Abnormal Longitudinal, Base-to-Apex Myocardial Perfusion Gradient by Quantitative Blood Flow Measurements in Patients With Coronary Risk Factors

Miguel Hernandez-Pampaloni, MD, PhD; Felix Y.J. Keng, MD; Takashi Kudo, MD, PhD; James S. Sayre, PhD; Heinrich R. Schelbert, MD, PhD

Background—A longitudinal, base-to-apex myocardial perfusion gradient has been described in patients with coronary artery disease (CAD) and was attributed to diffuse coronary luminal narrowing. We asked whether an abnormal perfusion gradient also existed in patients without CAD but with coronary risk factors. We measured myocardial blood flow (MBF) with $^{13}$N-ammonia and PET at rest and during hyperemia in patients with coronary risk factors but without CAD.

Methods and Results—Regional MBF was measured in absolute units with $^{13}$N-ammonia and PET at rest and during dipyridamole hyperemia in 36 patients with coronary risk factors (age, 55±10 years) and in 36 age-matched (age, 53±10 years) and in 28 young (age, 25±5 years) normal subjects. MBF was determined globally, for each of the 3 coronary territories, and in the mid and mid-to-apical sections of the left ventricle (LV). Myocardial perfusion on qualitative analysis was normal at rest and during hyperemia, and no flow defects were present. MBF in absolute units was similar in the 3 coronary territories. However, hyperemic MBFs in the mid-to-apical LV section were lower than in the mid LV section in the “at-risk” group (2.04±0.61 versus 1.71±0.40 mL·min$^{-1}$·g$^{-1}$; $P<0.004$) but not in the age-matched or in the young normal subjects.

Conclusions—The abnormal longitudinal, base-to-apex perfusion gradient observed during dipyridamole MBF suggests the presence of a functional and/or structural alteration of the coronary circulation associated with coronary risk factors, possibly reflecting developing coronary atherosclerosis or preclinical CAD.

Key Words: blood flow • circulation • tomography • risk factors

Quantitative analysis of dipyridamole PET myocardial perfusion images in patients with angiographic coronary artery disease (CAD) revealed a graded, longitudinal, base-to-apex myocardial perfusion gradient. Importantly, this perfusion abnormality occurred independent of dipyridamole-induced regional flow defects. Because it was observed also in angiographically minimal, non–flow-limiting disease, it was attributed to fluid dynamic consequences of diffuse luminal narrowing of the epicardial coronary arteries. We hypothesized that this novel concept might apply also to patients without CAD but with coronary risk factors. Investigations with intracoronary flow velocity probes and quantitative angiography demonstrated a flow-dependent dilation of the epicardial coronary arteries in response to vascular smooth muscle–relaxing agents such as adenosine or papaverine injected distally into the coronary circulation. This normal dilation is thought to be mediated by release of relaxing factors from the endothelium in response to high flow velocity–dependent shear stresses. This flow-dependent dilation of the epicardial coronary artery is diminished or even absent in CAD or in the presence of coronary risk factors alone including hypercholesteremia, smoking, diabetes, or a family history of CAD. If the epicardial conduit vessels do not dilate, resistance to higher velocity flows would increase because, among other determinants, it is a function of the fourth power of the luminal radius. This then could also cause a progressive, proximal-to-distal decline in pressure in the epicardial coronary arteries and be associated with a graded, longitudinal, base-to-apex perfusion abnormality. To test our hypothesis, we measured regional myocardial blood flow (MBF) and evaluated its relative distribution with $^{13}$N-ammonia and PET in patients with coronary risk factors (“at-risk patients”). For comparison, we also studied age-matched (“older normal subjects”) and, to exclude age-related differences, younger (“young normal subjects”) healthy normal subjects without risk factors for CAD.

Methods

Patient Population

The study population consisted of 3 groups (Table 1): (1) 36 patients (age, 55±10 years) with coronary risk factors but without clinical evidence of CAD, referred to as “at-risk patients,” (2) 36 age-
TABLE 1. Characteristics of Study Population

<table>
<thead>
<tr>
<th></th>
<th>At Risk (n=36)</th>
<th>Older (n=36)</th>
<th>Young (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±10</td>
<td>53±10</td>
<td>25±5</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>18/18</td>
<td>18/18</td>
<td>14/14</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>207±42</td>
<td>190±41</td>
<td>146±30</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>41±9</td>
<td>49±16</td>
<td>59±9</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>125±36</td>
<td>115±36</td>
<td>77±30</td>
</tr>
<tr>
<td>HDL/LDL</td>
<td>0.36±0.14</td>
<td>0.47±0.23</td>
<td>0.83±0.3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64±9</td>
<td>64±11</td>
<td>64±10</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126±21</td>
<td>117±16</td>
<td>104±6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74±11</td>
<td>69±7</td>
<td>61±8</td>
</tr>
<tr>
<td>Rate-pressure product*</td>
<td>8.0±1.6</td>
<td>7.4±1.8</td>
<td>6.8±1.4</td>
</tr>
<tr>
<td>MBF, mL · g⁻¹ · min⁻¹</td>
<td>0.8±0.19</td>
<td>0.76±0.21</td>
<td>0.6±0.11</td>
</tr>
<tr>
<td>Coronary resistance*</td>
<td>128±31</td>
<td>126±21</td>
<td>123±24</td>
</tr>
</tbody>
</table>

Findings at rest

Values are mean±SD.

Rate-pressure product is measured in [(mm Hg · min⁻¹) · 10³]; coronary vascular resistance was calculated from the ratio of mean arterial blood pressure to MBF.

*P<0.001 vs young and P<0.02 vs older normal subjects by ANOVA.
†P<0.05 vs young and older normal subjects by ANOVA.

Evaluation and Measurement of MBF

Positron Emission Tomography

A positron emission tomograph (ECAT EXACT HR+, CTI/Siemens) with an effective isotropic resolution of 10-mm full-width at half-maximum and a 15.5-cm axial field of view was used. Transmission images were recorded first for 20 minutes. Beginning with each intravenous ¹⁵N-ammonia injection (15 to 20 mCi), transaxial image sets were acquired serially (12 frames of 10 seconds each, 2 frames of 30 seconds each, 1 frame of 60 seconds, and 1 frame of 900 seconds). Between MBF measurements, 45 minutes were allowed for physical decay of ¹⁵N. Dipyridamole (0.56 mg/kg) was infused intravenously for 4 minutes, and ¹⁵N-ammonia was injected without applying handgrip 3 minutes later. A 2-lead ECG was monitored continuously while arterial blood pressure and a 12-lead ECG were recorded every minute at baseline and during and for 5 minutes after dipyridamole. Heart rate and systolic blood pressure during the first 2 minutes of each image acquisition sequence were averaged.

Relative Distribution of MBF

The 12 serially acquired transaxial image sets were each reoriented into short-axis images and assembled into polar maps. From the last, 900-second image set, short-axis, vertical, and horizontal long-axis cuts and a polar map were obtained for visual and quantitative analysis of the relative distribution of myocardial tracer uptake. Two independent observers unaware of the study participants’ classification analyzed the images and polar maps. The polar maps obtained at baseline and after dipyridamole were also analyzed semiquantitatively by comparison to a database of normal. Myocardial perfusion was defined as normal if the regional myocardial ¹⁵N activity was within 2 SD of the normal mean. For assessing relative myocardial tracer concentrations, regions of interest (ROI) corresponding to each of the 3 coronary territories and, further, to the mid and mid-to-apical circumferences (subsequently defined as “basal” and “apical” ROIs) of the LV were assigned to the polar maps (Figure 1). Mean regional activity concentrations were related to the 5% pixels with the highest activity in each polar map.

Figure 1. Schematic representation of polar maps of MBFs and assignment of regional interest. A, Three coronary artery territories; B, circumferential ROIs for mid or basal (B) and mid-to-distal or apical (A) portion of LV. LAD indicates left anterior descending; RCA, right coronary artery; and LCX, left circumflex.
**Calculation of MBF**

MBF was determined (in mL · min⁻¹ · g⁻¹) for the entire LV myocardium, subsequently referred to as global MBF, and for each of the 3 coronary vascular territories. Importantly, MBF was also measured selectively in the “basal” and the “apical” sections of the LV from circular ROIs as described above (Figure 1). The sectorial coronary artery territory and the 2 circumferential ROIs were then copied to the serial polar maps acquired during the first 2 minutes after tracer injection, and regional myocardial time-activity curves were generated. A small (25 mm³) ROI was centered in the LV blood pool at a basal short-axis slice to derive the arterial input function. Partial volume effects were corrected with a recovery coefficient that assumed a uniform 1-cm-thick LV wall.⁷ Time-activity curves were corrected for physical decay and fitted with a previously validated 2-compartment model.⁸ The apical and most basal LV portions were excluded from quantitative analysis to avoid errors caused by partial volume effects or by interindividual variations in reorientation parameters.

**Data Analysis**

Mean values are given with standard deviations. Hemodynamic parameters and global and regional MBF at rest and during hyperemia were analyzed by repeated-measures ANOVA. Post hoc comparisons were made by means of Scheffé analysis, which examines the differences between all possible pairs means while controlling the significance level. Multiple linear regression analyses were performed to search for possible correlations between hemodynamic variables, risk factors, regional differences in MBF, and perfusion gradients along the LV myocardium. A value of $P<0.05$ was considered statistically significant.

**Results**

**Hemodynamic Parameters**

At rest, heart rate and systolic and diastolic blood pressures were similar for the 3 groups, whereas the rate-pressure product in the older normal subjects and the “at-risk” patients was higher (Table 1). During dipyridamole-induced hyperemia, heart rate and blood pressures were similar in the 3 groups.

**Relative Distribution of MBF**

Visual and semiquantitative analysis of the reoriented rest and dipyridamole perfusion images and of the polar maps revealed homogeneous tracer uptake in the 3 study groups. There were no rest- or stress-induced regional flow defects. The relative tracer concentrations were similar in the 3 coronary territories in the 3 study groups. Furthermore, they did not differ between the “basal” and “apical” myocardial circumferences at rest and during hyperemia in the “at-risk” patients or in the young and older normal subjects (Table 2). Relative $^{13}$N-ammonia concentrations in the 3 coronary artery territories and in the “basal” and “apical” circumference of the LV myocardium were nearly identical in men and women in all study groups, excluding possible sex-related differences.

**MBF in Absolute Units**

At rest, global MBF was similar for the 3 groups but tended to be higher in the older normal subjects and the “at-risk” patients than in the young normal subjects (Table 1 and Figure 2). Of note, in the older normal subjects, MBF tended to be higher in women than in men, but this difference was not statistically significant. In the “at-risk” group, however, MBF at rest was higher in women than in men ($P<0.02$; Table 3); this was probably related to the higher rate-pressure products in women than in men ($8450±1320$ versus $7679±18621$, respectively, NS) because more women than men (5 versus 2) had hypertension.

During hyperemia, global MBFs were similar in the 3 study groups but tended to be lower in the “at-risk” patients, in whom the myocardial perfusion reserve was lower than in the older and young normal subjects (Table 1). Thus, combining the moderately but not significantly higher rest and moderately lower hyperemic MBFs in the “at-risk” patients resulted in a lower perfusion reserve (Figure 2).

Dipyridamole induced comparable hyperemic MBFs in each of the 3 coronary territories in the 3 study groups (Table 4). ANOVA found no significant interterritory differences in MBF in any of the study groups, although hyperemic MBFs in the right coronary artery territory of the “at-risk” group tended to be lower. Comparisons of hyperemic MBFs in the base-to-apex direction demonstrated similar values for the basal and apical LV sections in the 2 normal groups. In the “at-risk” patients, however, hyperemic MBFs in the apical section were lower than those in the 2 control groups (by 18% and by 10%, respectively, $P<0.002$). Importantly, hyperemic

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**TABLE 2. Relative N-13 Ammonia Uptake in Basal and Apical LV Segments**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Rest</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Apical</td>
</tr>
<tr>
<td>Young normal subjects</td>
<td>81.9±4.3%</td>
<td>83.7±4.7%</td>
</tr>
<tr>
<td>Older normal subjects</td>
<td>82.4±3.9%</td>
<td>83.0±3.9%</td>
</tr>
<tr>
<td>At-risk patients</td>
<td>82.9±3.9%</td>
<td>81.7±6.1%</td>
</tr>
</tbody>
</table>

All $P=NS$.
MBFs were 11% lower in the apical than in the basal LV sections in the “at-risk” group (Figures 3 and 4).

Myocardial Flow Resistances
From the ratio of mean arterial blood pressure to MBF, an index of coronary vascular resistance was calculated. Only during hyperemia was the global coronary resistance higher in the “at-risk” group than in the two control groups (Table 1). However, the resistance was higher in the apical LV section in the “at-risk” patients when compared with that in the older and young normal subjects (52±13 versus 40±12 versus 37±10 mm Hg/mL · g⁻¹ · min⁻¹; P<0.02) but was similar for the 3 groups in the basal LV section (49±9 versus 39±12 versus 37±12 mm Hg/mL · g⁻¹ · min⁻¹; P=NS).

Multiple Linear Regression Analysis
There was a significant association between the MBF gradient from the basal to the apical LV section and all coronary risk factors (P<0.01). No differences were identified between risk factors. All coronary risk factors were correlated with a diminished perfusion reserve (P<0.04) except for smoking, for which the MBF reserve was higher (P<0.0001).

Discussion
A perfusion gradient between the mid and the mid-to-apical sections of the LV myocardium during dipyridamole hyperemia in patients without clinical evidence of CAD but with coronary risk factors is the major finding of the current study. The gradient is independent of sex because it was present in both men and women at risk and is independent of age because it was not observed in older and in young normal subjects without risk factors. Finally, such gradient occurred despite normal dipyridamole hyperemic MBFs because they did not differ from those in young and older normal subjects. Because of its longitudinal, base-to-apex direction, the observed gradient appears to be consistent with the recently reported graded, longitudinal perfusion gradient in patients with angiographically only minimal CAD attributed to fluid dynamic effects of diffuse luminal narrowing of the epicardial coronary arteries.¹

We had postulated that even functional alterations of the coronary circulation might lead to such perfusion gradient. Invasive studies report an ~10% to 15% flow-mediated dilation of the epicardial conduit vessels in normal individuals in response to increases to coronary flow after distal intracoronary injection of direct vascular smooth muscle relaxing agents such as adenosine or papaverine.²⁻⁵ In patients with coronary risk factors, this flow-dependent dilation of the epicardial coronary arteries is diminished or absent.⁴⁻⁵ We therefore hypothesized that the physiological, normal dilation of the coronary conduit vessels diminishes the resistance to higher velocity flows because, according to the Poiseuille equation, the resistance to flow is a function of the fourth power of the radius of the conduit vessel. If such dilation is attenuated or absent, as reported for patients with coronary risk factors, then the resistance to higher coronary flows during dipyridamole in our study would markedly increase, exert similar fluid dynamic effects as observed in minimal anatomical CAD,¹ cause a progressive proximal to distal decline in pressure in the epicardial coronary arteries, and, hence, lead to a longitudinal base-to-apex perfusion gradient.

However, because coronary angiography and intracoronary ultrasound were not performed in our patients, the exact mechanism(s) accounting for our findings remain uncertain. Besides functional abnormalities, structural abnormalities of the coronary arterial wall could also explain the perfusion gradient. For example, diffuse luminal narrowing as proposed by Gould et al¹ could have been present, at least in some of our patients. Even if the luminal cross-sectional area of the epicardial coronary artery is not reduced,⁹ an increased thickness of the arterial wall and/or atherosclerotic plaques as observed with intracoronary ultrasound, especially in patients

### Table 3. Global MBF (mL · g⁻¹ · min⁻¹) in Men and Women in Three Study Groups at Rest and During Dipyridamole Hyperemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Rest</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Young normal</td>
<td>0.61±0.09</td>
<td>0.71±0.14</td>
</tr>
<tr>
<td>Older normal</td>
<td>0.66±0.10</td>
<td>0.89±0.29</td>
</tr>
<tr>
<td>At-risk patients</td>
<td>0.71±0.13*</td>
<td>0.93±0.21</td>
</tr>
</tbody>
</table>

*P<0.02 vs women.

### Table 4. Mean MBF (mL · g⁻¹ · min⁻¹) per Coronary Territory of Three Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>0.61±0.12</td>
<td>0.70±0.14</td>
<td>0.69±0.17</td>
<td>1.99±0.55</td>
<td>2.16±0.49</td>
<td>2.18±0.61</td>
</tr>
<tr>
<td>Older</td>
<td>0.73±0.24</td>
<td>0.84±0.28</td>
<td>0.71±0.19</td>
<td>2.09±0.60</td>
<td>2.16±0.64</td>
<td>2.04±0.70</td>
</tr>
<tr>
<td>Risk factor</td>
<td>0.81±0.23</td>
<td>0.85±0.19</td>
<td>0.77±0.21</td>
<td>1.84±0.44</td>
<td>1.95±0.46</td>
<td>1.72±0.47</td>
</tr>
</tbody>
</table>

All P=NS by ANOVA (repeated measures).

LAD indicates left anterior descending; LCX, circumflex coronary artery; and RCA, right coronary artery.
with coronary risk factors, may serve as another explanation. An increase in stiffness of the epicardial coronary arteries might then mechanically attenuate their ability to dilate. The previously observed inverse correlation between the degree of regional intimal thickening and the acetylcholine-induced changes in the luminal cross-sectional area of epicardial coronary arteries suggests further the possibility of a functional and physical barrier effect of the thickened intima to diffusion of nitric oxide from the endothelium to the vascular smooth muscle or its rapid inactivation by superoxide anions and, hence, again an impairment in the vasodilator function.

Global dipyridamole flows in our “at-risk” patients did not differ significantly from those in the 2 control groups. This may have been because of the different risk factors in that group. For example, in 13 (36%) of the at-risk patients, long-term smoking was the only risk factor. Consistent with previously reported normal hyperemic MBFs in long-term smokers, they demonstrated the highest flow reserve on PET13,14 was present in 18 (or 50%) of our patients. Despite their different effects on hyperemic MBFs, both, smoking and hypercholesteremia were, however, associated with the base-to-apex perfusion gradient in our study. Moreover, PET studies demonstrated significant improvements in hyperemic MBFs after 4 to 6 months of treatment with HMG-CoA reductase inhibitors in patients with angiographically severe, minimal, or no CAD.13,15 The relatively short time period during which hyperemic MBFs improved implicates functional rather than morphological changes as the reasons for the beneficial drug effects. This possibility is supported further by an improved responsiveness of the epicardial coronary arteries to intracoronary acetylcholine after a 6-month course of HMG-CoA reductase inhibitor treatment in patients with CAD.16

The perfusion gradient in our study was not related to age, because it was not observed in age-matched and in young normal subjects, nor was it dependent on sex. Young women revealed higher hyperemic MBFs than did young men. An earlier study attributed these higher MBFs to sex-related differences in lipid profiles.17 Plasma lipid levels in our young women were, however, normal. Vasoactive effects of sex hormones may be one explanation, because all young women were studied during mid-cycle, when plasma levels of estrogen are high and of progesterone are low. Furthermore, no significant differences in MBF between men and women were found in the “at-risk” group. All women in this group were postmenopausal by clinical criteria. Although all but 3 women were receiving HRT, the perfusion gradient was noted in all women in the at-risk group but in none in the age-matched normal group. Therefore, HRT did not appear to affect the perfusion gradient.

Although statistically significant, the perfusion gradient in our study was of relatively small magnitude and less than predicted by Gould’s findings. Moreover, the gradient was noted only when dipyridamole MBFs were measured in absolute units but not when their relative distribution was evaluated on polar maps. Several reasons may explain these differences. One is that our patients had less severe coronary artery abnormalities than those in the previous report1 and therefore had a less pronounced perfusion gradient. Second, myocardial 13N-ammonia concentrations as the net tracer uptake correlate with MBF in a nonlinear fashion.18 Because the portion of the curve describing this correlation is relatively flat in the hyperemic flow range, mild MBF differences may have remained undetected when evaluating only the relative distribution of tracer uptake. Measurements of MBF correct for the nonlinearity of the myocardial 13N-ammonia net uptake so that mild to moderate perfusion differences are identified. Third, the perfusion gradient was measured in our study only over a relatively short longitudinal distance of the LV myocardium, that is, from the mid to the mid-to-apical portion of the LV. Had the same analysis approach been used as in the previous study,1 it is possible that it might have demonstrated similar slopes for the graded, base-to-apex decline in perfusion and a more prominent perfusion gradient.

Conclusions and Clinical Implications
Our observations support and, at the same time, expand on the concept of a graded, longitudinal, base-to-apex decline in LV myocardial perfusion that integrates fluid dynamic effects on flow in the epicardial coronary arteries with downstream consequences on myocardial tissue perfusion. Furthermore, the perfusion gradient adds to the noninvasive characterization of the functional and structural state of the coronary circulation in humans. It may aid in the detection of diffuse CAD despite only mild alterations on angiography or of preclinical coronary atherosclerosis. Longitudinal studies would seem to be warranted for determining whether morphological or only functional alterations or both account for our observations and further, whether the observed perfusion
gradient may be useful for monitoring responses to therapeutic approaches.

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References


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