Flow-Dependent Coronary Artery Dilatation in Humans

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To determine the role of endothelium-mediated flow-dependent coronary dilatation in humans, we studied the coronary dilatation exerted by maximal pharmacologic increase of coronary flow in 14 patients with normal coronary arteries. Biplane views of the circumflex (Cx) and left anterior descending (LAD) coronary arteries were obtained before and 80 seconds after inducing a maximal increase in flow selectively in the Cx by injecting 7 mg papaverine through a 2F infusion catheter in the midportion of the Cx (n=10). The diameter of the proximal Cx segment (exposed to increased flow but not to papaverine directly) increased with papaverine by 11.1±4% (range, 5.2–16.4%, p < 0.001 vs. control), whereas the LAD diameter did not change. LAD and Cx diameters increased by 18.3% and 21.2% after nitroglycerin given into the left main artery, which showed the preserved capability of the LAD to dilate. In four patients with normal coronary arteries and six patients with coronary artery disease (CAD, non-flow-limiting stenosis), a similar protocol was applied with the LAD for the assessment of flow-dependent dilatation. Simultaneously, intracoronary blood flow velocity was measured by an intracoronary Doppler catheter. Papaverine-induced coronary flow reserve (peak/resting velocity ratio) in the LAD was 4±0.7 (range, 3.5–5) in normal arteries and was 3.5±0.6 (range, 2.7–4.4) in CAD. The diameter of the proximal LAD segment (exposed to increased flow, but not to papaverine directly) was increased by 6.5±0.5% (range, 6.1–7.2%) in normal arteries and by 4.6±4% (range, 0–8.6%) in CAD, whereas Cx diameters did not change in normal arteries or in CAD. These results show substantial flow-dependent coronary dilatation in humans, which indicate that vascular tone of intact coronary arteries is markedly modulated by changes in flow. However, flow-dependent coronary dilatation may be limited in atherosclerotic coronary arteries and impaired endothelial function that in turn would increase coronary vasomotor tone in these patients. (Circulation 1989;80:466–474)

Control of vascular diameter by changes in flow was first reported by Schretzenmayr,1 who observed dilatation of the in situ canine femoral artery in response to increments in femoral artery blood flow. Recent experimental studies strongly suggest that this vasodilatation in response to increased flow is mediated by release of endothelium-derived relaxing factor (EDRF), possibly initiated by the signal of shear stress on the endothelium.2–4 Stretch-activated calcium channels in endothelial cells may mediate this release of EDRF under these conditions.5 Flow-dependent, EDRF-mediated control of vasomotor tone would provide a flow-related dilator feedback to oppose the constrictor force of the myogenic response to increased intraluminal pressure, thereby coordinat- ing vasomotor changes in the vascular network.6 Although this fundamental mechanism may have important clinical implications, for example, in coronary artery disease, it has, so far, never been investigated in the coronary circulation in humans. Accordingly, the present study was designed to elucidate the role of flow-dependent dilatation of epicardial coronary arteries in humans. To show changes in coronary diameter by increments in flow, we injected papaverine subselectively into the midportion of the circumflex (Cx) or the left anterior descending (LAD) coronary arteries in patients with normal coronary arteries. We hypothesized that the transient maximal coronary flow elicited by papaverine7 would cause flow-dependent dilatation of the proximal segment of the coronary artery exposed to increased flow but not to papaverine.

Methods

Patients

Fourteen patients (nine men and five women; aged 54±7 years; range, 34–64 years) with angio-
graphically normal coronary arteries undergoing coronary angiography for the diagnosis of chest pain syndromes were selected for the study. In addition, a left dominant circulation including a large diameter of the proximal segment of the Cx and LAD was mandatory for inclusion. Patients with left ventricular hypertrophy, diabetes mellitus, and manifest hypertension were excluded except for one patient with a history of hypertension but without left ventricular hypertrophy and normal coronary reserve. Left ventricular ejection fraction was greater than 65% in all patients, and left ventricular ventriculography revealed no abnormalities of regional wall motion. In addition, six patients with coronary artery disease were studied. These patients had luminal irregularities of the LAD but no flow-limiting stenosis (stenosis <30%) was present in the left coronary system. Informed consent for the investigational protocol was obtained from each patient. The study protocol was approved by the Ethical Committee of the University of Freiburg.

Protocol 1

Patients were studied in the fasting state. Vasodilators and premedication were withheld for at least 12 hours. No patient was receiving β-blocker therapy before and during the study. After diagnostic angiography with documentation of normal coronary arteries, an 8F Judkins-type guiding catheter was introduced into the left main coronary artery, and optimal views of the Cx and the proximal segment of the LAD were chosen to exclude overlapping of the Cx and LAD by their branches. Additional 5,000 IU heparin was given, and a 5F pacing catheter was positioned in the apex of the right ventricle. For preparing the setup as described, a time period of at least 20 minutes elapsed between the diagnostic angiography and the experimental protocol. Five to seven milliliters of nonionic contrast medium (iopromide, Schering, Berlin, FRG) was injected at intervals of at least five minutes to exclude dye-induced coronary vasodilation. Recent studies showed that injection of contrast medium is associated with transient vasodilation. However, this response completely dissipated after 1 minute.8 The electrocardiogram leads I and aVF and arterial pressure (through the guiding catheter) were monitored continuously during the study.

A 0.012-in. guidewire was positioned in the distal Cx (patients, 1–10), and a 2F soft-tipped infusion catheter (Monorail Bonzel, Schneider, Zurich, Switzerland) was advanced through the guidewire into the midportion of the Cx. The guidewire was then withdrawn. Biplane views of the Cx and proximal LAD were obtained by injection of contrast medium after 1 ml 0.9% saline through the infusion catheter into the midportion of the Cx. Five minutes after this control angiogram, 7 mg papaverine was injected through the infusion catheter into the midportion of the Cx. Coronary angiograms were repeated 80 seconds after inducing a maximal flow increase by the injection of papaverine (dissolved in 1 ml 0.9% saline). Proper position of the infusion catheter was verified by injection of contrast medium through the infusion catheter into the midportion of the Cx (patients, 1–10) or LAD (patients, 11–14). Special attention was given to any angiographic evidence for potential contrast reflux into the proximal portion of the vessel to definitively exclude any unintentional injection of papaverine into the proximal portion of the vessel (see Figure 1). Therefore, power injection of 3 ml contrast medium through the infusion catheter was performed without visualizing reflux of dye into the proximal part of the Cx (resp LAD). In contrast, 1 ml papaverine was infused during 15 seconds, which corresponded to 4 ml/min. Given an antegrade flow of 30–40 ml in the Cx, retrograde flow of papaverine within the Cx (resp LAD) can be excluded. The dose of papaverine was selected on the basis of previous observations that maximal coronary flow is achieved by 12 mg papaverine given in the left main artery.7 Thus, 7 mg papaverine, given in the midportion of the Cx, should elicit maximal coronary vasodilator response. The time lag of 80 seconds between injection of papaverine and coronary angiography was selected on the basis of the time course of maximal vasodilatory effect of papaverine (approximately 25–30 seconds)7 and the time course of maximal flow-dependent dilatation observed in conscious dogs (50–60 seconds).2,9

Coronary angiography was repeated after 0.3 mg nitroglycerin administered through the guiding catheter into the left main artery, with left anterior and right anterior oblique views and patient positions identical to those during control and papaverine injections.

Protocol 2

In a second protocol, coronary diameters and intracoronary blood flow velocity was assessed simultaneously in four patients with normal coronary arteries (patients, 11–14) and in six patients with coronary artery disease. Only those patients were studied in whom a stable position of the Doppler catheter could be maintained throughout the study that yielded a reliable Doppler signal recording. A 3F 20-MHz coronary Doppler catheter (Monorail Bonzel, Schneider) was advanced into the LAD (this vessel proved to be superior for intracoronary Doppler blood flow velocity studies). Flow-dependent coronary dilatation was assessed by injecting 7 mg papaverine into the midportion of the LAD and measuring the diameter of proximal LAD segment, whereas the proximal Cx segment served as control vessel in these patients. Coronary blood flow velocity was continuously recorded before and after injection of papaverine through the Doppler catheter. Coronary reserve was calculated as the ratio of peak mean coronary blood flow
velocity after papaverine to resting coronary blood flow velocity. Repeated measurements of papaverine-induced coronary blood flow reserve in five patients yielded an excellent reproducibility (first/second measurement: $3.3 \pm 0.59/3.22 \pm 0.52$, $r=0.91$, $p=0.033$). Papaverine was used because this vasodilator induces a maximal fall in coronary vascular resistance, has few side effects, and has the advantage of a short duration of action (less than 2 minutes). In contrast, dipyridamole exerts an undesirable long-lasting systemic effect, and adenosine has been shown to exert direct myocardial effects, which increases arterial pressure possibly by a reflex mechanism.

Quantitative Coronary Arteriography
Coronary angiography was performed with a simultaneous biplane multidirectional isocentric radiographic system (Siemens Bicor, Erlangen, FRG). The coronary arteries under study were positioned in the isocenter, and special care was taken to avoid overlapping of coronary segments. Biplane cineangiograms were recorded at a frame rate of 25 frames/sec. End-diastolic cineframes were

Figure 1. Representative left coronary angiogram depicting the proximal segments of the circumflex and left anterior descending coronary artery (right oblique view) during control (Panel A), after papaverine (Panel B), after contrast injection through the intracoronary infusion catheter (Panel C), and after nitroglycerin administered into the left main (Panel D). Note that the contrast medium injected into the infusion catheter flows distally from the tip (arrow) of the infusion catheter. After the injection of papaverine into the distal circumflex (through the infusion catheter, see arrow), substantial dilatation of the proximal circumflex segment occurred (two arrows).
the vessel segment, in seconds.14 In brief, after interactive delineation of a centerline within the vessel segment to be measured, the computer automatically generates a number of scanlines perpendicular to the centerline. The first and second derivative function of the densograms along each scanline are then computed, and the contour point is defined as 60% of the distance between the extrema of the first and second derivative. With use of the detected contour points, the computer then automatically generates a refined centerline of the vessel segment, and the edge detection algorithm is repeated. Each individual scanline is smoothed by a second-order polynomial fit, and smoothing of the contour is obtained by averaging eight neighboring scanlines. Calculation of the exact radiologic magnification factor of the measured segment is used to scale the data from pixels to millimeters as previously described.14 In brief, by knowing the geometric properties of the biplane isocentric radiographic system, the spatial coordinates of every point of interest, whose corresponding projections are well defined within the fields of view of the two image intensifier entrance fields, can be calculated in a three-dimensional coordinate system around the isocenter of the radiographic system.15 The position of the x-ray foci and of the centers of the image intensifier entrance fields can be computed from the rotational parameters of the system stands. The exact radiologic magnification factor is defined as the quotient of focus–projection of–point of interest–distance/focus–point of interest–distance for both of the portraying radiographic systems. Small lead markers on the surface of the image intensifier input phosphors serve as the local two dimensional coordinate systems and provide for conversion of pixels in absolute dimensions. Thereby, inaccuracies introduced by the catheter as a scaling device are avoided.16

This technique was previously validated in phantom studies. The accuracy and precision of quantitative angiographic measurements were determined from the analysis of cinefilms of a Plexiglas block with precision-drilled models of coronary arteries with diameters of 2, 3, and 3.5 mm (corresponding to the vessel diameters expected in this study) filled with contrast medium and filmed under 10 cm of water. The accuracy of the contour detection technique was defined by the average difference of the computed results with the true values, and the precision was defined by the pooled standard deviations of the differences. These phantom measurements revealed an accuracy of 2.63±0.2% (mean±SD) and a precision of 1.9±0.5%. The reproducibility of the measurements (repeated analysis of the cineangiograms by one analyst) revealed a coefficient of variation of 1.06%. The interobserver variability associated with the calculation of the radiologic magnification factor was 1.74% (coefficient of variation).

Six- to eight-millimeter segments from angiographically normal vessels and vessels with luminal irregularities were measured. A series of diameter measurements were obtained for each scanline for the length of the arterial segment, displayed in graph form, showing diameter versus segment length, and the mean diameter value was calculated. Whenever possible, measurements were performed in both views of the biplane images, and the diameter values of both views were averaged. Only single-plane analysis was performed for those coronary segments showing overlapping with other parts of the coronary tree in one view. Anatomic landmarks were used to reproduce these regions of interest spatially in repeated measurements to assess serial changes.

Statistical Analysis

All data are expressed as mean±SD. Statistical comparisons of vessel diameter during control after papaverine and nitroglycerin were made by analysis of variance for repeated measures followed by the Student-Newman-Keuls test.17 The statistical significance of differences between groups was determined with Student’s t test. The hemodynamic data (papaverine vs. control) were analyzed by the paired t test. A p value less than 0.05 was considered to indicate statistical significance.

Results

The diameters of the proximal Cx during control, papaverine, and nitroglycerin are depicted in Table 1. The diameter of the proximal Cx, which was not exposed to papaverine but to augmented flow, increased in all patients studied, indicating flow-dependent dilatation of the proximal Cx segment. This increase in diameter averaged 11.1±4.1% (p<0.001 papaverine vs. control) after subselective injection of papaverine into the midportion of the Cx (Table 1). Nitroglycerin (given into the left main artery) increased identical proximal Cx segments by 21.2 (p<0.001 vs. control and vs. papaverine). A critical assumption of our protocol implied that no or only negligible recirculation of papaverine would occur that might directly affect coronary dilatation of the proximal Cx segment. Therefore, we determined the diameters of both proximal LAD and Cx segments in all patients. Recirculation of papaverine injected into the midportion of the Cx should cause increased diameter of the Cx and the LAD. However, the diameter of the proximal LAD slightly decreased after papaverine injection into the Cx (control, 2.93±0.62 mm; papaverine, 2.87±0.56 mm; −2.1%, NS). Similarly, unchanged diameter of the control vessel precludes that the contrast medium
itself or hemodynamic effects of papaverine were contributing factors to the selective proximal dilatation. After nitroglycerin injection into the left main, LAD diameters increased by 18.3 (3.47±0.77 mm, \( p < 0.001 \) vs. control), indicating the preserved vasodilatory capability of the LAD. Figure 1 depicts the coronary angiogram of one patient during control after papaverine and nitroglycerin.

Coronary blood flow velocity, measured in four patients, increased to 4.0±0.7 times resting velocity (range, 3.5–5.0) after injection of papaverine in the midportion of the LAD, indicating normal coronary reserve in these patients (see Figure 2). After papaverine-induced augmentation in coronary flow, the diameter of the proximal LAD increased by 6.5% compared with control; nitroglycerin increased

**Table 1.** Diameters of the Proximal Circumflex Segment or Left Anterior Descending Coronary Artery Segment During Control, After Intracoronary Papaverine, and After Nitroglycerin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control (mm)</th>
<th>Papaverine (mm)</th>
<th>% change vs. control</th>
<th>Nitroglycerine (mm)</th>
<th>% change vs. control</th>
<th>Δ MAP (mm Hg)</th>
<th>Δ HR (beats/min)</th>
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<tr>
<td>1</td>
<td>3.35</td>
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<td>Mean</td>
<td>3.09</td>
<td>3.38€</td>
<td>9.79*</td>
<td>3.67\‡</td>
<td>19.18</td>
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<td>0.42</td>
<td>9.0</td>
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</table>

*Note, that the percent change of dilatation averaged 11.1% for patients 1–10 (proximal circumflex segment); in patients 11–14, flow-dependent dilatation in the proximal left anterior descending coronary artery averaged 6.5%; the mean of 9.79 represents the average values for all 14 patients.

\( \text{Δ MAP} \), change in mean arterial pressure after papaverine compared with control; \( \text{Δ HR} \), change in heart rate after papaverine compared with control.

**Figure 2.** Example of hyperemia pharmacologically induced with intracoronary papaverine into the midportion of the left anterior descending coronary artery through the 3F Monorail Doppler catheter. From top to bottom, electrocardiogram (ECG), arterial pressure (AoP), and phasic and mean Doppler signal. The calibration scale refers to the mean coronary blood flow velocity (CBFV).
identical LAD diameters by 14%. Thus, the magnitude of flow-dependent dilatation of the proximal LAD (exposed to increased flow but not to papaverine directly) in these patients was even less compared with those patients in which coronary flow was not determined (Table 1). Of note, substantial increases in flow were observed in all patients as judged from the fast washout of contrast medium after injection of papaverine.

In six patients with coronary artery disease, the proximal LAD diameter increased by 4.6±4% (range, 0–8%) after injection of papaverine into the midportion of this vessel (see Table 2). The response to papaverine varied widely in patients with coronary artery disease, and in fact, in two patients with atherosclerotic coronary arteries (including the proximal LAD segment), no flow-dependent coronary dilatation was observed. When compared with the group with angiographically normal coronary arteries, the magnitude of flow-dependent dilatation was significantly reduced in patients with coronary artery disease (p<0.02). The change in increase in diameter of the proximal LAD averaged 0.22±0.05 mm in the four patients with normal coronary arteries and was 0.12±0.1 mm in the six patients with coronary artery disease; this difference was not quite significant (p=0.059) because of the wide variation of flow-dependent dilatation in patients with atherosclerotic arteries (range, 0–0.22 mm).

The diameter of the proximal Cx did not change in these six patients with coronary artery disease. In contrast, nitroglycerin dilated the proximal segment of the LAD and the Cx by 8.7±3.8%, resp 17±6%. The vasodilatory effect of nitroglycerin on LAD diameters was significantly impaired compared with the nitroglycerin-induced increase in LAD diameters (14.3±4.1) of the patients with normal coronary arteries (p<0.05). The coronary flow reserve of the six patients with coronary artery disease averaged 3.5±0.6 (range, 2.7–4.4), which was not significant compared with the coronary flow reserve of patients with normal coronary arteries.

Only minor changes in heart rate and mean arterial pressure were observed with the injection of papaverine. Individual changes (control vs. after intracoronary papaverine) are depicted in Tables 1 and 2. Nitroglycerin increased heart rate by 9±3 beats/min and reduced mean arterial pressure by 12±5 mm Hg (p<0.01).

Transient electrocardiographic changes (T wave inversion or QT prolongation) occurred after papaverine in 15 of the 21 patients in those leads represented by the injected coronary artery. Similar observations were reported by Wilson and White. The cause of these electrocardiographic changes are unclear; however, the extent of QT prolongation and the potential for ventricular arrhythmias appear to be dose dependent. Ventricular premature beats were seen frequently, but in only one patient, self-terminating ventricular tachycardia was encountered. Two patients in whom the protocol was attempted experienced coronary spasm after the intracoronary guidewire was inserted; however, this spasm was promptly relieved by intracoronary nitroglycerin, and the investigational protocol was stopped.

**Discussion**

The major finding of this investigation is the demonstration of flow-dependent dilatation of epicardial coronary arteries in humans. This conclusion is based on our analysis of the LAD and the Cx diameters. The subselective injection of papaverine into the Cx (resp LAD) allowed us 1) to use the other major vessel as control and 2) to administer a relatively low dose of papaverine. Proximal coronary dilatation occurred exclusively in that vessel, which was exposed to increased flow, whereas the diameter of the control vessel remained unchanged. Thus, the mechanism of proximal coronary vasodilatation cannot be attributed to hemodynamic factors, contrast medium, or recirculation of papaverine (in sufficient doses to exert coronary vasodilation). Moreover, coronary vasodilatation mediated by dye was recently shown to be transient
and dissipates within 1 minute. However, dye was injected at intervals of at least 5 minutes. In addition and of note, only minor, insignificant changes in arterial pressure and heart rate were observed after papaverine. Finally, the papaverine injection in the midportion of the vessel may have resulted in retrograde flow, thereby causing vasodilatation of the proximal segment directly. Power injection of 3 ml contrast through the infusion catheter did not reveal reflux of dye to the proximal segment. In contrast, papaverine was injected at a flow rate of 4 ml/min. Given an antegrade blood flow of 30–40 ml/min in the proximal Cx, reflux of papaverine is highly improbable. Moreover, a recent study indicates that papaverine elicits only moderate dilatation (+3% in diameter) of epicardial coronary arteries (in patients without premedication) when injected into the left main.18 Because coronary angiography in that study was performed 30 seconds after injection of papaverine, this approach exclusively tested the vasodilatory effect of papaverine on epicardial coronary arteries. In contrast, flow-dependent dilatation is likely to emerge 60 seconds after changes in flow.2

The increase in coronary diameter of angiographically normal coronary arteries, which was elicited by maximal pharmacologic increases in flow, proved to be quite substantial (+10%), indicating that flow-dependent dilatation should be considered an important regulatory mechanism in the coronary circulation in humans. Thus, vascular tone of intact coronary arteries in humans appears to be markedly modulated by changes in flow.

In animal studies, flow-dependent dilatation of coronary vessels has been shown by several investigators, but the percent increase in diameter in these instrumented animals did not exceed 5–6%,2,9 The maximal vasodilator response to nitroglycerin in these chronically instrumented dogs averaged 7–8% (Holtz, personal communication). However, instrumentation with ultrasonic crystals does restrict dilatation of vessels due to fibrotic tissue as pointed out by Holtz et al.2 This fibrotic restriction may explain our finding that both the flow-dependent and nitroglycerin-induced vasodilatation was more pronounced in humans. Moreover, the magnitude of coronary dilation induced by nitroglycerin (+18% in the LAD) compares favorably with recent studies.19

The present study did not address the mechanism of this flow-dependent dilatation, but recent experimental studies strongly suggest that this vasodilatation is endothelium dependent2 and mediated by the release of EDRF,3,4 which is believed to be nitric oxide.20 Interestingly, recent experimental studies indicate that this regulatory mechanism operates in resistance vessels as well.21,22 EDRF may regulate vessel diameters in a flow-dependent manner. In fact, EDRF may coordinate the behavior of vascular resistance vessels.21 There is evidence that nitric oxide acts as active metabolite through which nitroglycerin stimulates soluble guanylate cyclase.23 Thus, EDRF (nitric oxide) and nitroglycerin appear to exert their relaxant effects through a common cellular pathway, involving activation of soluble guanylate cyclase.24 However, the dilatory effect of high-dose exogenous nitroglycerin was significantly stronger than flow-mediated increases in coronary diameter of angiographically normal coronary arteries. As estimated from the present data, maximal pharmacologically mediated increases in flow exert approximately 50% of the maximal dilatation induced by high-dose intracoronary nitroglycerin.

If vascular tone of intact arteries is modulated by changes in flow, then dysfunction of endothelium (that is, in arteriosclerotic arteries) would cause increased coronary vasomotor tone because an important dilatory mechanism is not operating (or substantially diminished). Indeed, endothelial dysfunction has been shown to occur in patients with arteriosclerotic coronary arteries.25,26 The results of the present study may indicate that flow-dependent coronary dilatation is attenuated in patients with coronary artery disease, which is in keeping with recent experimental data. This conclusion is supported by a preliminary report of Nabel et al.,27 suggesting impaired flow-mediated dilatation in arteriosclerotic human coronary arteries. Although it is tempting to speculate that the diminished flow-dependent coronary vasodilatation is secondary to endothelial dysfunction, for example, due to reduced release of EDRF, an alternative explanation should be considered. The vasodilatory effect of nitroglycerin on LAD diameters was significantly reduced as well. This suggests that the capability of the LAD to dilate was limited in these patients with arteriosclerotic coronary arteries. To further elucidate the mechanisms involved in the impaired coronary vasodilatation, functional studies using endothelium-dependent vasodilatating agents (such as acetylcholine) seem to be warranted, for example, in combination with the evaluation of the vascular wall by intravascular ultrasound imaging techniques.28 Indeed, preliminary data from our laboratory suggest that flow-dependent coronary vasodilatation is preserved despite acetylcholine coronary vasoconstriction.29

The present finding of substantial flow-dependent coronary dilatation in humans may have important clinical implications. Diminished coronary flow due to severe stenosis may limit flow-dependent coronary dilatation downstream (distal to the stenosis). Sustained dilatation of epicardial coronary arteries after transient increases in flow suggests that changes in shear stress are not necessarily maintained during the period of vascular dilatation.30 In the canine carotid artery, long-term adaptive changes in vessel diameter in response to long-term changes in flow were observed and correlated with the rate of protein turnover.31 This would indicate long-term structural adaptations of the vessel secondary to altered flow rate. In addition, recent studies with
endothelin, a potent endothelial vasoconstrictor peptide, indicate that flow-dependent inhibition of endothelin production may contribute to the long-term endothelium-mediated flow-induced vasodilatory responses. Recently, it was reported that coronary reserve after coronary angioplasty of critical stenosis (restricting coronary flow chronically) was not normalized immediately after successful angioplasty. However, coronary reserve eventually improved several weeks after angioplasty. Thus, improved coronary flow may have caused vascular adaptation leading to improved flow-dependent coronary vasodilatation over time. Moreover, there is evidence from experimental studies that long-term increases in flow cause an enhanced dilatatory capacity of the vessel, possibly due to increased release of EDRF.

In summary, the results of the present study show substantial flow-dependent coronary dilatation in humans, which indicates that vascular tone of intact coronary arteries in humans is markedly modulated by changes in flow. However, flow-dependent coronary dilatation appears to be limited in patients with coronary artery disease, which in turn may contribute to increased coronary vasomotor tone in these patients.

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References


KEY WORDS • papaverine • endothelium-derived relaxing factor
• endothelium-mediated dilatation • Doppler ultrasound
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