fibrous scar was present in the LAD region in 3 of 22 (14%) vs. 8 of 55 (15%) (P = 1.000).

Discussion

The significance of CBs in cardiac disease has been a controversial issue for more than 50 years and specifically in HCM since the 1980s. This ambiguity stems in part from the unique haemodynamic features of the coronary arterial system, in which forward flow occurs predominantly in diastole (only ~15% in systole), whereas tunnelled segments of the LAD coronary typically compress in systole (i.e. the 'milking effect'). In addition, older autopsy surveys of human hearts reported CBs to be not uncommon findings in 5% to 86% of cases (and <5% with angiography), suggesting that most were probably normal or incidental variants or benign anomalies of little or no particular pathophysiologic significance. Finally, two angiographic reports in HCM patients concluded that CBs, although not rare (15 and 28% of cases, respectively), were not of particular clinical significance and were not regarded as a specific risk factor for sudden death in adults or young patients with HCM.

On the other hand, some investigators have regarded CBs to be a probable cause of myocardial ischaemia, acute myocardial infarction, and even sudden death in young people including trained athletes. In particular, one report incriminated CB as a potential determinant of myocardial ischaemia and cardiac arrest in a small group of 36 children with HCM, of whom 28% had CBs. Furthermore, other clinical studies have attached pathophysiological significance to CBs by demonstrating persistent diastolic arterial compression that potentially reduces diastolic coronary blood flow and compromises vasodilator reserve. Moreover, administration of short-acting beta-blockers during atrial pacing to patients with CBs has been reported to alleviate anginal symptoms and signs of ischaemia by reducing vascular compression, increasing luminal diameter, and normalizing flow velocities within the tunnelled arterial segments. This effect presumably results from a negative chronotropic effect that prolongs diastole and thereby improves coronary perfusion.

This debate regarding the significance of CBs has relevance to current clinical practice, because the consideration of this anomaly as a sudden death marker for young HCM patients would greatly impact risk stratification, particularly given the current availability of non-invasive high resolution imaging techniques capable of assessing the presence and anatomical patterns of CBs. Therefore, because of the historical uncertainty surrounding this issue, as well as the absence of relevant pathological data in large patient populations, we have assessed the presence of CBs in more than 250 hearts either with HCM or other diseases with and without LV hypertrophy. In this analysis, we found CBs to be significantly more common in HCM than in other cardiac diseases, including aortic stenosis due to bicuspid valve as a cause of sudden death. Furthermore, CBs proved to be relatively common in HCM patients, including those who had died suddenly (i.e. ~40%). Nevertheless, the prevalence of CBs in patients with sudden death did not differ significantly from that in patients dying of chronic progressive heart failure or from other causes. Finally, the presence of CB was unrelated to LV wall thickness, heart weight, age, or gender.

Coronary artery bridges submerged within the myocardium at a more substantial depth of 2 mm or more (up to 8 mm) would...
seem to intuitively convey greater potential risk. The distinction between superficial and deep CBs in producing myocardial ischaemia in the tributary territory of the abnormal vessel has been previously noted. However, we found deep CBs to be more common in HCM than in controls, whereas no such differences were evident between HCM patients with or without LV septal myocardial scars, nor between those with sudden or heart failure deaths.

On the other hand, given the frequent association of CBs and HCM-related sudden death, our findings do not exclude the possibility that CB could contribute to increased risk in HCM, thereby potentially impacting management decision-making for selected patients. For instance, HCM patients with CB should always undergo functional assessment of ischaemia in the LAD territory. The finding of a long and deep CB judged responsible for angina pectoris and myocardial ischaemia in the anterior LV wall could lead to the consideration for intervention with intracoronary...
stent implantation, surgical supra-arterial myotomy (un-roofing), or coronary artery bypass grafting. 43–45

Although this study represents the first systematic pathological investigation addressing CBs in HCM, we recognize that our data cannot entail functional implications. It should be emphasized that this is an autopsy-based study that cannot address overall risk stratification for individual patients. A sizeable proportion of our patients died suddenly without ascertainment of reliable clinical data assessing their risk status, on the basis of conventional risk factors.1,2,13,14,45 Therefore, we are unable to judge the relative contribution of CBs to the overall risk profile for sudden death in our patients.

We conclude, from the present observations in a large autopsy-based study as well as previously published clinical data,16,17,32 that CB is a common anomaly in HCM that cannot be systematically regarded as a predictive marker for sudden death. In this regard, our observations are pertinent to perspectives on clinical practice, given their consistency with available data (including angiographic)16,17 which suggest CBs cannot per se be regarded as a marker of increased risk nor a justification of routine testing for CBs (e.g. with coronary arteriography or computed tomography angiography) in the risk assessment of young HCM patients. Nevertheless, CBs are a frequent morphological component of phenotypically expressed HCM and the precise pathophysiological significance of these anomalies in individual patients remains uncertain, suggesting management decision-making on a case-by-case basis.

Acknowledgement
The authors wish to thank Dr Jack Titus, St Paul, MN for his contribution in initiating this investigation.

Funding
This study was supported by the Registry for Cardio-cerebro-vascular Pathology, Veneto Region, Venice; Ministry of Health, Rome; and CARIPARO Foundation, Padova, Italy.

Conflict of interest: none declared.

References