Influence of Age and Hemodynamics on Myocardial Blood Flow and Flow Reserve

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Background. Aging is associated with changes of the systolic blood pressure that may increase cardiac work and myocardial blood flow at rest and reduce the myocardial flow reserve. This might be misinterpreted as age-related impairment of the coronary vasodilator capacity.

Methods and Results. Myocardial blood flow was quantified at rest and after administration of intravenous dipyridamole in 40 healthy volunteers (12 women and 28 men) with \(^{15}\text{N}\)-ammonia and positron emission tomography. Eighteen of the normal subjects were less than and 22 were older than 50 years (31±9 versus 64±9 years). The resting rate-pressure product was lower in the younger than in the older subjects (6895±1070 versus 8634±1890; P<0.01). Myocardial blood flow at rest averaged 0.76±0.17 mL·min\(^{-1}\)·g\(^{-1}\) in the younger volunteers and 0.92±0.25 mL·min\(^{-1}\)·g\(^{-1}\) in the older volunteers (P<0.05). Hyperemic blood flows did not differ between younger and older subjects (3.0±0.8 versus 2.7±0.6 mL·min\(^{-1}\)·g\(^{-1}\); P=NS); however, minimal coronary resistance was higher in the older subjects. Corrected for indexes of coronary driving pressure, hyperemic flow was lower in older than in younger normal subjects. The higher resting blood flows combined with similar hyperemic flows resulted in a lower myocardial flow reserve in the older than in the younger normal subjects (4.1±0.9 versus 3.0±0.76; P<0.001). The flow reserve was more closely correlated with resting than with hyperemic blood flows.

Conclusions. Aging does not alter significantly dipyridamole-induced hyperemic flows; although coronary vascular resistance after dipyridamole was somewhat increased in older subjects. The gradual decline of the myocardial blood flow reserve correlates with an age-related increase of baseline myocardial work and blood flow. These findings suggest that the reduced flow reserve with age is primarily due to increased cardiac work and blood flow at rest rather than to an abnormal vasodilator capacity.

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Key Words • positron emission tomography • blood flow, myocardial • flow reserve • aging

The coronary circulation can accommodate marked increases in blood flow in response to increased oxygen demand or pharmacological vasodilation. Substances such as dipyridamole or adenosine augment coronary blood flow by lowering rather selectively the coronary resistance independent of oxygen demand.\(^1\)\(^2\) Maximal achievable flows might differ among pharmacological agents such as adenosine, dipyridamole, or papaverine,\(^3\)\(^4\) with only submaximal vasodilation in some individuals.\(^5\) The magnitude of the flow response, called the myocardial flow reserve, is defined as the ratio of hyperemic to resting blood flow.

Age-related increases of systolic blood pressure\(^6\)\(^7\) or of heart rate at rest\(^8\) would be expected to increase myocardial oxygen demand and, consequently, blood flow. Accordingly, the observed myocardial blood flow reserve might be attenuated in older subjects, as recently reported.\(^9\) If such attenuation as a function of age does exist, it might lead to erroneous interpretations of quantitative measurements of blood flow in the older population with a higher prevalence of coronary artery disease.\(^10\) Accordingly, the present study was undertaken to determine in a group of healthy subjects whether the myocardial blood flow reserve was related to age and, if so, what factors accounted for such possible changes.

Methods

Study Population

The study population consisted of 40 healthy volunteers (19-86 years; 12 women and 28 men). Of these, 18 were less than (31±9 years) and 22 were more than 50 years old. Subjects were divided into younger (aged 20-50 years; 12 men and 8 women) and older (aged 60-86 years; 10 men and 12 women) groups. Six hypertensives (aged 65±7 years; 3 men and 3 women) and eight normotensives (aged 60±6 years; 4 men and 4 women) served as controls.

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years old (63±8 years; P<0.0001). This grouping was chosen because the incidence of coronary artery disease increases sharply beyond the age of 50 years.¹⁰ None of the volunteers had a history of a prior cardiac event or of smoking or had elevated total or low density lipoprotein cholesterol levels, hypertension, or diabetes mellitus. Only subjects with normal blood pressure (according to Joint National Committee on Hypertension criteria) were included.¹¹ Resting blood pressures were <160/90 mm Hg in the older subjects and <140/90 mm Hg in the younger subjects. All had a normal resting ECG and underwent a symptom-limited treadmill test. They achieved at least 93% of the age-predicted work load. None developed chest pain or ECG changes indicative of myocardial ischemia. Thus, all had a low probability for coronary artery disease.¹² Each subject signed an informed consent form approved by the UCLA Human Subject Protection Committee.

Positron Emission Tomography

All subjects refrained from ingesting caffeinated beverages or theophylline-containing medications for 24 hours before the positron emission tomography (PET) study. Myocardial blood flow at rest and after administration of 0.56 mg/kg dipyridamole i.v. infused over 4 minutes was quantified noninvasively with ¹³N-ammonia and serial PET imaging.

The whole-body tomograph (model 931/8; CTI/Siemens, Knoxville, Tenn.) used in this study acquires 15 transaxial planes with an in-plane spatial resolution of 6.5 mm full-width half-maximum (FWHM), has an interplane spacing of 6.75 mm, and covers a 10-cm axial field of view. The images were reconstructed using a Shepp filter with a cutoff frequency of 3 cycles per pixel, resulting in an effective in-plane resolution of 11 mm FWHM.

A 20-minute transmission scan was acquired for correction of photon attenuation. Beginning with the intravenous bolus administration of ¹³N-ammonia (10–12 mCi), serial images were acquired for 19 minutes (12 frames of 10 seconds each, two frames of 30 seconds, one frame of 60 seconds, and one frame of 900 seconds). Forty-five minutes later, after physical decay of ¹³N-activity, 0.56 mg/kg dipyridamole i.v. was infused over 4 minutes. Four minutes after the dipyridamole infusion, a second dose of ¹³N-ammonia (10–12 mCi) was injected, and an identical image acquisition protocol was used. Patient movement was minimized by fastening a Velcro strap across the patient’s chest. Arterial blood pressure was measured twice during the first 2 minutes after each ¹³N-ammonia injection. ECGs were recorded continuously during the first 2 minutes of the resting and hyperemic ¹³N-ammonia study.

PET Image Analysis

From the serially acquired data, 15 static transaxial images were reconstructed. Each of these image sets was reoriented on a Macintosh computer into six contiguous short-axis cross sections of the left ventricle, progressing from the apex to the base.¹³,¹⁴ The six short-axis cross sections obtained from the last image set, recorded for 900 seconds, were assembled into a polar map of the myocardial ¹³N-ammonia uptake. To determine the presence of resting or stress-induced flow defects, these polar maps were compared with reference polar maps established in 11 healthy volunteers.¹⁴

Quantification of Blood Flow

To obtain quantitative estimates of rest and hyperemic myocardial blood flows, three serially acquired short-axis cross sections (basilar, midventricular, and apical; Figure 1) were selected in each subject. To each of the three cross sections, three 90° sectorial regions of interest were assigned. They corresponded to the distribution of the left anterior descending, left circumflex, and right coronary arteries (Figure 1).¹⁵ The regions, which were placed on the first image frame that clearly visualized the left ventricular myocardium, were copied.
to the first 12 serially acquired $^{13}$N-ammonia images (i.e., the initial 120 seconds of data after tracer injection), and regional myocardial tissue time-activity curves were obtained. Time-activity curves from the three corresponding sectors in the three planes were then averaged, and three time-activity curves for the three vascular territories were obtained. A 25-mm$^2$ region of interest (10 pixels) was placed in the left ventricular blood pool and copied to the first 12 frames of the serially acquired images to obtain the arterial tracer input function.$^{16}$

Partial volume effects were corrected with a recovery coefficient that assumed a homogeneous myocardial wall thickness of 1 cm. The myocardial $^{13}$N activity curves also were corrected for spillover of activity from the blood pool to the myocardium and for physical decay of $^{13}$N. The time-activity curves were then fitted with a previously validated two-compartment tracer kinetic model.$^{17}$ The arterial input function was not corrected for $^{13}$N metabolites because the degree of metabolite contamination during the initial 2 minutes after tracer administration is rather small.$^{17}$

Statistical Analysis

Values are given as mean±SD. One-way ANOVA was used for comparison of intergroup differences. Correlations were sought using the least-squares linear regression analysis. $P<0.05$ was considered statistically significant.

Results

Comparison With a Data Base of Normal Subject Values

Visual inspection of the transaxial and short-axis images revealed homogeneous myocardial $^{13}$N activity uptake both at rest and after dipyridamole. The comparison of blood flow maps with a previously established data base of 11 normal subjects$^{14}$ further confirmed the normal myocardial $^{13}$N uptake at rest and during hyperemia. The normal $^{13}$N-ammonia uptake together with the absence of ECG abnormalities and chest pain during and after the dipyridamole infusion provided further evidence that the subjects were free of significant coronary artery disease.

Hemodynamic Findings and Age

None of the subjects had a history of hypertension. Only one of the older subjects had a blood pressure of 155/90 mm Hg; it was <145/90 mm Hg in all other older subjects. None of the younger subjects had a blood pressure >130/85 mm Hg.$^{11}$ Table 1 lists the hemodynamic findings at rest and during dipyridamole stress. At baseline, systolic, diastolic, and mean blood pressures and the rate-pressure product were higher in the older than in the younger subjects ($P<0.01$). Heart rates also tended to be higher in the older subjects ($P=0.061$). After dipyridamole, only the diastolic and mean aortic blood pressures differed between the two groups. Accordingly, the dipyridamole-induced increase in the rate-pressure product was greater in the younger than in the older volunteers ($67\pm27\%$ versus $41\pm25\%$; $P<0.01$). However, peak heart rates and rate-pressure products were similar in both groups. For the entire population, systolic, diastolic, and mean blood pressures and the rate-pressure product at rest correlated with age. After dipyridamole, only diastolic and mean blood pressures correlated with age ($r=0.34$ and 0.36; respectively; $P<0.05$ for both; Figure 2).

Myocardial Blood Flow and Age

The coefficients of variations of regional flow measurements ranged from 8% to 12% and were similar for rest and hyperemric studies ($P=NS$). The estimates of blood flow did not differ between the three myocardial regions or vascular territories at rest and after dipyridamole ($P=NS$ by ANOVA; Table 2). Therefore, a single value for an average myocardial blood flow was obtained for each subject.

At rest, myocardial blood flows correlated linearly with the rate-pressure product (Figure 3). There also

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**Table 1. Hemodynamic Findings Grouped According to Age and Sex**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;50</th>
<th>&gt;50</th>
<th>Men (n=11)</th>
<th>Women (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31±9</td>
<td>64±9*</td>
<td>66±9</td>
<td>62±9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>61±9</td>
<td>67±11</td>
<td>68±13</td>
<td>66±10</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>92±10</td>
<td>92±14</td>
<td>90±14</td>
<td>94±14</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113±10</td>
<td>127±13†</td>
<td>122±11</td>
<td>132±13</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>123±12</td>
<td>130±13</td>
<td>126±11</td>
<td>133±14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>68±8</td>
<td>78±8§</td>
<td>75±9</td>
<td>81±6</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>69±9</td>
<td>78±9§</td>
<td>75±8</td>
<td>81±9</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>6895±1069</td>
<td>8634±1886§</td>
<td>8433±2108</td>
<td>8818±1731</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>11 291±1450</td>
<td>11 920±2217</td>
<td>11 310±2009</td>
<td>12 487±2332</td>
</tr>
<tr>
<td>Mean aortic blood pressure (mm Hg)</td>
<td>83±7</td>
<td>95±7*</td>
<td>91±7</td>
<td>98±6§</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>87±7</td>
<td>95±9§</td>
<td>92±9</td>
<td>98±9</td>
</tr>
</tbody>
</table>

*P<0.0001, †P<0.001, §P<0.05, ¶P<0.01 vs. <50 years; ¶¶P<0.05 vs. men.
were statistically significant correlations between blood flow and heart rate and systolic and mean blood pressures. After dipyridamole, hyperemic blood flows were no longer correlated with the rate-pressure product (Figure 3), heart rate, or systolic, diastolic, or mean aortic pressures. Hyperemic blood flows were independent of age (Figure 4).

If grouped according to age, blood flow at rest was significantly higher in the older than in the younger volunteers (0.92±0.25 versus 0.76±0.17 mL·g⁻¹·min⁻¹; P<0.05; Table 2). Flow values after dipyridamole tended to be lower in the older than in the younger subjects (3.06±0.76 versus 2.64±0.58 mL·g⁻¹·min⁻¹; P=NS; Table 2).

To separate effects of blood pressure and of heart rate on hyperemic blood flows, mean and diastolic blood pressures in subjects with comparable heart rates (from 90 to 105 beats per minute; n=18) were compared with blood flows, yet no significant correlations were found (r=0.32 and 0.30, respectively). Conversely, to examine possible effects of heart rates, hyperemic flows were plotted against heart rate for subjects with comparable mean aortic (from 90 to 100 mm Hg) or diastolic blood pressures (from 75 to 85 mm Hg). Again, no significant correlations were observed (r=0.02 and 0.04, respectively). To further relate hemodynamic to flow data, coronary resistance was calculated by dividing mean aortic blood pressure by myocardial blood flow. At rest, coronary resistance was similar for both age groups (109±33 versus 115±29 mm Hg·mL⁻¹·g⁻¹·min⁻¹).

**Myocardial Flow Reserve**

The higher resting blood flows and a tendency toward lower hyperemic blood flows in the older volunteers resulted in a markedly lower myocardial flow reserve; it averaged only 3.01±0.73 compared with 4.08±0.90 in the younger volunteers (P<0.0001; Table 2). Overall,

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**TABLE 2. Myocardial Blood Flow and Flow Reserve**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;50</th>
<th>&gt;50</th>
<th>Men (n=11)</th>
<th>Women (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest blood flow (mL·g⁻¹·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>0.75±0.18</td>
<td>0.90±0.26*</td>
<td>0.91±0.27</td>
<td>0.89±0.28</td>
</tr>
<tr>
<td>LCX</td>
<td>0.77±0.18</td>
<td>0.94±0.28*</td>
<td>0.98±0.30</td>
<td>0.92±0.23</td>
</tr>
<tr>
<td>RCA</td>
<td>0.75±0.20</td>
<td>0.91±0.23*</td>
<td>0.91±0.24</td>
<td>0.90±0.22</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.76±0.17</td>
<td>0.92±0.25*</td>
<td>0.94±0.25</td>
<td>0.91±0.25</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>12±6</td>
<td>11±5</td>
<td>11±5</td>
<td>10±6</td>
</tr>
<tr>
<td>Dipyridamole blood flow (mL·g⁻¹·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>2.90±0.74</td>
<td>2.61±0.52</td>
<td>2.51±0.50</td>
<td>2.64±0.60</td>
</tr>
<tr>
<td>LCX</td>
<td>3.03±0.81</td>
<td>2.76±0.72</td>
<td>2.67±0.60</td>
<td>2.76±0.85</td>
</tr>
<tr>
<td>RCA</td>
<td>3.05±0.85</td>
<td>2.65±0.63</td>
<td>2.64±0.80</td>
<td>2.60±0.52</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3.0±0.76</td>
<td>2.66±0.58</td>
<td>2.61±0.54</td>
<td>2.73±0.63</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>9±6</td>
<td>9±6</td>
<td>9±7</td>
<td>8±6</td>
</tr>
<tr>
<td>Mean myocardial flow reserve</td>
<td>4.08±0.9</td>
<td>3.01±0.73†</td>
<td>2.95±0.77</td>
<td>3.07±0.72</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SD, standard deviation.

*P<0.05, †P<0.001 vs. <50 years.
the myocardial flow reserve declined as a function of age (Figure 5). The strongest correlation was found between resting rate-pressure products and flow reserve \( y = -0.0004x + 6.6; r = 0.74; P < 0.0001 \) followed by resting blood flows and flow reserve \( y = -2.73x + 5.83; r = 0.65; P < 0.0001 \), age and flow reserve (Figure 5), and that between hyperemic blood flows and the flow reserve \( y = 0.62x + 1.74; r = 0.45; P < 0.01 \). After dipyridamole, coronary resistance fell yet was higher in the older than in the younger subjects \( 38.10 \) versus \( 31.8 \) mm Hg \( \cdot \) mL \(^{-1} \) \( \cdot \) g \(^{-1} \) \( \cdot \) min \(^{-1} \); \( P < 0.05 \).

Influence of Sex on Hemodynamics and Blood Flow

Because of radiation safety concerns, only normal, postmenopausal women \( n = 11 \) were included in the study. Hemodynamic parameters, blood flow, and flow reserve were similar for men \( n = 11 \) and women \( n = 11 \) in the older age group. Sex-related differences existed only for mean aortic blood pressure (Tables 1 and 2).

Discussion

In the present study, cardiac work and myocardial blood flow at rest in normal subjects increased with age.

In contrast, dipyridamole-induced hyperemic flows were unrelated to age, suggesting that a normal hyperemic response to dipyridamole is maintained in the older population. The sex-independent increase of resting flows together with a tendency to lower hyperemic flows resulted in a significant reduction in myocardial flow reserve in the older subjects. Because resting flows correlated better than hyperemic flows with the observed flow reserve, the attenuated flow reserve in older volunteers resulted primarily from higher blood flows at rest, most likely as a function of the higher cardiac work at rest.

Study Limitations

Several limitations might have influenced the results of this study. Foremost are the possibility that coronary artery disease or left ventricular hypertrophy was present and that there were age-related changes in left ventricular wall thickness.

Presence of cardiovascular disease. Despite careful screening of all subjects, only coronary angiography would have ruled out definitively significant coronary artery disease. Its use was deemed unjustified in these entirely asymptomatic and apparently healthy volunteers without coronary risk factors. On the other hand, rest-stress myocardial blood flow imaging with PET accurately identifies coronary artery disease. The fact that myocardial uptake of \(^{13}\)N-ammonia was homogeneous at rest and after dipyridamole administration combined with the absence of chest pain and ECG changes provides additional evidence that the subjects were free of significant coronary artery disease.

Age-related changes in wall thickness. To correct for the partial volume-related underestimation of true myocardial \(^{13}\)N-ammonia activity concentrations, the left ventricular wall thickness was assumed to be uniform and 1 cm in all subjects. The validity of this assumption is supported in part by autopsy findings in 765 subjects without cardiac disease. Wall thickness was found to be constant from the third to the eighth decade of life (1.26 versus 1.14 cm) with a modest although statistically significant decrease to about 1 cm in the ninth decade. Only the dimension of the interventricular septum increased with age. Accordingly, flow estimates from the interventricular septum were excluded from this study (Figure 1). The autopsy data are in agreement with echocardiographic findings. The left ventricular mass was independent of age in normotensive subjects with normal hemodynamic responses to exercise. The Framingham Study also suggests that aging in a healthy population is not necessarily associated with an increase in left ventricular mass. Other echocardiographic data suggest, however, some increase in wall thickness with age that affects both the septum and the free wall and amounts to about 1 mm from the fourth to the seventh decade of life.

Because wall thickness was not measured in the present study, age-dependent changes cannot be ruled out entirely. Nevertheless, most of the evidence available in the literature together with the absence of clinical evidence of hypertension or left ventricular hypertrophy argues against such an increase in wall thickness. Even if wall thickness would have been increased by about 1 mm in the oldest subjects, flow would have been overestimated by about only 6%. This
error would have neither affected the finding of a reduced flow reserve in the older population because rest and hyperemic blood flows would have been affected equally by this adjustment nor significantly altered the age dependency of rest blood flow or the maintenance of the hyperemic response.

**Determinants of Resting Myocardial Blood Flow**

Myocardial blood flow at rest depends on oxygen demand, which in turn is related to cardiac work. Flow measurements with coronary sinus catheters or Doppler velocity probes have confirmed the relation between cardiac work and rest blood flow in normal subjects and in normal myocardium of patients with coronary artery disease. Systolic blood pressure as a determinant of cardiac work increases with age. It possibly results from intimal thickening of the large arteries with an associated decline in the compliance of the vascular system. Increases in resting heart rates further result in higher cardiac work and, consequently, coronary blood flow, which in turn reduces the observed myocardial blood flow reserve. A trend toward higher heart rates together with significant increases in systolic blood pressures with age caused a net increase in rate-pressure products and, thus, cardiac work at rest. Accordingly, resting blood flows were higher in the older population. Quantitative measurements of myocardial blood flow at rest should therefore be related to indexes of cardiac work to be interpreted appropriately.

**Systemic Effects of Dipyridamole**

There is little information on whether aging modulates the pharmacological effects of dipyridamole. A recent study reported both significantly larger increases and higher maximal heart rates in younger than in older volunteers. Consistent with these observations, heart rates and rate-pressure products increased more in the younger than in the older volunteers. Nevertheless, maximal achieved heart rates and rate-pressure products were similar for both groups and were comparable to those reported previously. Given the differences between dipyridamole-induced changes but comparable maximal achieved hemodynamic parameters, it remains unclear whether there was an age-related difference in the pharmacological effect on the systemic circulation.

**Determinants of Hyperemic Blood Flows**

Dipyridamole increases plasma adenosine levels and causes direct coronary vasodilation. The agent therefore uncouples blood flow from oxygen demand and, consequently, from cardiac work. Accordingly, hyperemic blood flows were found to be unrelated to the rate-pressure product. The magnitude of dipyridamole-induced hyperemia depends on the coronary driving pressure, changes in heart rates with a shortening of diastolic flow, and antagonistic effects of, for example, theophylline and its derivatives, but it might also be dose dependent. As a possible additional factor, the vasodilator capacity of the coronary circulation may be changed as a function of age.

Increases in the heart rate from 100 to about 250 beats per minute significantly shortened the diastole and thus reduced hyperemic blood flows in experimental animals. However, intracoronary Doppler flow-velocity probes failed to demonstrate a significant effect of pacing-induced increases of heart rates from 76 to 120 beats per minute on the magnitude of hyperemic coronary blood flows in humans. Because heart rate changes in the present study were similarly small, they are unlikely to account for interindividual differences in hyperemic flows.

There is disagreement as to whether the mean or the diastolic blood pressure reflects more accurately the coronary driving pressure. Direct comparisons of either value with hyperemic blood flows failed to reveal significant correlation. As another means of relating hemodynamic parameters to blood flow, coronary resistances were calculated. Although similar for both age groups at rest, coronary resistances during hyperemia were significantly higher in the older than in the younger subjects.

Coronary resistance was estimated from the ratio of mean aortic blood pressure to myocardial blood flow (mm Hg · mL⁻¹ · g⁻¹ · min⁻¹). The estimates do not account for extravascular compressive forces, diastolic ventricular pressures, or critical closing pressures that might modulate coronary vascular resistance. Moreover, they are based in this study on myocardial rather than coronary blood flow. Nevertheless, the 22.6% difference in minimal coronary resistances between the age groups is considered significant. The higher “minimal” coronary resistance in the older population might argue for an age-related attenuation of coronary vasodilator capacity in the older population, which appears to be consistent with previously published data. Alternatively, lower compliance of the left ventricle with age might lead to increased end-diastolic pressures, which would increase coronary resistance by increasing the critical closing pressure or increasing extravascular compressive forces.

Hyperemic flows varied considerably among subjects and ranged from 1.8 to 4.4 mL · g⁻¹ · min⁻¹. This relatively wide range is similar to that observed previously and might be attributable to differences in the dietary state or to a variable pharmacological effect of dipyridamole. For example, the standard dose of dipyridamole (0.56 mg/kg) does not produce consistently maximal vasodilation in all individuals.

A previous study in healthy volunteers also failed to demonstrate a significant correlation between hyperemic flow and age. Only after hyperemic flows were grouped according to age was there a significance difference between subjects less than and those more than 50 years old. In the present study, hyperemic blood flows were unrelated to age, although they tended to be lower in subjects less than 50 years old. The reason for this discrepancy is uncertain. One possibility is that there are differences in the dietary state such as, for example, intake of coffee within 12 hours of the dipyridamole infusion. Another possibility is that mean and diastolic blood pressures during the dipyridamole-induced hyperemia were higher in the older than in the younger normal volunteers in the present but not in the previous study. It therefore might be argued that a potentially lower hyperemic response in the older normal subjects might have been offset by a higher coronary driving pressure as evidenced by the significantly lower ratios of hyperemic flows to diastolic or mean blood pressure in the older volunteers.
Myocardial Perfusion Reserve

Similar to the current findings, invasive or noninvasive measurements with intracoronary Doppler\textsuperscript{36,37} or with PET\textsuperscript{35} have reported twofold to fivefold flow increases after pharmacological vasodilation in normal volunteers or in normal myocardium of patients with coronary artery disease. In agreement with these previous observations,\textsuperscript{9} the myocardial flow reserve was significantly higher in younger than in older volunteers. In the present study, it declined gradually with age. However, correlations closer than those between age and flow reserve ($F=15.5$) were noted between resting rate-pressure product or resting blood flow and flow reserve ($F=47.2$ and 28.8, respectively). Although, by definition, hyperemic flows also determine the myocardial flow reserve, their relation was relatively poor ($F=8.8$). In choosing single predictors for the myocardial flow reserve, it might be useful to discriminate between significant and useful correlations.\textsuperscript{38} Not only is a useful correlation significant, but the $F$ value has to be four times higher than the selected point of the $F$ distribution ($4.1=F[1%, 38%, 5%]$). According to this analysis, only the correlations between resting rate-pressure product or resting blood flow and the flow reserve were useful. Thus, resting blood flow or rate-pressure products are stronger determinants of the flow reserve than are hyperemic blood flows or age.

Study Implications

The findings of the present study have several implications. First, quantitative estimates of myocardial blood flow now readily available through noninvasive means vary considerably among individuals. Although some of this variability might be method related, it also is related to cardiac work and, in turn, to oxygen demand. Thus, measurements of rest blood flow must be related to indexes of cardiac work, as, for example, the rate-pressure product, to distinguish normal from abnormal values. Second, the dilator capacity of the coronary circulation is relatively well maintained over a wide range of ages, although the observed higher coronary resistance values in the older subjects suggest that some impairment of vasodilation may also have contributed to the impaired vasodilator reserve. However, because of an age-related increase in cardiac work and, consequently, myocardial blood flow at rest, the myocardial blood flow reserve declines with age. Therefore, quantitative estimates of the myocardial blood flow reserve must be related to blood flow at rest or to age to be interpreted adequately. The importance of such adjustments to age or the rate-pressure product at rest is underscored by recent observations in patients with coronary artery disease.\textsuperscript{39} The flow reserve in myocardium supplied by normal vessels in these patients was only 2.9. Compared with young normal volunteers, this value is abnormally low. However, it might have been considered normal had it been compared with myocardial blood flow reserves in an age-matched group of normal subjects.

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