Microvascular response to metabolic and pressure challenge in the human coronary circulation

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Microvascular response to metabolic and pressure challenge in the human coronary circulation. Am J Physiol Heart Circ Physiol 301: H434–H441, 2011. First published May 13, 2011; doi:10.1152/ajpheart.01283.2010.—In vivo observations of microcirculatory behavior during autoregulation and adaptation to varying myocardial oxygen demand are scarce in the human coronary system. This study assessed microvascular reactions to controlled metabolic and pressure provocation [bicycle exercise and external counterpulsation (ECP)]. In 20 healthy subjects, quantitative myocardial contrast echocardiography and arterial applanation tonometry were performed during increasing ECP levels, as well as before and during bicycle exercise. Myocardial blood flow (MBF; ml·min⁻¹·g⁻¹), the relative blood volume (rBV; ml/ml), the coronary vascular resistance index (CVRI; dyn·s·cm⁻²·g⁻¹), the pressure-work index (PWI), and the pressure-rate product (mmHg/min) were assessed. MBF remained unchanged during ECP (1.08 ± 0.44 at baseline to 0.92 ± 0.38 at high-level ECP). Bicycle exercise led to an increase in MBF from 1.03 ± 0.39 to 3.42 ± 1.11 (P < 0.001). The rBV remained unchanged during ECP, whereas it increased under exercise from 0.13 ± 0.033 to 0.22 ± 0.07 (P < 0.001). The CVRI showed a marked increase under ECP from 7.40 ± 3.38 to 11.05 ± 5.43 and significantly dropped under exercise from 7.40 ± 2.78 to 2.21 ± 0.87 (both P < 0.001). There was a significant correlation between PWI and MBF in the pooled exercise data (slope: +0.162). During ECP, the relationship remained similar (slope: +0.153). Whereas physical exercise decreases coronary vascular resistance and induces considerable functional capillary recruitment, diastolic pressure transients up to 140 mmHg trigger arteriolar vasoconstriction, keeping MBF and functional capillary density constant. Demand-supply matching was maintained over the entire ECP pressure range.

METHODS

Study subjects. Twenty healthy volunteers were included in the study. All gave written informed consent to participate. The study was approved by the Ethics Committee of the Kanton of Bern, Switzerland. Minimum age required for inclusion was 18 yr. In women, pregnancy, as assessed by a serum β-human chorionic gonadotropin <2 IU/L, was excluded in advance. History of cardiovascular, respiratory, renal, hepatic, or cerebral disease or surgery, allergic reactions to the echocardiographic contrast, intake of any cardiovascular medication, and acute illness were exclusion criteria. In a baseline echocardiographic examination, valvular abnormalities, aortic dilatation, any intra- or extracardiac shunt, systolic or diastolic left ventricular (LV) dysfunction, LV hypertrophy, systolic right ventricular dysfunction or dilatation, and pulmonary artery hypertension were excluded. Twenty-two individuals were initially examined. Two persons were excluded after the baseline echocardiographic exam because of mild aortic regurgitation and suspicion of aortic valve fibroelastoma, respectively.

Study protocol. The study was performed in a crossover design of two equally sized groups. After the initial baseline examination, the participants were randomized to a group “ECP first” or “exercise first” to equally distribute potential carry-over effects. ECP and exercise were performed during two different visits. A period of 14 days without sport activity preceded both visits. An ECP apparatus (model TS3; Vasomedical, Westbury, NY) provoked incremental diastolic pressure augmentations. Air cuffs were wrapped around the lower limbs and hips and attached to the pressure tank. ECP cuff pressure level was increased stepwise from 0, 80, 160, 240, to a maximum of 300 mmHg. Each step was maintained for ~15 min for stabilization. Myocardial perfusion measurements were performed during the last 5 min of each step. Typical therapeutic ECP settings recommended in clinical studies were used (1, 3, 34, 46). Effective inflation and deflation time points were monitored using phonocardiographic microphones placed on the surface of the cuffs. The accuracy of pressure buildup inside the cuffs was monitored by

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means of an electronic manometer that was additionally attached to the counterpulsation system.

A variable load supine bicycle ergometer (Ergoline; Pilger Medizin Elektronik, Zofingen, Switzerland) was used with lateral tilting of the bicycle up to 25° for data acquisition, if needed. Participants were asked to perform exercise at a steady target heart rate of 0.80 times the maximum rate (220 minus the age) for 45 min. Sphygmomanometric blood pressure was taken every 2 min. A 12-lead electrocardiogram was monitored throughout the entire examination. Safety criteria were applied according to international guidelines. Hemodynamic measurements were taken at baseline and during the last minutes of exercise. In case no acceptable echo window could be found during peak exercise, the participants were asked to reduce the effort until reliable echocardiographic measurements could be retrieved.

**MCE.** MCE was performed on an Acuson Sequoia 512 (Acuson, Mountain View, CA) equipped with a 4V1c cardiac transducer and Cadence Pulsed Imaging. An ultrasound contrast agent (Sonovue; Bracco Geneva, Switzerland) was administered intravenously at a constant rate of 0.5 ml/min. The interventricular septum was depicted from the apical four-chamber or parasternal short axis view. The following ultrasound settings were used: transducer frequency at 1.5 MHz, dynamic range at 50 dB, time gain compensation and postprocessing curve linear, triggered 75-ms frame-to-frame interval, and clip length at 300 frames. The exam consisted of a microbubble destruction-replenishment sequence. Two to three clips were acquired for each protocol step. The original echocardiographic DICOM-files were exported to a workstation for offline analysis. The volumetric model used for MBF quantification was previously validated by Vogel et al. (47). An interactive software (PerfusionFitter) was developed for semiautomated perfusion calculations within user-defined regions of interest, result visualization, and dataset handling (Matlab 7; Mathworks, Natick, MA). Results from multiple clips were averaged for every protocol step.

**Other echocardiographic parameters.** Before each MCE, 2-D, M-mode, and Doppler echocardiographic exams were performed. Stroke volume and cardiac output were calculated using the continuity equation across the left ventricular outflow tract. LV ejection fraction according to:

\[
\text{LVEF} = \frac{\text{stroke volume}}{\text{LV end-diastolic volume}}
\]

The original tonometric pressure tracings and corresponding electrocardiograms (ECGs). Counterpulsation induces variable diastolic pressure transients (arrow), depending on the external counterpulsation (ECP) level. An example without (left) and during high-level ECP (right) is illustrated here. Superimposition is used to retrieve an average pressure profile.

**Statistical analyses.** The comparisons of continuous variables between the different ECP levels were performed with repeated-measures ANOVA and Dunn’s post hoc tests. ECP 0 was used as reference value for post hoc comparisons in ECP data. For comparisons of continuous variables before and during exercise, paired Student’s t-tests were used. Correlations between continuous variables were assessed by linear regression analysis. The degree of similarity between two bivariate data distributions was assessed using Mahalanobis distance (D^2) calculations. Outliers were defined as points with a D^2 > 2, i.e., lying 2 SDs outside the biaxial data variance of the reference group. Bland-Altman analyses were used for variability assessment of MBF. All statistical analyses were performed on Prism 5 GraphPad Software (La Jolla, CA) and Matlab 7 (Mathworks). All continuous variables, including variability of MBF, are given as means ± SD. A P value < 0.05 was considered statistically significant.
RESULTS

Of the 20 individuals included in the study, 12 were men, 8 were women, mean age was 30.3 ± 8.5 yr, and LV ejection fraction was 64.5 ± 3.6%. A total number of 377 myocardial contrast clips were analyzed, yielding an average of 2.8 clips per protocol step. In two individuals, no echo window could be found during exercise due to excessive shadowing artifacts from breathing. Overall, the curve fitting of contrast replenishment was robust. The median $r^2$ values of the fitted exponential curves were between 0.67 and 0.73 during ECP, 0.59 during exercise, and 0.72 at rest. The interobserver agreement of MBF was $0.015 ± 0.263 \text{ml-min}^{-1}\cdot\text{g}^{-1}$ in 30 randomly selected clips. As expected, this agreement was lower compared with MCE during resting conditions ($0.007 ± 0.120 \text{ml-min}^{-1}\cdot\text{g}^{-1}$; Ref. 47). The variability of two consecutive measurements was $0.061 ± 0.269 \text{ml-min}^{-1}\cdot\text{g}^{-1}$ in 200 randomly selected clips (100 pairs of 2 consecutive measurements).

The hemodynamic parameters during ECP and exercise are listed in Table 1.

End point variables. MBF, rBV, blood exchange rate (β), and CVRI were the primary end point variables. There was no significant change in MBF throughout the entire ECP protocol ($P = 0.16, F = 1.692$), ranging from 1.08 ± 0.44 at baseline to a minimum of 0.89 ± 0.31 at ECP 80 and 0.92 ± 0.38 ml/min−1·g−1 at ECP 300 (Fig. 2). On the other hand, bicycle exercise lead to a more than threefold increase in MBF from 1.03 ± 0.39 to 3.42 ± 1.11 ($P < 0.001$). Similarly, the rBV remained unchanged during ECP, whereas it increased under exercise from 0.132 ± 0.033 to 0.222 ± 0.071 ml/ml ($P < 0.001$). The CVRI showed a marked increase under ECP from 7.40 ± 3.38 to a maximum of 11.05 ± 5.43 dyn·s·cm−5/g, as well as a significant drop under bicycle exercise from 7.40 ± 2.78 to 2.21 ± 0.87 dyn·s·cm−5/g (both $P < 0.001$). Accordingly, β was significantly reduced under ECP ($P < 0.05$) but markedly increased under exercise ($P > 0.001$).

Table 1. Hemodynamic data during ECP and bicycle exercise

<table>
<thead>
<tr>
<th></th>
<th>ECP 0</th>
<th>ECP 80</th>
<th>ECP 160</th>
<th>ECP 240</th>
<th>ECP 300</th>
<th>Bicycle Rest</th>
<th>Bicycle Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min−1</td>
<td>60±1</td>
<td>62±14</td>
<td>62±11a</td>
<td>65±10a</td>
<td>68±11a</td>
<td>65±10</td>
<td>154±20</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>120±10</td>
<td>115±10</td>
<td>115±12</td>
<td>110±9a</td>
<td>112±10</td>
<td>121±9</td>
<td>158±18</td>
</tr>
<tr>
<td>DBP mean, mmHg</td>
<td>79±11</td>
<td>96±14b</td>
<td>110±12b</td>
<td>123±12</td>
<td>132±15b</td>
<td>80±8</td>
<td>81±9</td>
</tr>
<tr>
<td>DPB minimal, mmHg</td>
<td>73±11</td>
<td>74±9</td>
<td>71±8</td>
<td>72±9</td>
<td>71±10</td>
<td>75±7</td>
<td>76±11</td>
</tr>
<tr>
<td>MBF, ml·min−1·g−1</td>
<td>1.08±0.44</td>
<td>1.00±0.48</td>
<td>0.89±0.31</td>
<td>0.85±0.40</td>
<td>0.92±0.38</td>
<td>1.03±0.39</td>
<td>3.42±1.11</td>
</tr>
<tr>
<td>rBV, ml/ml</td>
<td>0.137±0.055</td>
<td>0.134±0.055</td>
<td>0.136±0.037</td>
<td>0.143±0.041</td>
<td>0.156±0.050</td>
<td>0.132±0.033</td>
<td>0.222±0.071f</td>
</tr>
<tr>
<td>MV, min−1·100 g−1</td>
<td>6.69±1.12</td>
<td>6.74±1.31</td>
<td>6.46±1.21</td>
<td>6.47±1.00</td>
<td>6.87±1.02</td>
<td>6.71±1.07</td>
<td>19.90±5.28</td>
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<tr>
<td>PRP, mmHg/min</td>
<td>7.058±1.410</td>
<td>7.103±1.602</td>
<td>7.244±1.841</td>
<td>7.178±1.420</td>
<td>7.631±1.380</td>
<td>7.811±1.410</td>
<td>24.33±3.985f</td>
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<tr>
<td>Circular function</td>
<td>157±22</td>
<td>161±57</td>
<td>137±20</td>
<td>129±15a</td>
<td>125±17b</td>
<td>164±53</td>
<td>166±55</td>
</tr>
<tr>
<td>Meridional τ, kdyn/cm2</td>
<td>66±15</td>
<td>67±33</td>
<td>58±14</td>
<td>52±10</td>
<td>50±1a</td>
<td>68±28</td>
<td>70±35</td>
</tr>
<tr>
<td>Septum diastolic, cm</td>
<td>0.968±0.141</td>
<td>0.978±0.151</td>
<td>1.038±0.147</td>
<td>1.022±0.139</td>
<td>1.056±0.124a</td>
<td>0.971±0.214</td>
<td>0.949±0.257</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>94.0±25.2</td>
<td>96.8±27.0</td>
<td>90.9±23.8</td>
<td>91.9±28.3</td>
<td>91.3±24.7</td>
<td>85.9±31.4</td>
<td>77.7±26.1</td>
</tr>
<tr>
<td>LVEVS, ml</td>
<td>33.4±9.6</td>
<td>33.0±9.8</td>
<td>30.2±9.8</td>
<td>31.2±11.1</td>
<td>28.7±11.0b</td>
<td>32.5±16.3</td>
<td>19.7±6.7</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>64.5±3.6</td>
<td>65.7±4.6</td>
<td>67.0±4.5</td>
<td>66.2±3.8</td>
<td>68.9±6.0b</td>
<td>63.2±6.8</td>
<td>73.5±7.7</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.43±1.12</td>
<td>4.98±1.44</td>
<td>4.18±1.15</td>
<td>4.39±1.15</td>
<td>4.68±1.10</td>
<td>3.88±0.90</td>
<td>13.96±5.49f</td>
</tr>
<tr>
<td>EMax (no units)</td>
<td>6.40±1.32</td>
<td>6.16±1.94</td>
<td>5.35±1.38</td>
<td>5.62±1.32</td>
<td>5.79±0.80</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are means ± SD. ECP, external counterpulsation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBF, myocardial blood flow; rBV, relative blood volume; β, blood exchange rate; CVRI, coronary vascular resistance index; PWI, pressure-work index; PRP, pressure-rate product; τ, wall stress; LVEDV, left ventricular end-diastolic volume; LVEVS, left ventricular end-systolic volume; EMax, the ratio between the early diastolic transmural peak flow velocity (E) and the early diastolic (e') peak velocities of the septal portion of the mitral annulus. *P < 0.05, **P < 0.01, ***P < 0.001, compared with ECP 0. $P < 0.01$, $P < 0.001$, compared with Bicycle Rest.

There was a significant positive correlation between indexes of $MV_2$ and MBF in the pooled bicycle data (PWI-MBF relation: $r = 0.87, P < 0.0001$, slope: 0.162; PRP-MBF relation: $r = 0.83, P < 0.0001$, slope: 1.38×10−7, Fig. 3). In the pooled ECP data, the regression analyses showed a similar correlations (PWI-MBF relation: $r = 0.43, P < 0.0001$, slope: 0.153; PRP-MBF relation: $r = 0.40, P < 0.0001$, slope: 1.06×10−5). Bivariate data distribution comparisons yielded a high degree of similarity between ECP and exercise: The median Mahalanobis distances $D^2$ of the ECP data from the exercise reference data were 0.97 (using PWI) and 1.03 (using PRP). In both, 97 of 100 ECP data points had a $D^2$ value ≤2. Thus, only 3% of the ECP data points could be considered lying outside the exercise data distribution.

Control parameters. As expected, mididiastolic pressure gradually increased in the course of ECP from 79 ± 11 at baseline to a maximum of 132 ± 15 mmHg at ECP 300, being statistically significant from ECP 80 upward. Accordingly, mean diastolic pressure increased from 83 ± 10 to 100 ± 11 mmHg under ECP. During exercise, diastolic pressure values remained unchanged compared with resting conditions. Heart rate accelerated under ECP from 60 ± 11 to a maximum of 68 ± 11 beats/min ($P < 0.001$). Concomitantly, systolic pressure dropped from 120 ± 10 to 112 ± 10 mmHg ($P < 0.01$). Overall, there was no significant change in the predicted $MV_2$ throughout the ECP protocol, whereas in bicycle exercise, there was a threefold increase of the two indexes during peak exercise (both $P < 0.001$). Both meridional and circumferential LV wall stress decreased, and LV ejection fraction increased from 64.4 ± 3.6 to 68.9 ± 6.0% ($P < 0.01$) during ECP, demonstrating its efficacy in LV afterload reduction. Cardiac output, however, showed no significant changes during ECP. End-diastolic LV volume showed no significant changes by ECP, unlike end-systolic volume, which significantly decreased at ECP 300. Diastolic septal wall thickness signifi-
significantly increased from 0.968 ± 0.141 to 1.056 ± 0.124 cm (P = 0.011) under ECP. There was no significant change of the E/e' during ECP (6.40 ± 1.32 at baseline, 5.79 ± 0.80 at ECP 300).

**DISCUSSION**

The present study demonstrates that diastolic pressure transients do not influence MBF and rBV but strongly increase the coronary vascular resistance. In contrast, exercise leads to a marked decrease in resistance, as well as to an increase in rBV and MBF. The relations between indexes of MV˙O₂ and MBF were not altered by ECP.

**Vasodilation and functional capillary density during exercise.** During exercise, the threefold increase in MBF in our study reflects the upward shift of the autoregulation plateau induced by metabolic and flow-mediated vasodilatory factors (14). The present exercise data are in accordance to previous studies (6, 14, 24, 27). The blood flow increase was not only achieved by accelerating erythrocyte passage through the capillary network (increased β) but also by increasing myocardial blood volume. Since 90% of the myocardial blood resides in the capillaries, rBV measurements predominantly reflect capillary blood volume (29). To our knowledge, the rBV increase from 13 to 22% (+69%) constitutes a new observation in the human myocardium. It suggests the ability of the myocardial microcirculation to recruit additional capillary channels as a means to increase flow during exercise, i.e., a capillary reserve mechanism. A similar amount of exercise-induced capillary recruitment (approximately +50%) has been described in animal red skeletal muscle by Honig et al. (21) after rapid in situ freezing of muscle tissue. At rest, only one-third of the capillaries were perfused by erythrocytes. It has been suggested that terminal arterioles able to impede erythrocyte passage exert an active regulatory role for capillary recruitment and de-recruitment (precapillary sphincters), whereas more proximal segments independently regulate flow and pressure but not erythrocyte passage (21). Other hypotheses favor a passive mechanism of erythrocyte distribution to the capillaries (17).

**Arteriolar resistance increase and stable myocardial flow during ECP.** The stability of the MV˙O₂ predictors throughout all ECP steps confirms that no significant change in myocardial oxygen demand occurred during this protocol. LV peak systolic wall stress and systolic pressure decreased as an expression of counterpulsation-induced ventricular unloading, but heart rate concomitantly increased, thus balancing myocardial oxygen demand (15). It can thus be assumed that no metabolically provoked shift of the autoregulation plateau occurred. This represents a necessary condition for the cross-talk-free observation of autoregulatory activity and unbiased MBF comparison between ECP levels. The stability of MBF and the increase of coronary vascular resistance with incremental ECP were very consistent (Fig. 2). There was a visually obvious

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**Fig. 2.** Pressure dependence of myocardial blood flow (MBF), relative blood volume, blood exchange rate, and coronary vascular resistance index during various ECP levels and bicycle exercise. Error bars in the x- and y-direction represent SD. *P < 0.05 compared with ECP 0; #P < 0.001 compared with bicycle rest.
slowing of contrast replenishment in echocardiography, reflected by the reduction of the blood exchange rate $\beta$. Such slowing of capillary passage is consistent with arteriolar constriction (2). We therefore interpret our data on ECP as the result of coronary autoregulation activity, reacting with increasing arteriolar vasoconstriction to incremental diastolic pressure transients. Since no upward trend of the pressure-flow curve was observed in the upper range, we conclude that in healthy individuals, autoregulation remains intact up to $\approx 140$-mmHg diastolic pressure transients.

**Autoregulation and myogenic vasoconstriction.** The in vivo behavior of autoregulation in the high pressure range has not yet been studied in humans. Rather, investigations have been focusing on low perfusion pressure (10, 22, 23, 28, 29, 48). In CAD, compensatory vasodilation occurs distal to coronary stenoses when pressure is low. Severe coronary stenoses lead to exhaustion of autoregulation, and thus to the inability of the coronary vessel to satisfy increased demand by further vasodilation (19, 29).

The mechanisms involved in autoregulation include passive and active processes in the arterioles. While in low transmural pressure the passive elastic properties of the arteriole contribute to its resistance (22), the distensibility of the vessel wall is exhausted at values exceeding 80 mmHg (42). We assume, therefore, that active vasoconstriction was the principal cause of the resistance changes observed in this study, although a certain increase in interstitial counterpressure may have blunted the transmural gradient. The most important active mechanism involved in cerebral, splanchnic, skeletal muscle, and myocardial autoregulation has been attributed to myogenic vasoconstriction (11). Bayliss (5) first described the important role of luminal pressure for arterial tone in 1902. Myogenic constriction in cardiac tissue could be demonstrated microscopically in arterioles isolated from left ventricles in pigs (26) and from human right atrial appendages (36). In the intact coronary circulation, myogenic activity is more difficult to demonstrate, because vasoactive pharmacological agents usually induce significant alterations in myocardial oxygen de-
mand and may directly interact with the arterioles under investigation. Myogenic vasoconstriction could be observed following diastolic pressure transients in dogs, indicating a dominant role for autoregulation (31, 40), whereas in the intact human heart, such direct evidence has been lacking. The coronary vascular resistance increase under ECP observed in the present study is consistent with such myogenic activity.

Michaels et al. (33) demonstrated a significant increase in intracoronary Doppler flow velocity immediately after onset of ECP in humans during cardiac catheterization. The apparent inconsistency with out data is resolved by considering the time-course of the myogenic response: the maximum vasoconstriction after application of a constant luminal pressure in isolated coronary arterioles occurs after 3–4 min in pigs and 4–5 min in humans (26, 36). Although the pressure stimulus during counterpulsation is intermittent, full coronary constriction may nevertheless require several minutes of counterpulsation to restabilize myocardial blood flow, as suggested by the data of the present study, and as ascertained by Michaels et al. (33).

Demand-supply matching and capillary recruitment. A typical linear relationship between oxygen demand and blood supply could be found in bicycle exercise testing. This relationship was not abandoned during ECP, as supported by the following three findings: first, regardless of the ECP level, MBF and predicted MV˙O2 remained unchanged in within-subject comparisons (Fig. 2). Second, in the predicted MV˙O2-MBF relations, ECP data reside within the exercise data distribution, as assessed by Mahalanobis distance analysis. Third, the regression lines in ECP and exercise have similar nonzero slopes and intercepts (Fig. 3). We conclude that the MV˙O2-MBF relation was not relevantly shifted by ECP; hence, demand-supply matching was maintained in the physiologic range.

Surprisingly, the rBV did not change under ECP, indicating that no capillary functional recruitment or de-recruitment occurred. The arteriolar constriction, thus, seems effective in preventing the capillary system from adopting functional changes over a wide range of pressure challenges. In an animal study, Le et al. (28) showed that high diastolic pressure was associated with a decrease in rBV, as well as an increased MBF and coronary sinus oxygen saturation. The authors concluded that the protection of the capillary bed from overpressure was prioritized over demand-supply matching via recruitment of arteriovenous shunts. However, these results were achieved using phenylephrine infusions, an experiment mimicking a hypertensive crisis with considerable increase in myocardial oxygen demand (approximately +200%) rather than the autoregulatory behavior per se. Nonetheless, capillary bypass shunting as an escape mechanism that initiates above a hypothetical myogenic working range is an interesting suggestion. It cannot be excluded in our and other studies (50).

Clinical considerations. In the last years, ECP has emerged as an alternative therapeutic strategy in patients with refractory angina pectoris and CHF. Clinical studies have demonstrated its ability to reduce angina in CAD (1, 3, 34) and to improve exercise tolerance and dyspnea in CHF (16). The present study was not designed to elucidate the reasons for the clinical benefit of chronic ECP therapy. Nevertheless, some clinical considerations on mechanisms involved in counterpulsation, whether applied externally or by an intra-aortic balloon pump, are given here. As shown in this study, counterpulsation cannot “force” MBF to rise in coronary vessels with intact autoregulatory function. On the other hand, pressure transients fail to propagate into the distal segments of vessels affected by severe stenoses (30). These mechanisms should not be ignored in acute counterpulsation therapies. An important restriction regarding the inability of counterpulsation to increase myocardial flow acutely, however, must be acknowledged: in individuals with coronary collaterals, counterpulsation seems effective. We suggest that this efficacy is particularly pronounced if the myocardial territory at risk is in a state of exhausted autoregulation. In an experiment using coronary ligation, counterpulsation has been shown to acutely increase collateral flow in dogs, a species with abundant coronary collaterals (7). In CAD patients, sustained collateral vessel growth has recently been demonstrated in two studies after an ECP treatment course (8, 18). This effect is considered the result of repeated shear stress increases within the collateral channels, the most potent stimulus for arteriogenesis (20). Acute and chronic exercise has also been shown to increase collateral flow in humans (32, 41, 45, 51). ECP and physical exercise, thus, differ with regard to coronary arteriolar vasomotion and capillary recruitment in the acute setting but share a common effect: collateral flow stimulation.

Limitations. It would have been preferable to measure myocardial oxygen consumption directly from the coronary oxygen content or by acquiring LV pressure-volume loops (43). The noninvasive MV˙O2 indexes used in this study must be considered substitutes with limited reliability, particularly in intersubject comparisons (4, 39, 43). The PWI is an interesting method because it accounts not only for pressure generation but also for stroke work, whereas the PRP is the most widely used noninvasive substitute in clinical routine. Both indexes, however, are based on a strongly simplified parametrization of the myocardial metabolism.

Arterial pressure does not entirely reflect perfusion pressure without venous backpressure measurements. Due to the noninvasive nature of this study, no central venous pressure measurements were performed. Two invasive studies showed that during ECP central venous pressure acutely increased by 3–4 mmHg in a mixed patient population (35) and, in patients with acute, revascularized myocardial infarction (44). Such an increase of backpressure, however, is too small to counterbalance an arterial diastolic pressure augmentation of 53 mmHg. Similarly, left ventricular end-diastolic pressure (LVEDP) was not directly measured but estimated noninvasively using Ele’. Given the limited sensitivity of this Doppler echocardiographic parameter, small LVEDP-changes may have occurred despite constant Ele’. These are considered too small, however, to potentially ignite a diastolic flow impediment by increasing intramyocardial pressure and causing a collapse of the microvasculature (waterfall phenomenon) (13). We (12) previously described phenomena during collateral-dependent perfusion in humans consistent with this model and found that LVEDP levels of ≥25 mmHg were mandatory. The Ele’ clearly indicates that such levels were not reached in our study population.

The radial pressure profile, as assessed by applanation tonometry, does not fully reflect the coronary arterial pressure profile. Considering the presence of strong perturbances such as during ECP, it is questionable whether a conversion from radial to central pressure using the inverse aortic-to-radial
transfer function proposed by Chen et al. (9) would result in reasonable central pressure curves. The nature of the diastolic pulse wave is not fundamentally different in the radial and coronary artery: in both cases, it consists of a forward-propagating compression wave (25, 38). Although the absolute pressure values may slightly differ in the coronary arteries, we believe that radial pressure measurement does not hamper the coronary analysis in this case. The intracoronary pressure measurements obtained by Michaels et al. (33) during ECP showed similar values.

Because of the technical difficulties in retrieving good echocardiographic clips during exercise, hemodynamic data do not reflect the maximum effort in all participants. Therefore, it remains unclear whether the functional capillary recruitment is rather an “on/off” phenomenon.

**Conclusions.** Whereas physical exercise decreases coronary vascular resistance and induces considerable functional capillary recruitment, diastolic pressure transients up to 140 mmHg trigger myogenic arteriolar vasoconstriction, keeping not only myocardial blood flow but also functional capillary density constant. Demand-supply matching was maintained over the entire range of pressure challenges.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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