Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy

Paul Knaapen,1 Tjeerd Germans,1 Paolo G. Camici,4 Ornella E. Rimoldi,4 Folkert J. ten Cate,5 Jurrien M. ten Berg,6 Pieter A. Dijkmans,1 Ronald Boellaard,2 Willem G. van Dockum,1 Marco J. W. Götte,1 Jos W. R. Twisk,3 Albert C. van Rossum,1 Adriaan A. Lammertsma,2 and Frans C. Visser1

1Department of Cardiology, 2Department of Nuclear Medicine and PET Research, 3Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Institute for Cardiovascular Research, Amsterdam; 4Department of Cardiology, Thoraxcenter Erasmus Medical Center, Rotterdam; and 5Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands; and 4Medical Research Council Clinical Science Center and National Heart and Lung Institute, Imperial College, Hammersmith Campus, London, United Kingdom

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Knaapen P, Germans T, Camici PG, Rimoldi OE, ten Cate FJ, ten Berg JM, Dijkmans PA, Boellaard R, van Dockum WG, Götte MJ, Twisk JW, van Rossum AC, Lammertsma AA, Visser FC. Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy. Am J Physiol Heart Circ Physiol 294: H986–H993, 2008. First published December 21, 2007; doi:10.1152/ajpheart.00233.2007.—Impaired hyperemic myocardial blood flow (MBF) in hypertrophic cardiomyopathy (HCM), despite normal epicardial coronary arteries, results in microvascular dysfunction. The aim of the present study was to determine the relative contribution of extravascular compressive forces to microvascular dysfunction in HCM. Eighteen patients with symptomatic HCM and normal coronary arteries and 10 age-matched healthy volunteers were studied with PET to quantify resting and hyperemic MBF at a subendocardial and subepicardial level. In HCM patients, MRI was performed to determine left ventricular (LV) mass index (LVMI) and volumes, echocardiography to assess diastolic perfusion time, heart catheterization to measure LV outflow tract gradient (LVOTG) and LV pressures, and serum NH2-terminal pro-brain natriuretic peptide (NT-proBNP) as a biochemical marker of LV wall stress. Hyperemic MBF was blunted in HCM vs. controls (2.26 ± 0.97 vs. 2.93 ± 0.64 ml·min⁻¹·g⁻¹, P < 0.05). In contrast to controls (1.38 ± 0.15 to 1.25 ± 0.19, P = not significant), the endocardial-to-epicardial MBF ratio decreased significantly in HCM during hyperemia (1.20 ± 0.11 to 0.88 ± 0.18, P < 0.01). This pattern was similar for hypertrophied septum and lateral wall. Hyperemic MBF was inversely correlated with LVOTG, NT-proBNP, left atrial volume index, and LVMi (all P < 0.01). Multivariate regression analysis, however, revealed that only LVMi and NT-proBNP were independently related to hyperemic MBF, with greater impact at the subendocardial layer. Hyperemic MBF is more severely impaired at the subendocardial level in HCM patients. The level of impairment is related to markers of increased hemodynamic LV loading conditions and LV mass. These observations suggest that, in addition to reduced capillary density caused by hypertrophy, extravascular compressive forces contribute to microvascular dysfunction in HCM patients.

hypertrophic cardiomyopathy; outflow tract obstruction; coronary microcirculation; imaging

A BLUNTED PERFUSION RESERVE, despite angiographically normal coronary arteries, is a feature of hypertrophic cardiomyopathy (HCM) (4). This finding is indicative of coronary microvascular dysfunction, the extent of which serves as an important prognostic marker for an unfavorable outcome (8, 19). Detrimental effects of inherent myocardial ischemia most likely contribute to the pathogenesis of symptoms and result in disease progression (6, 8). Involved mechanisms of microvascular dysfunction include reduced capillary density and vascular remodeling (16, 23). In addition to increased vascular resistance, however, extravascular compressive forces due to elevated left ventricular (LV) cavity pressure and wall stress caused by diastolic dysfunction and outflow tract obstruction might also contribute to perfusion abnormalities (13, 21). Extravascular pressure would be expected to influence perfusion, predominantly in the subendocardial layers (13, 21). Indeed, selective impairment of subendocardial perfusion during pharmacologically induced impairment of hyperemia has been demonstrated in the septum of patients with HCM (10). Knowledge of the relative contribution of extravascular resistance to total microvascular dysfunction in HCM, however, is scarce (7, 24). The latter is related to difficulties in simultaneous assessment of hemodynamic load and transmural perfusion distribution in absolute terms. Nevertheless, insight into the mechanisms of microvascular dysfunction could be of clinical importance in development and application of (new) therapeutic approaches (8, 10).

Therefore, the present study was conducted to determine the interplay between transmural perfusion distribution and extravascular compressive forces in patients with symptomatic HCM, with or without obstruction, with use of currently available advanced imaging techniques.

METHODS

Study Population

Patients. Eighteen consecutive symptomatic patients with HCM (functional New York Heart Association class II or III, despite optimized medical therapy) were enrolled in the study. HCM was diagnosed by the presence of a nondilated and hypertrophied LV, in the absence of any other systemic or cardiac disease, on two-dimensional (2D) echocardiography (maximal wall thickness >15 mm in adult index patients). All patients exhibited asymmetric septal hyper-

Address for reprint requests and other correspondence: P. Knaapen, Dept. of Cardiology, 6D 120, VU Univ. Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands (e-mail: p.knaapen@vumc.nl).

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trophy. The study protocol consisted of invasive LV pressure measurements, PET, cardiovascular MRI, and echocardiography. All examinations were performed on the same day, except for the invasive measurements, which were performed within 2 wk of the other tests. The PET and echocardiographic measurements of two obstructive HCM patients have been previously reported by Soliman et al. (24) in a comparative study of perfusion PET vs. contrast echocardiography.

Exclusion criteria were any absolute or relative contraindication to PET or MRI (e.g., pacemaker, claustrophobia, or pregnancy), atrial fibrillation, and history of coronary artery disease (CAD). The study protocol consisted of invasive LV pressure measurements, PET, cardiovascular MRI, and echocardiography. All volunteers was receiving any form of treatment. Enrollment criteria had any other cardiovascular risk factor. Accordingly, none of the HCM patients had any history of cardiovascular disease, all were nonsmokers, and none

Normal controls. Subendocardial and subepicardial myocardial blood flow (MBF) in HCM patients was compared with that in healthy controls, and all patients gave written informed consent.

PET. All scans were performed in 2D mode with use of an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN). Subjects were monitored constantly with single-lead electrocardiography, and blood pressure was measured every minute. After a transmission scan, MBF was measured using 1,100 MBq of 15O-labeled water (H 215O) under resting conditions and during pharmacologically (adenosine, 140 μg·kg −1·min −1) induced hyperemia, as described previously in detail (15). Emission data were corrected for physical decay of 15O and for dead time, scatter, randoms, and photon attenuation. The H 215O emission sinograms were reconstructed using filtered backprojection with a Hanning filter at 0.5 of the Nyquist frequency, resulting in a transaxial spatial resolution of ~7 mm full width at half-maximum. During the PET acquisition, venous blood was drawn and the NH2-terminal pro-brain natriuretic peptide (NT-proBNP, expressed in ng/l) was determined as a biochemical marker of LV wall stress (25).

MRI. Scans were performed on a 1.5-T whole body scanner (Magnetom Sonata, Siemens, Erlangen, Germany) with use of a six-element phased-array radio-frequency receiver body coil. All images were electrocardiographically gated and acquired during repeated breath holds in mild expiration of 10–15 s, depending on heart rate. After localization of scout scans, cine images were acquired with a segmented balanced steady-state free-precession sequence. Image parameters were as follows: 5 mm slice thickness, 5 mm slice gap, <50 ms temporal resolution, 3.2 ms repetition time, 1.54 ms echo time, 60° flip angle, and 1.3 × 1.6 mm typical image resolution. After three long-axis view cines (2-, 3-, and 4-chamber views), a stack of 10–12 LV short-axis cines were acquired for full coverage of the LV. A stack of 6–10 transversely oriented slices were planned on an

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<th>Table 2. Hemodynamics during rest and hyperemia</th>
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<td>Controls</td>
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<td>Heart rate, beats/min</td>
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<tr>
<td>Rest</td>
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<tr>
<td>Hyperemia</td>
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<td>Systolic BP, mmHg</td>
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<td>Diastolic BP, mmHg</td>
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<td>MAP, mmHg</td>
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<td>RPP, mmHg·min</td>
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Values are means ± SD. HCM, hypertrophic cardiomyopathy; BP, blood pressure; MAP, mean arterial pressure; RPP, rate-pressure product; NS, not significant. *P < 0.05 vs. control.

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end-diastolic (ED) two-chamber view, starting at the level of the lower leading edge of the mitral valve annulus, to cover the entire left atrium (LA) (26).

Echocardiography. Transthoracic echocardiography was performed (Vivid 7, General Electrics-Vingmed, Milwaukee, WI) according to the American College of Cardiology/American Heart Association/American Society of Echocardiography guidelines (9). Pulsed-wave Doppler was used to derive the peak outflow tract pressure gradient across the subvalvular obstruction [peak LV outflow tract gradient (LVOTG)]. Mitral regurgitation and systolic anterior motion of the mitral valve were graded qualitatively. LV ejection time (LVET) was measured on the continuous-wave Doppler trace from the opening to the closure of the aortic valve. To assess diastolic LV function, pulsed-wave Doppler transmirtal inflow and tissue Doppler data were obtained from the apical four-chamber view, and subsequently peak early transmitral-to-peak late mitral inflow velocity ratio (E/A) was obtained.

Invasive measurements. Using a Judkins technique, an A6F pig-tail catheter was positioned in the LV and an A7F Judkins guiding catheter in the ascending aorta. Subsequently, LV ED pressure (LVEDP), LV end-systolic pressure (LVESP), and peak LVOTG were determined. Additionally, coronary angiography excluded significant CAD in all patients. No epicardial coronary “bridging” was observed in any of the patients.

Data Analysis

PET. Transaxial parametric MBF images were generated as described previously (2). Subsequently, these images were reoriented according to the dynamic H215O images. Regions of interest (ROIs) were defined on these images corresponding to septal, anterior, lateral, and inferior walls of the LV in the basal, mid, and apical planes (15). Additional ROIs were defined in the LA and right ventricular chamber. This latter set of ROIs was projected onto the dynamic H215O images to generate image-derived input functions. The standard single-tissue compartment model, together with these input functions, was used to determine MBF (ml·min⁻¹·g⁻¹ perfusible tissue) for all myocardial tissue time-activity curves. Subendocardial and subepicardial layers were identified by dividing myocardial ROIs with a central line. Coronary vasodilator reserve was calculated as the ratio of hyperemic MBF to resting MBF. Inasmuch as resting MBF is related to the rate-pressure product (RPP = systolic blood pressure × heart rate), corrected resting MBF [(MBF + RPP) · 10,000] was also determined. Additionally, LV RPP was calculated: LV pressure (peak LVOTG + systolic blood pressure) × heart rate. Total (regional) coronary resistance was calculated as the ratio of mean arterial pressure to MBF.

MRI. For LV volume analysis, epicardial and endocardial contours were manually drawn on all ED and end-systolic (ES) LV short-axis images. Global LV function parameters, including ED volume (LVEDV), ES volume (LVESV), ejection fraction (LVEF), and myocardial mass, were derived from epicardial and endocardial contours on the cine images with use of the MASS software package (MEDIS, Leiden, The Netherlands). For LA volume analysis, endocardial contours were drawn on all LA data sets in ES. The LA appendix was included in the LA volume, and pulmonary veins were excluded. A straight line was drawn between the leading edges of the mitral valve annulus to delineate LA and LV. The LA volume was calculated from

Table 3. Subendocardial and subepicardial blood flow and CVR in HCM patients and healthy controls

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<th>Rest</th>
<th>Hyperemia</th>
<th>CVR</th>
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<tr>
<td></td>
<td>Endo</td>
<td>Epi</td>
<td>P</td>
</tr>
<tr>
<td>Control</td>
<td>1.09±0.24</td>
<td>0.80±0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HCM</td>
<td>1.00±0.24</td>
<td>0.84±0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
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Values are means ± SD. Endo and Epi, subendocardial and subepicardial blood flow (ml·min⁻¹·g⁻¹); CVR, coronary vasodilator reserve. *P < 0.01 vs. rest.
summation of LA areas on transverse image planes multiplied by slice distance. LA and LV areas were indexed to body surface area. The same regions on the short-axis slices were defined as described above for determination of ES and ED wall thicknesses and diameters.

Diastolic perfusion time calculation. The R-R interval was measured at rest and during hyperemia on the electrocardiograms obtained during the PET scans. Diastolic perfusion time (DPT) (s/min) = (R-R interval / LVET) × heart rate was subsequently calculated (15, 21).

Statistics

Values are means ± SD. For comparison of two data sets, a paired or unpaired Student’s t-test was performed where appropriate. Multiple data sets were compared using multivariate ANOVA, and specific differences were identified by a Student’s t-test corrected for multiple comparisons with Bonferroni’s adjustment. Linear and nonlinear regression was used to analyze the relationship between variables. Univariate and multivariate regression analyses were used to determine the parameters that could predict the impairment in hyperemic MBF. In the multivariate analyses, a stepwise forward selection procedure, with an entry probability for each variable set at 0.05, was used. Multiple data sets were compared using ANOVA. All analyses were performed using SPSS 12 (SPSS, Chicago, IL). P < 0.05 was considered significant.

RESULTS

Patient characteristics are given in Table 1. All except four patients, in whom side effects were considered intolerable, used β-receptor- and/or Ca²⁺ channel-blocking agents. Systolic anterior motion was observed in 13 of 18 patients, and average mitral regurgitation grade was 1.5 ± 0.8. In 12 patients, LVOTG was ≥30 mmHg and mean LVEDP was 21 ± 11 mmHg.

Hemodynamics

The hemodynamic parameters obtained during PET under resting and hyperemic conditions for controls and HCM patients are shown in Table 2. There were no differences in resting heart rate or blood pressure between groups. Heart rate increased significantly in both groups during adenosine infusion, although the increase was less pronounced in HCM patients (P < 0.05 vs. controls). In contrast to controls, systolic and diastolic blood pressure significantly decreased under hyperemic conditions in HCM patients. In addition, DPT for HCM patients decreased from 40 ± 4 to 33 ± 5 s/min from resting to hyperemic conditions (P < 0.01).

Transmural MBF

Global resting transmural MBF averaged over the entire LV was similar for patients and controls (0.90 ± 0.21 vs. 0.94 ± 0.21 ml·min⁻¹·g⁻¹, P = NS). After correction for hemody-
Coronary microvascular dysfunction (LVRPP or RPP), however, MBF was significantly lower in the HCM patients than in controls (0.92 ± 0.25 vs. 1.30 ± 0.38 ml·min⁻¹·g⁻¹, P < 0.01). In controls, the distribution pattern of MBF was homogeneous. In contrast, in HCM patients, MBF was significantly lower in the septum than in the lateral wall (0.82 ± 0.20 vs. 0.98 ± 0.25 ml·min⁻¹·g⁻¹, P < 0.01). As expected, transmural hyperemic MBF (2.26 ± 0.97 vs. 2.93 ± 0.64 ml·min⁻¹·g⁻¹, P < 0.05) and coronary vasodilator reserve (2.66 ± 1.32 vs. 3.26 ± 1.05, P < 0.05) were blunted in HCM patients compared with controls. In addition, the regional distribution differences during rest in HCM patients became homogeneous during maximal vasodilation, with similar hyperemic MBF values for the interventricular septum and lateral wall (2.23 ± 1.07 vs. 2.30 ± 0.86 ml·min⁻¹·g⁻¹, P = NS).

Subendocardial vs. Subepicardial MBF

As shown in Fig. 1 and listed in Table 3, in patients and controls, resting MBF was significantly higher in the subendocardial layer than in the subepicardium (both P < 0.01), with endocardial-to-epicardial ratios of 1.20 ± 0.11 and 1.38 ± 0.15, respectively, although the endocardial-to-epicardial ratio was greater in the control group (P < 0.01 between groups). During hyperemia, there was a nonsignificant reduction in the endocardial-to-epicardial ratio in controls to 1.25 ± 0.19 (P = NS). In patients, however, MBF increased to a lesser extent in the subendocardium than subepicardium, inducing a significant reduction in the endocardial-to-epicardial ratio (0.88 ± 0.18, P < 0.01) compared with resting conditions. This pattern was observed in the septum and lateral wall.

Coronary Resistance

Average total resting coronary resistance was similar between controls and HCM patients (93 ± 28 vs. 104 ± 24 mmHg·ml⁻¹·min⁻¹·g⁻¹, P = NS), whereas minimal hyperemic coronary resistance was significantly increased in HCM patients (28 ± 6 vs. 41 ± 16 mmHg·ml⁻¹·min⁻¹·g⁻¹, P < 0.05).

Determinants of Resting and Hyperemic MBF and Coronary Resistance in HCM

Under resting conditions, transmural MBF was linearly correlated to LVRPP (r = 0.51, P < 0.05). None of the other parameters listed in Table 4 were related to resting MBF. Hyperemic MBF was correlated to LVOTG, LV mass index (LVMI), LA index, and NT-proBNP and could best be fitted in a logarithmic manner (Table 4, Fig. 2). LV pressures, systolic or diastolic blood pressure, and diastolic function parameters such as E/A and DPT were not related to hyperemic perfusion. When multivariate analysis was performed, only NT-proBNP
and LVMI were independently related to hyperemic MBF, and the combination of these two parameters in the model could predict 88% of hyperemic MBF values in these patients. As displayed in Fig. 3, subendocardial hyperemic MBF correlated significantly better to NT-proBNP and LVMI than subepicardial hyperemic MBF (both \( P < 0.01 \)). In addition, with decreasing values of hyperemic MBF, the disparity between subendocardial and subepicardial perfusion increased.

Multivariate analysis of the determinants of total minimal hyperemic coronary resistance yielded similar results: only LVMI (\( \beta = 0.46, P < 0.01 \)) and NT-proBNP (\( \beta = 0.62, P < 0.01 \)) were independently and (positively) logarithmically related to minimal coronary resistance.

**Regional ED Wall Thickness and Systolic Wall Thickening in Relation to Hyperemic MBF**

Regional analysis of all myocardial segments revealed that hyperemic MBF decreased in proportion to the increase in ED wall thickness (Fig. 4). Moreover, systolic wall thickening of the regional segments was related to hyperemic MBF.

**DISCUSSION**

The present study confirms the previously demonstrated pronounced subendocardial hyperemic perfusion impairment in HCM patients. The contribution of extravascular forces, however, has been poorly characterized (7, 24). The results of the present study indicate that, in addition to the extent of hypertrophy, the degree of outflow tract obstruction and related stress, i.e., extravascular compressive forces, plays an important role in the microvascular dysfunction in HCM. These findings expand on the limited data available by studying an HCM population with varying stages of hypertension and outflow tract obstruction and by comparing the transmural distribution pattern with that measured in healthy volunteers. In addition, results were obtained using a combination of advanced imaging techniques such as PET, MRI, and echocardiography, together with invasive measurements.

Resting MBF in HCM was within normal range compared with healthy control subjects and was directly related to LVRPP. Heart rate and LV ES cavity pressure are main determinants of the energy requirements of the myocardium (3, 6, 7). Under resting conditions, therefore, autoregulation of the microvascular bed will occur through vasodilation in response to varying demand. Inasmuch as loading conditions and, consequently, oxidative metabolism are greater in the subendocardial layer of the myocardium, resting perfusion will be augmented relative to the subepicardial layer (13). This phenomenon was observed in the present study in healthy volunteers and HCM patients and has previously been demonstrated not only in HCM patients (10), but also in LV hypertrophy due to aortic stenosis (13, 21).

Compared with healthy volunteers, hyperemic MBF was severely blunted, with particularly pronounced hypoperfusion at the subendocardial layer. Inasmuch as none of the patients displayed significant epicardial stenosis at coronary angiography, this finding is indicative of microvascular dysfunction (4). This observation could not be ascribed to differences in perfusion pressure between groups, inasmuch as hyperemic coronary resistance was significantly increased compared with controls.

As mentioned above, the extent of hypertrophy was independently and inversely related to hyperemic perfusion, which implies that the reduced capillary density that accompanies increased LV mass is responsible for the microvascular dysfunction (16, 23). The decrease in hyperemic perfusion in relation to an increase in regional ED wall thickness further supports this hypothesis and has recently also been demonstrated by Petersen and colleagues (20).

In addition to capillary density, however, the present study suggests that increased hemodynamic loading conditions, as reflected by the outflow tract gradient, LA dimensions, and the levels of the biochemical marker NT-proBNP, are additional important factors of microvascular dysfunction in HCM. Similarly, increased levels of plasma BNP have previously been linked to myocardial ischemia in HCM (17), and coronary vascular reserve is more severely hampered in patients with outflow tract obstruction than in those without such obstruction (14). Recently, using contrast echocardiography, Soliman et al. (24) reported similar relations between impaired flow reserve, LV mass, and the degree of outflow tract gradient in severely symptomatic obstructive HCM patients. This hypothesis is further corroborated by Rajappan and co-workers (21), who recently demonstrated that increased hemodynamic loading conditions are related to the extent of microvascular dysfunction in patients with pressure-overload cardiomyopathy due to aortic stenosis. Moreover, and similar to the findings in the present study, a logarithmic relationship between hyperemic...
perfusion and load was shown, and there was a greater impact of extravascular forces at the subendocardial level.

During pharmacologically induced maximum vasodilation, the autoregulatory mechanisms of the microvessels are exhausted and, in addition to vascular resistance, extravascular compressive forces, such as wall stress and diastolic perfusion time, become the predominant determinants of perfusion. In addition, wall stress decreases from the subendocardial to subepicardial layer (Laplace’s law); therefore, an opposite transmural gradient in hyperemic perfusion can be observed. In contrast to patients with aortic stenosis (21), however, diastolic perfusion time did not influence hyperemic perfusion in the population examined in the present study (21).

Hyperemic perfusion in the epicardial layers did not significantly differ between controls and HCM patients. This lack of hyperemic perfusion impairment in the epicardial layers, which are least affected by wall stress according to Laplace’s law, strongly suggests that not arterial remodeling but, rather, extravascular compressive forces play a predominant role in the increased vascular resistance in the subendocardial layers of HCM patients.

Clinical Implications

The results from the present study also provide insight into therapeutic approaches that may be beneficial in HCM. Attempting to improve microvascular function and, thereby, possibly altering the clinical course in a positive manner would require reducing LV mass and/or diminishing wall stress, rather than improving diastolic filling time and function. This may explain why pharmacological treatment with β-receptor- or Ca2+ channel-blocking agents, which primarily act on diastolic function parameters, have proven to be ineffective in relieving microvascular dysfunction (10, 12). In contrast, diminishing wall stress in HCM patients with dynamic outflow tract obstruction through a surgical myectomy or percutaneous alcohol ablation of the interventricular septum seems to augment coronary vascular reserve (5, 14), although currently available data are limited, and this issue requires further investigation. The concomitant long-term regression of afterload-dependent hypertrophy in septal and remote myocardium after such a procedure may result in restoration of capillary density and, thereby, contribute to the favorable microvascular effects (26).

Limitations

The parameters of extravascular forces, such as NT-proBNP, LVEDP, and LVOTG, were determined during resting conditions and related to hyperemic perfusion induced by adenosine infusion. During vasodilating stress, however, pre and afterload values may be altered. Nussbacher et al. (18) demonstrated that adenosine increases LVEDP in healthy controls and patients with LV dysfunction. Although data are lacking, in HCM patients adenosine likely also augments LVEDP by an increase in LVOTG. Furthermore, hyperemic diastolic filling time was calculated under the presumption that ejection time between rest and stress conditions was the same. These limitations may have obscured a potential correlation between diastolic filling time, LVEDP, and microvascular dysfunction in the present study.

HCM displays great regional differences in morphological and functional disease expression. Nonetheless, most of the parameters investigated, e.g., outflow tract obstruction, LV mass, and filling time, are global parameters and may not be fully representative of regional disease variability. The widespread perfusion abnormalities, however, offer an opportunity to link these global parameters to microvascular dysfunction. Nevertheless, more studies that investigate cause-and-effect relationships, particularly at a regional level, are warranted.

Given the resolution of the currently used PET scanner, the distinction between subendocardial and subepicardial MBF could reliably be made in the hypertrophied interventricular septum (10). The estimation of the endocardial-to-epicardial ratio in the less hypertrophied lateral wall of HCM patients, however, is at the edge of the technical capabilities of this scanner. On the other hand, a sophisticated modeling procedure was used that accounts for partial volume effects and spillover artifacts from the LV blood pool. Using this procedure, Rimoldi et al. (22) recently demonstrated in animals the feasibility of distinguishing subendocardial from subepicardial perfusion in myocardium, the wall thickness of which is similar to that in healthy humans. Nonetheless, spillover effects from the subendocardial to epicardial layer, and vice versa, do occur and lead to underestimation of absolute transmural differences in perfusion with decreasing dimensions.

An alternative explanation for a blunted hyperemic perfusion in HCM patients would be a reduced sensitivity to adenosine. Although this effect has been shown to exist, the influence is minor and can probably be disregarded (1). Furthermore, mechanical dyssynchrony is frequently observed in HCM, even in the absence of electrocardiographic conduction delay, which may have influenced regional resting and hyperemic perfusion values (11, 15). The role of dysynchrony requires further study.

Finally, pharmacological therapy of the patients was not discontinued because of ethical reasons. This might have influenced the results and has introduced bias compared with the control group. These agents, however, have been shown to have little effect on hyperemic perfusion in HCM (10, 12).

Conclusions

In patients with symptomatic HCM, the impairment in hyperemic perfusion is independently related to LV myocardial mass as well as increased hemodynamic loading conditions. These observations suggest that, in addition to reduced capillary density caused by hypertrophy, extravascular compressive forces contribute to microvascular dysfunction in HCM patients.

REFERENCES

5. Cannon RO 3rd, McIntosh CL, Schenke WH, Maron BJ, Bonow RO, Epstein SE. Effect of surgical reduction of left ventricular outflow...


