Syncope and ventricular arrhythmias in hypertrophic cardiomyopathy are not related to the derangement of coronary microvascular function

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Non-sustained ventricular tachycardia on Holter and syncope have been considered risk factors for sudden death in hypertrophic cardiomyopathy.

Aims In these patients the coronary vasodilator reserve is impaired despite normal coronaries, so we evaluated the correlation between the severity of coronary vasodilator reserve impairment and the occurrence of syncope and non-sustained ventricular tachycardia.

Methods and Results Eighty-four patients with hypertrophic cardiomyopathy (62 males, age 43 ± 12 years) had a two-dimensional echocardiographic study and a 48-h Holter. Myocardial blood flow was measured by positron emission tomography, at baseline and after diprydamole, and the coronary vasodilator reserve was computed as diprydamole myocardial blood flow/baseline myocardial blood flow. In 27 patients, subendocardial and subepicardial myocardial blood flow was measured in the septum and the subendocardial/subepicardial ratio was computed. Twenty of 84 patients had at least one syncopal episode, and 26 had at least one run of non-sustained ventricular tachycardia on Holter. Baseline and diprydamole myocardial blood flow, coronary vasodilator reserve, and baseline and diprydamole subendocardial/subepicardial myocardial blood flow ratio were similar in patients with and without syncope and with and without non-sustained ventricular tachycardia on Holter. However, patients with non-sustained ventricular tachycardia had larger left ventricular end-diastolic (47 ± 6 vs 44 ± 5 mm, P<0.05) and endsystolic diameters (30 ± 6 vs 27 ± 4 mm, P<0.05).

Conclusions (1) Coronary vasodilation is not more severely impaired in patients with hypertrophic cardiomyopathy and syncope or non-sustained ventricular tachycardia. (2) The left ventricle is more dilated in hypertrophic cardiomyopathy with non-sustained ventricular tachycardia.

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Key Words: Hypertrophic cardiomyopathy, myocardial blood flow, ventricular tachycardia, positron emission tomography.

Introduction

Hypertrophic cardiomyopathy is a disease characterized by left ventricular hypertrophy of unknown cause, that is usually asymmetrical, and associated with microscopic evidence of myocardial fibre disarray[1]. Hypertrophic cardiomyopathy is associated with significant morbidity, and a mortality rate of 1% to 4% per annum[2–4]. The most common cause of mortality is sudden cardiac death due to ventricular arrhythmias[5,6], and the presence of non-sustained ventricular tachycardia on Holter monitoring is considered a risk factor in adult patients[5,6]. An association between myocardial perfusion abnormalities detected by thallium-201 scintigraphy and cardiac arrest and syncope has been reported[7], but a clear link between ‘myocardial ischaemia’ and ventricular arrhythmias has not been demonstrated, so far.

Using positron emission tomography in patients with hypertrophic cardiomyopathy we have previously demonstrated that the coronary vasodilator reserve is severely impaired both in hypertrophied and non-hypertrophied myocardium[8] despite normal coronary arteries. In addition, abnormal transmural distribution of myocardial blood flow has been demonstrated in some patients with very thick interventricular septae[9].

Key Words: Hypertrophic cardiomyopathy, myocardial blood flow, ventricular tachycardia, positron emission tomography.
The aim of this paper was to ascertain whether a relationship exists between the severity of the impairment of the coronary vasodilator reserve and the occurrence of ventricular arrhythmias in hypertrophic cardiomyopathy.

Methods

Study population

Eighty-four patients with hypertrophic cardiomyopathy (62 males, age 43 ± 12 years) were studied. Patients were enrolled in two centres in Italy (UO Malattie Cardiovascolari, Ospedale di Pescia, Pistoia and UO Cardiologia S. Luca, Ospedale di Careggi, Florence) and in two centres in England (Department of Cardiological Sciences, St George's Hospital Medical School, London and Hammersmith Hospital, London). The diagnosis of hypertrophic cardiomyopathy was based on the echocardiographic evidence of myocardial hypertrophy (wall thickness ≥ 15 mm) in the absence of any other cardiac or systemic cause for left ventricular hypertrophy [1-14]. Asymmetrical septal hypertrophy was the most common type of the disease in this cohort and no patient had isolated midventricular or apical hypertrophy. Left ventricular outflow tract obstruction was considered to be present when a left ventricular outflow tract pressure gradient ≥ 30 mmHg (measured by Doppler echocardiography) was present at rest. The presence of typical angina pectoris was assessed by the London School of Hygiene questionnaire [15]. The patients with hypertrophic cardiomyopathy and typical angina underwent coronary angiography and were enrolled if they had not significant coronary artery disease. The presence of dyspnoea was graded according to the New York Heart Association classification.

Study protocol

The positron emission tomography studies were performed in two centres: at the CNR Institute of Clinical Physiology, Pisa, Italy (58 patients) and at the MRC Cyclotron Unit, Hammersmith Hospital, London, United Kingdom (26 patients).

All patients underwent baseline 2D echocardiography and 48-h ambulatory ECG monitoring. Myocardial blood flow was then measured with positron emission tomography, at rest and during pharmacologically-induced hyperaemia. All studies were performed after an appropriate period of pharmacological washout.

The study protocol was approved by the local research ethics committees of each institution involved in the study and written informed consent was obtained from each patient before entry.

Echocardiography and Holter monitoring

M-mode, two-dimensional, and Doppler echocardiography were performed using a standard approach. Measurements of cardiac dimensions (left ventricular end-diastolic diameter and left ventricular end-systolic diameter) and myocardial thickness (septal and free wall thickness) were recorded and fractional shortening calculated (normal values >29%) according to the criteria of the American Society of Echocardiography [16].

Patients underwent 48-h Holter monitoring within the week of the positron emission tomography study. Non-sustained ventricular tachycardia was defined as three or more consecutive ectopic ventricular beats with a heart rate ≥ 120 beats · min⁻¹; ventricular tachycardia was defined as sustained when lasting more than 30 s.

Positron emission tomography measurement of myocardial blood flow

Measurement of myocardial blood flow was made at baseline and after the intravenous administration of dipyridamole (0.56 mg · kg⁻¹ over 4 min). One ECG lead was continuously monitored during the study period and a complete 12 lead ECG was recorded every minute during dipyridamole infusion and up to 10 min following the end of infusion. Blood pressure was measured every minute by an automatic cuff sphygmomanometer during dipyridamole infusion and for 10 min thereafter.

A three-slice tomograph (ECAT 3, CTI Inc., Knoxville, TN, U.S.A.) was used in Pisa, while a 15-slice tomograph (ECAT 931-08/12, CTI Inc., Knoxville, TN, U.S.A.) was used in London. Myocardial blood flow was measured using ¹³N-labelled ammonia in Pisa, and ¹⁵O-labelled water, from inhaled ¹⁵O-labelled carbon dioxide, in London. Both techniques have been validated in respective centres [17,18]. In both centres, the subjects were positioned on the scanner couch and a 5 min rectilinear transmission scan was recorded to facilitate positioning of the left ventricle within the window of view of the camera. Subsequently, a 20 min transmission scan was performed to correct the emission scans for tissue attenuation. After the transmission scan, the emission scans were performed.

¹³N-ammonia myocardial blood flow. For each myocardial blood flow measurement, the tracer was slowly injected intravenously over a period of 15–20 s. Dynamic acquisition was started at the same time as the tracer was injected, as previously reported [12]. Hyperaemic myocardial blood flow was measured 50 min later to allow for tracer decay, following the same injection and acquisition protocol. Injection of ¹³N-ammonia was begun 4 min after the end of the infusion of dipyridamole.

¹⁵O-water myocardial blood flow. Radioactive gases were delivered via a face mask. A blood pool scan was performed by inhalation of ¹⁵O-labelled carbon monoxide, and after a 10 min period to allow for decay, ¹⁵O-carbon dioxide, which is rapidly converted into ¹⁵O-water by carbonic anhydrase in the lung [19], was administered. A 7 min dynamic acquisition was started.
Regional and transmural distribution of myocardial blood flow. The coefficient of variation of myocardial blood flow measurements (coefficient of variation, %) used as an index of the homogeneity of regional flow distribution, was determined at baseline and after dipyridamole by dividing the standard deviations of regional myocardial blood flow values by the average myocardial blood flow value, expressed as a percentage. In 27 out of 84 hypertrophic cardiomyopathy patients in whom the maximal septal thickness was at least twice the spatial resolution of the positron emission tomography cameras (i.e. approximately 8 mm full width at half maximum), the interventricular septum could be split into an inner and outer half in order to measure subepicardial and subendocardial myocardial blood flow. The subendocardial to subepicardial flow ratio (subendocardial/subepicardial) was computed at baseline and after dipyridamole, and used as an index of the homogeneity of the transmural distribution of septal flow.

Statistical analysis

All data are expressed as mean ± SD. ANOVA was used to compare the data sets obtained in Pisa and in London, and to compare flow data between patients with and without non-sustained ventricular tachycardia on Holter. The Fisher test was used to check the significance of differences. The Chi-square test was applied to check the significance of the incidence of left ventricular outflow tract obstruction, typical angina and impairment of fractional shortening between patients with and without non-sustained ventricular tachycardia on Holter monitoring. A value of P ≤ 0.05 was considered statistically significant.

Results

Clinical, echocardiographic and Holter monitoring data

Twenty-five out of 84 patients had a history of typical angina pectoris, and 20/84 patients had had at least one syncopal episode. Nine patients had left ventricular outflow tract obstruction at rest (<50 mmHg).

The septal thickness was 22 ± 5 mm (range 15–40 mm) and that of the posterior wall 12 ± 4 mm (range 8–28 mm). In the 27 patients in whom the subendocardial/subepicardial flow ratio was measured, the septal thickness was 27 ± 5 mm (range 20–40 mm). Left ventricular end-diastolic and end-systolic diameters were 45 ± 5 mm and 28 ± 5 mm, respectively. Mean fractional shortening was 39 ± 9% and 12 patients had an abnormal fractional shortening (i.e. ≤ 29%).

During Holter monitoring, no patient had sustained ventricular tachycardia while 26 had at least one run of non-sustained ventricular tachycardia. Eleven out of the 27 hypertrophic cardiomyopathy patients in whom the subendocardial/subepicardial myocardial blood flow ratio was measured had non-sustained ventricular tachycardia on Holter monitoring. No difference was found between patients with and without non-sustained ventricular tachycardia with regard to septal (23 ± 5 vs 21 ± 5 mm, P = ns) and posterior wall thickness (12 ± 4 vs 11 ± 3 mm, P = ns), or fractional shortening (37 ± 9 vs 39 ± 9%, P = ns). However, patients with non-sustained ventricular tachycardia had larger left ventricular end-diastolic (47 ± 6 vs 44 ± 5 mm, P < 0.05) and end-systolic diameters (30 ± 6 vs 27 ± 4 mm, P < 0.05).

Amongst the 20 patients who had at least one syncopal episode, eight had typical angina, three had left ventricular outflow tract obstruction, and two had abnormal fractional shortening. Amongst the 26 patients with non-sustained ventricular tachycardia on Holter, nine had typical angina, one had left ventricular outflow tract obstruction, and six had abnormal fractional shortening. The presence of typical angina pectoris, left ventricular outflow tract obstruction, and low fractional shortening was not greater in patients who had syncope or in patients with non-sustained ventricular tachycardia on Holter (P = ns).

Positron emission tomography data

Mean myocardial blood flow measured in hypertrophic cardiomyopathy in Pisa was not different from that measured in London, either at baseline (0.85 ± 0.33 vs 0.82 ± 0.23 ml·min⁻¹·g⁻¹, P = ns) or after dipyridamole (1.50 ± 0.71 vs 1.52 ± 0.38 ml·min⁻¹·g⁻¹, P = ns). From here onward the myocardial blood flow data from the two populations will be reported together.

When flow data of patients with and without syncope and patients with and without non-sustained ventricular tachycardia on Holter were compared, no differences were found regarding baseline and dipyridamole myocardial blood flow, coronary vasodilator reserve or for baseline and dipyridamole coefficient of variation (Table 1). The subendocardial/subepicardial myocardial blood flow ratio in patients with and without non-sustained ventricular tachycardia was not different at baseline (1.04 ± 0.16 vs 1.08 ± 0.20, P = ns) or after dipyridamole (0.90 ± 0.21 vs 0.88 ± 0.23, P = ns).

Discussion

In the present study, no correlation could be demonstrated between the severity of microvascular dysfunction, as assessed by measuring the coronary
vasodilator reserve, and the occurrence of syncope or the presence of non-sustained ventricular tachycardia on Holter. However, patients with non-sustained ventricular tachycardia had larger left ventricles.

**Ischaemia and arrhythmias in hypertrophic cardiomyopathy**

Based on the reports from two tertiary referral centres, non-sustained ventricular tachycardia on Holter has long been considered a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. Although these data have been challenged recently, the presence of non-sustained ventricular tachycardia on Holter still represents an event that should lead to a more detailed characterization to identify those individuals who are most likely to benefit from targeted therapy to the initiating mechanisms of sudden death.

The working hypothesis of the present study was that a different flow distribution, even if unable to affect mechanical activity of the cells, could be involved in the occurrence of 'mechanical' or 'electrical' syncope. In fact, the non-compliant left ventricle of these patients could become even less compliant during ischaemia due to reduced flow reserve, with sudden reduction in stroke volume and cardiac output causing syncope. Moreover, ischaemia could alter electrical condition and favour the re-entry phenomenon causing arrhythmias. Arrhythmias could be related to ischaemia by another mechanism. Repeated ischaemic crises could lead to myocardial scarring and constitute the basis for abnormalities in intramyocardial electrical propagation which, in turn, may represent the basis for arrhythmias.

We found no difference in coronary vasodilator reserve, and regional or transmural distribution of myocardial blood flow between patients with and without non-sustained ventricular tachycardia on Holter. This finding is in contrast with previous reports. Von Dohlen et al. found a higher prevalence of non-sustained ventricular tachycardia on Holter in patients with a positive thallium-201 scan in comparison to patients with normal perfusion (5/11 vs 0/17). However, the group was small (28 patients) and 5/11 patients with non-sustained ventricular tachycardia on Holter also had conduction abnormalities requiring pacemaker implantation. In another paper, Dilsizian et al. reported that the presence of ischaemia was frequently related to cardiac arrest and syncope. However, the latter study was aimed to investigate the mechanisms of sudden death in young patients with hypertrophic cardiomyopathy in whom the pathophysiology of sudden cardiac death can differ greatly from that in adults. In fact, complex ventricular arrhythmias on Holter and during programmed electrical stimulation are uncommon in the young even when there is a history of previous cardiac arrest. In the present study, only five out of 84 patients were less than 25 years old (19–23 years), making ours and Dilsizian's studies hardly comparable. It is likely that if patients with arrhythmic potential could be better identified using electrophysiological techniques such as programmed ventricular stimulation or analysis of the fractionation of paced right ventricular electrogram, this might have permitted the discovery of a relationship between flow abnormalities and ventricular arrhythmias.

An association between non-sustained ventricular tachycardia on Holter and the extent of hypertrophy, as reported by other authors, has not been confirmed in the present paper. However, the investigation was not designed to test this issue and the assessment of hypertrophy could have been too gross to disclose any possible correlation.

Patients with non-sustained ventricular tachycardia showed higher left ventricular end-diastolic and end-systolic diameters. In a recent paper on the prognostic significance of non-sustained ventricular tachycardia in asymptomatic patients with hypertrophic cardiomyopathy, among 30 patients excluded because they were in functional class III or IV, 10 died (six of whom died suddenly), during 58 months of follow-up. In this context, warning arrhythmias (and sudden death) seem to be a piece of the puzzle of ventricular decompensation, being probably related to myocyte replacement fibrosis rather than to myocyte disarray.

**Table 1  Myocardial blood flow data and relationship with Holter data**

<table>
<thead>
<tr>
<th>Syncope</th>
<th>No syncope</th>
<th>NSVT</th>
<th>No NSVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>bas MBF</td>
<td>0.79 ± 0.27</td>
<td>0.86 ± 0.31</td>
<td>0.77 ± 0.29</td>
</tr>
<tr>
<td>dip MBF</td>
<td>1.42 ± 0.46</td>
<td>1.53 ± 0.67</td>
<td>1.34 ± 0.62</td>
</tr>
<tr>
<td>CVR</td>
<td>1.78 ± 0.49</td>
<td>1.83 ± 0.65</td>
<td>1.78 ± 0.71</td>
</tr>
<tr>
<td>bas CV</td>
<td>21 ± 10</td>
<td>17 ± 7</td>
<td>19 ± 6</td>
</tr>
<tr>
<td>dip CV</td>
<td>23 ± 12</td>
<td>21 ± 8</td>
<td>20 ± 7</td>
</tr>
</tbody>
</table>

Bas MBF and dip MBF = baseline and dipyridamole mean myocardial blood flow (ml/min/g); CVR = coronary vasodilator reserve; bas CV and dip CV = baseline and dipyridamole coefficient of variation (%). Syncope and no syncope, denote the presence and absence of syncope in the clinical history. NSVT and no NSVT denote the presence and absence of run(s) of non-sustained ventricular tachycardia on Holter monitoring.

**References**


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