Increased diastolic time fraction as beneficial adjunct of α₁-adrenergic receptor blockade after percutaneous coronary intervention

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Kolyva C, Verhoeff BJ, Spaan JA, Piek JJ, Siebes M. Increased diastolic time fraction as beneficial adjunct of α₁-adrenergic receptor blockade after percutaneous coronary intervention. Am J Physiol Heart Circ Physiol 295: H2054–H2060, 2008. First published September 12, 2008; doi:10.1152/ajpheart.91400.2007.—The effect of α₁-receptor blockade with urapidil on coronary blood flow and left ventricular function has been attributed to relief of diffuse coronary vasoconstriction following percutaneous coronary intervention (PCI). We hypothesized that an increase in diastolic time fraction (DTF) contributes to the beneficial action of urapidil. In eleven patients with a 63% (SD 13) diameter stenosis, ECG, aortic pressure (Pₐ) and distal intracoronary pressure (Pd), and blood flow velocity were recorded at baseline and throughout adenosine-induced hyperemia. Measurements were obtained before and after PCI and after subsequent α₁-receptor blockade with urapidil (10 mg iv). DTF was determined from the ECG and the Pa waveform. Functional parameters such as coronary flow velocity reserve, fractional flow reserve, and an index of hyperemic microvascular resistance (HRM) were assessed. Urapidil administration after PCI induced an upward shift in the DTF-heart rate relationship, resulting in a 3.1% (SD 2.7) increase in hyperemic DTF at a constant heart rate (P < 0.005) due to a shorter duration of systole. Hyperemic Pa and Pd decreased, respectively, by 6.1% (SD 6.6; P < 0.05) and 5.7% (SD 5.8; P < 0.01) after α₁-blockade. Although epicardially measured functional parameters were on average not altered by α₁-blockade due to concurrent changes in pressure and heart rate, HMR declined by urapidil in those patients where coronary pressure remained constant. In conclusion, α₁-receptor blockade after PCI produced a modest but significant prolongation of DTF at a given heart rate, thereby providing an adjunctive beneficial mechanism for improving subendocardial perfusion, which critically depends on DTF.

coronary circulation; angioplasty; microcirculation; diastole; α₁-adrenergic receptors

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POSTISCHEMIC LEFT VENTRICULAR dysfunction and impaired coronary flow reserve after balloon angioplasty have been attributed to the stimulation of α-adrenergic pathways in the vessel wall (9, 11, 12, 16), leading to vasoconstriction not only of the manipulated coronary artery but also of a normal control vessel (9, 20). These adverse effects could be diminished by prior or subsequent α₁-receptor blockade (9, 11, 12, 20, 27).

Coronary flow occurs predominantly during diastole (19, 31) and is therefore critically dependent on diastolic duration. Animal studies have demonstrated that in the maximally dilated coronary bed the duration of diastole is an important factor that limits subendocardial perfusion (1, 8). The relative duration of diastole per heart cycle, diastolic time fraction (DTF), decreases with increasing heart rate both in healthy humans and in patients with coronary artery disease (4). Notably, diastolic perfusion time, expressing the total amount of diastole relative to that of systole per minute, was shown to be closely related to stenosis severity at the onset of stress-induced myocardial ischemia in humans, whereas no such correlation was found with heart rate at the ischemic threshold (7).

It has recently been reported that DTF also depends inversely on coronary pressure (24), which is an important determinant of coronary perfusion since it influences microvascular resistance in the vasodilated coronary bed (14, 35). We hypothesized that the reported improvement in coronary blood flow and cardiac function with α₁-receptor blockade after balloon angioplasty may be in part due to a concomitant increase in the duration of diastole. Accordingly, the major aim of this study was to assess the effect of α₁-adrenergic receptor blockade after percutaneous coronary intervention (PCI) by balloon angioplasty and stent placement on DTF.

METHODS

Study population. Eleven patients [9 males; age 60 years (SD 6)] scheduled for elective coronary angioplasty were enrolled in this study. All patients suffered from stable angina and had a single de novo stenosis in the target vessel. Exclusion criteria were diffuse or triple-vessel disease, left main coronary artery stenosis (>50%) or a subtotal lesion in the vessel targeted for angioplasty, recent myocardial infarction (<6 wk), prior cardiac surgery, serious heart valve abnormalities, hypertrophic cardiomyopathy, or visible collateral vessels. The local Medical Ethics Committee approved the study protocol, and all patients gave written informed consent.

Hemodynamic measurements. All data were acquired during cardiac catheterization using a right femoral artery approach. Aortic pressure (Pₐ) was obtained via a 5F or 6F guiding catheter, which was advanced into the coronary ostium. Distal intracoronary pressure (Pd) and blood flow velocity distal to the target lesion were measured via a novel 0.014-in dual-sensor guide wire (Volcano, Rancho Cordova, CA) equipped with a Doppler sensor at the tip and a pressure sensor 3 cm proximal to the tip. The position of the wire was manipulated until an optimum and stable velocity signal was obtained, and attention was paid to maintain sensor position for measurements taken at different phases of the protocol. All signals were recorded on a personal computer at a sampling rate of 120 Hz after 12-bit analog-to-digital conversion for offline analysis.

Protocol. The patients continued their antianginal and antiplatelet medication as clinically indicated and received 1 mg lorazepam before cardiac catheterization. Heparin was administered at the beginning of the procedure (5,000–7,500 IU, intravenous bolus) followed by 0.1

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mg intracoronary nitroglycerin to minimize vascular tone in the large epicardial vessels. Hemodynamic measurements were obtained at resting conditions and during maximal hyperemia induced by 20–40 μg intracoronary adenosine, first in an angiographically normal reference vessel and then in the target vessel before and 3 min after PCI. The measurements were repeated 10–15 min after stent placement, at a time when maximal α1-adrenergic coronary vasoconstriction has been reported (9, 20). Finally, data were acquired 5–8 min following a 10-mg intracoronary bolus of the selective α1-receptor antagonist urapidil, when urapidil had reached its maximum effect (10, 12).

Data processing. Per-beat data analysis was performed using custom-made programs (Delphi, version 6.0; Borland Software). The duration of each heart cycle was determined from the interval between two consecutive R-peaks on the ECG. Systolic duration was defined as the time interval between the ECG R-peak and closure of the aortic valve as identified by the dicrotic notch in the Pp signal, corresponding to the first local maximum of the first derivative of the Pp signal after the ECG T-wave (Fig. 1). Subtracting the systolic from the RR interval yielded the duration of diastole, and DTF was calculated as diastolic duration divided by the RR interval.

Mid-systolic and end-diastolic hemodynamic values were derived during time intervals corresponding to the highest and lowest 10%, respectively, of the distal pressure signal as illustrated in Fig. 1. Rate pressure product (RPP), calculated as the product of heart rate and systolic Pp, served as an estimate of oxygen consumption. Fractional flow reserve (FFR) was determined as the ratio of Pd/Pp at maximal hyperemia and coronary flow velocity reserve (CFVR) as hyperemic divided by resting flow velocity. An index of average hyperemic microvascular resistance (HMR) was computed as the ratio of distal coronary pressure to flow velocity during maximal vasodilation (30, 35).

Statistical analysis. All variables are expressed as means (SD). Average per-beat data obtained at successive steps of the protocol were compared using ANOVA with repeated measures, followed by contrast analysis. Paired Student’s t-test was used to compare means before and after α-receptor blockade. Linear regressions were obtained for DTF and heart rate data obtained after PCI. The slopes of the regression lines obtained before and after urapidil administration were compared using a t-test. Analysis of covariance was performed to determine whether urapidil administration had a significant effect on the DTF-heart rate relationship (SPSS, version 12.0).

To remove effects of acute changes in heart rate before α-blockade and at maximum action of urapidil, representative values of DTF at center heart rate (DTF_C) were derived from the respective regression lines at a common center heart rate halfway within the range of recorded heart rates. Statistical significance was assumed at P < 0.05.

RESULTS

Clinical and angiographic features of the study population are listed in Table 1. Two lesions were located in the right coronary artery, six in the left anterior descending, and three in the left circumflex coronary artery. Diameter stenosis ranged from 43.0% to 86.8% before PCI. Treatment was successful with a residual stenosis of 0% (SD 12). No patient had diabetes mellitus, and all but one patient received β-blocking medication.

Hemodynamic effects of PCI and α1-receptor blockade. Figure 2 compares average hemodynamic parameters at each step of the protocol. PCI restored distal pressure and flow velocity during maximal vasodilation (P < 0.005), as well as functional parameters such as FFR and CFVR (both P < 0.005) to levels obtained in the reference vessel, whereas Pa, heart rate, and DTF remained constant. HMR decreased as perfusion pressure increased with treatment (P < 0.05). Hemodynamic or functional parameters did not change in the 15-min period after stent placement (Table 2). Flow velocity at rest remained constant throughout the protocol.

After α1-receptor blockade with urapidil, both hyperemic Pp and distal coronary pressure decreased by 6.1% (SD 6.6; P < 0.05) and 5.7% (SD 5.8; P < 0.01), respectively. Mid-systolic and end-diastolic pressures followed the same pattern. RPP during maximal hyperemia decreased by 5.9% (SD 7.3) after urapidil administration (P < 0.05). These changes were similar at resting conditions. On average, other hemodynamic and functional parameters remained unchanged after α1-receptor blockade.

DTF-heart rate relation before and after α1-receptor blockade. A significant inverse linear relation between DTF and heart rate was present in all patients before (P < 0.005) and after (P < 0.02) administration of urapidil, as shown in Fig. 3. The DTF-heart rate relations at rest and during maximal
Hyperemia shifted significantly upward after α<sub>1</sub>-blockade in eight out of 11 patients (P < 0.001). Changes in the remaining three patients showed a similar trend but did not reach significance.

This heart rate-independent shift was quantified by evaluating DTFC at respective center heart rates halfway within the range of recorded heart rates. DTFC averaged over all patients increased after urapidil by 3.1% (SD 2.7; P < 0.005) at maximal hyperemia and by 3.8% (SD 3.1; P < 0.005) at rest. The increase in DTFC was due to a decrease in systolic duration (P < 0.005). No significant difference was found between corresponding DTFC values at rest and during maximal hyperemia.

Acute changes in heart rate ranging from −5 to 10 beats/min (white arrow in Fig. 3) essentially prevented the urapidil effect on the DTFC-heart rate relation to be directly detectable from the actually measured DTFC values. Without the upward shift in the DTFC-heart rate relation, DTF at the actual heart rates after urapidil would have decreased by 2.0%, whereas the measured DTF increased by 1.7%, which can be attributed to a significant decrease in systolic duration (P < 0.05; Table 2).

Effect of concurrent changes in coronary pressure on microvascular resistance at maximal vasodilation: Figure 4 illustrates individual changes in hyperemic P<sub>d</sub> and DTFC after α<sub>1</sub>-receptor blockade and related changes in HMR. Hyperemic P<sub>d</sub> is an important determinant of HMR, and to reveal an effect of urapidil on HMR the data were separated into a group where P<sub>d</sub> before and after urapidil administration differed <5% (● in Fig. 4) and into a group where distal pressure after urapidil administration was always lower than before (○ in Fig. 4). No systematic difference between these two P<sub>d</sub> groups can be noted in the relationship between DTFC before and after urapidil. The constant P<sub>d</sub> group revealed a decrease in HMR by 10.5% (SD 5.6), with a strong correlation between HMR values before and after urapidil administration (r<sup>2</sup> = 0.93).

Hyperemic flow velocity increased after urapidil in this constant P<sub>d</sub> group (not shown).

The reduction in HMR in these patients is therefore to a large extent due to the blocking action of urapidil following α<sub>1</sub>-receptor stimulation after PCI. The decrease in P<sub>d</sub> after urapidil in the other group essentially limited this effect and resulted in an elevated HMR and a reduction in hyperemic flow velocity by 21%.

**DISCUSSION**

The key finding of the present study is that intracoronary administration of the selective α<sub>1</sub>-receptor blocking agent urapidil produced a significant increase in DTFC at rest and during maximal hyperemia.
EFFECT OF URAPIDIL ON DIASTOLIC TIME FRACTION

Table 2. Hemodynamic data before and after $\alpha_1$-blockade

<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>Stent, 15 min</th>
<th>Urapidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Baseline CFV, cm/s</td>
<td>22.8 (SD 5.6)</td>
<td>22.7 (SD 11.0)</td>
<td>22.3 (SD 12.3)</td>
</tr>
<tr>
<td>Systolic</td>
<td>17.0 (SD 6.9)</td>
<td>16.9 (SD 10.4)</td>
<td>16.5 (SD 11.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>24.7 (SD 6.3)</td>
<td>25.5 (SD 12.2)</td>
<td>25.6 (SD 14.0)</td>
</tr>
<tr>
<td>Hyperemic CFV, cm/s</td>
<td>62.9 (SD 14.0)</td>
<td>63.0 (SD 16.0)</td>
<td>60.5 (SD 18.8)</td>
</tr>
<tr>
<td>Systolic</td>
<td>54.9 (SD 14.7)</td>
<td>54.0 (SD 18.1)</td>
<td>49.6 (SD 22.2)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69.7 (SD 13.9)</td>
<td>72.3 (SD 15.9)</td>
<td>71.2 (SD 17.9)</td>
</tr>
<tr>
<td>$P_a$, mmHg</td>
<td>98 (SD 10)</td>
<td>101 (SD 12)</td>
<td>95 (SD 10)*</td>
</tr>
<tr>
<td>Systolic</td>
<td>136 (SD 21)</td>
<td>139 (SD 21)</td>
<td>128 (SD 15)†</td>
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<tr>
<td>Diastolic</td>
<td>78 (SD 7)</td>
<td>80 (SD 10)</td>
<td>76 (SD 8)*</td>
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<tr>
<td>Systolic</td>
<td>131 (SD 21)</td>
<td>134 (SD 18)</td>
<td>123 (SD 14)†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70 (SD 9)</td>
<td>73 (SD 11)</td>
<td>69 (SD 9)*</td>
</tr>
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<td>RPP, beats$^{-1}$·mmHg$^{-1}$</td>
<td>9,659 (SD 1,591)</td>
<td>10,092 (SD 1,964)</td>
<td>9,434 (SD 1,538)*</td>
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<tr>
<td>FFR</td>
<td>0.93 (SD 0.05)</td>
<td>0.94 (SD 0.04)</td>
<td>0.94 (SD 0.04)</td>
</tr>
<tr>
<td>CFVR</td>
<td>2.84 (SD 0.69)</td>
<td>3.05 (SD 0.97)</td>
<td>2.95 (SD 0.76)</td>
</tr>
<tr>
<td>HMR, mmHg·s/cm</td>
<td>1.52 (SD 0.40)</td>
<td>1.58 (SD 0.37)</td>
<td>1.60 (SD 0.49)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72 (SD 10)</td>
<td>73 (SD 12)</td>
<td>74 (SD 10)</td>
</tr>
<tr>
<td>RR interval, s</td>
<td>0.85 (SD 0.11)</td>
<td>0.84 (SD 0.14)</td>
<td>0.83 (SD 0.13)</td>
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<tr>
<td>Systolic</td>
<td>0.42 (SD 0.03)</td>
<td>0.42 (SD 0.04)</td>
<td>0.40 (SD 0.02)*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.43 (SD 0.10)</td>
<td>0.42 (SD 0.11)</td>
<td>0.42 (SD 0.12)</td>
</tr>
<tr>
<td>DTF</td>
<td>0.497 (SD 0.052)</td>
<td>0.497 (SD 0.047)</td>
<td>0.505 (SD 0.050)</td>
</tr>
<tr>
<td>DTFC</td>
<td>0.496 (SD 0.046)</td>
<td>0.496 (SD 0.046)</td>
<td>0.511 (SD 0.049)†</td>
</tr>
</tbody>
</table>

All values are means (SD) and represent hyperemic conditions unless otherwise indicated; $n$, number of patients. CFV, coronary flow velocity; $P_a$, aortic pressure; $P_d$, distal pressure; RPP, rate pressure product; FFR, fractional flow reserve; CFVR, CFV reserve; HMR, hyperemic microvascular resistance index; DTF, actual diastolic time fraction; DTFC, diastolic time fraction at center heart rate. *$P < 0.05$; †$P < 0.01$ compared with previous condition.

Urapidil after PCI induced an upward shift in the DTF-heart rate relationship, which amounted to a 3.1% increase in DTFC (range, 1.4% to 8.2%). For the subgroup in which coronary pressure remained constant after the urapidil administration, HMR was reduced by 10.5%.

Comparison with other studies on $\alpha_1$-blockade after angioplasty. Coronary resistance vessels receive autonomic innervation, and $\alpha_1$-adrenergic receptors are present in vessels with a diameter $<300$ $\mu$m (5, 16). Although $\alpha$-adrenergic coronary constriction tone is negligible under resting conditions, it has been shown to increase hyperemic coronary resistance in normal coronary vessels (18, 23). Pathophysiological conditions such as atherosclerosis sensitize resistance vessels to the constractive effect of $\alpha$-adrenergic receptors (2, 16). Previous studies have furthermore demonstrated that $\alpha$-adrenergic pathways in the vessel wall were acutely stimulated in patients who underwent balloon angioplasty (9, 12, 20). Gregorini et al. (9, 11, 12) observed that $\alpha_1$-mediated vasoconstriction developed over time (9, 11) and reached a maximum 15 min after angioplasty, resulting in a blunted flow reserve compared with shortly after the intervention (12).

Our results in terms of CFVR do not concur with these earlier findings in that CFVR was restored to values equal to the reference vessel after PCI and was not depressed 15 min later or enhanced by the subsequent administration of urapidil. These contrasting findings may be due to differences in adjunctive medication and initial outcomes of the PCI. Patients in the former study were sedated with neuroleptic analgesia, and CFVR was not improved by PCI (12). In addition, vasoactive medication was not discontinued in the present study, and all patients received an initial dose of intracoronary nitroglycerin, which may have attenuated the vasoconstrictive effects of PCI-induced $\alpha$-receptor stimulation.

In terms of hyperemic coronary resistance, $\alpha_1$-receptor blockade with doxazosin demonstrated a reduction not only in normal subjects (23) but also in patients 5 days after PCI (27). Coronary resistance in these studies was derived from myocardial blood flow determined with PET and mean arterial pressure obtained by cuff sphygmomanometry. In contrast, our measurements only confirm a reducing effect of urapidil on HMR in a group with minimal changes in coronary pressure. Hence, when studying the drug-induced effect on HMR, one has to be aware of altered mechanical conditions that have a marked influence on HMR, and in this respect especially DTF and coronary perfusion pressure are important, which were shown to exert opposite effects on subendocardial conductance (8). These possible mechanical pathways were not considered in earlier studies on the effects of $\alpha_1$-receptor blockade.

Interaction of mechanisms affecting HMR. The vasodilatory effect of urapidil on HMR has to be discerned from concurrent changes in other major determinants of hyperemic coronary resistance such as coronary pressure and DTF. Diastolic duration and perfusion pressure act in concert to alter microvascular resistance of the maximally vasodilated bed (32). The distending effect of coronary pressure on resistance vessels at maximal vasodilation causes HMR to vary in a direction opposite to a pressure change (14, 35). The compressive effects of heart contraction on intramural vessels decrease when DTF is increased. Animal studies showed that the sensitivity of HMR for DTF depends on coronary pressure (8). These studies also demonstrated that the pressure dependence of HMR holds for all layers in the myocardium, whereas the DTF effect is absent in the subepicardium and increases toward the subendocardium. In our study, we were not able to measure transmural differences of myocardial resistance and had to rely on the lumped hyperemic resistance downstream from the epicardial measurement location. Actual changes in DTF after urapidil administration were rather small in the present study despite the significant upward shift in the DTF-heart rate relation (see Fig. 3). Variations in coronary pressure were relatively larger,
PTCA, percutaneous transluminal coronary angioplasty.

...of simultaneously, and the effect of changes in coronary pressure studies was intracoronary pressure and flow velocity measured receptor blockade after PCI. However, in none of those group with minimal coronary pressure changes. Similar effects ing effect of...cross all myocardial layers and, hence, the perfusion enhanc-...ation of an endothelin-1 in coronary microvessels in response to substance that stimulates the production of the potent vasocon-...sor. Urapidil has a central hypotensive effect without reflex tachycar-...dilation (bottom) showing measurements in the target vessel after percutaneous coronary intervention (balloon angioplasty and stent placement) and after urapidil. Linear regressions were obtained for respective data before and after urapidil administration. After \( \alpha \)-blockade, the DTF-heart rate relation shifted upward \( (P < 0.001) \). Actual DTF did not change due to an increase in heart rate after urapidil (white arrow). Representative values for DTF\(_ C \) (dashed left arrows) were assessed at center heart rate (vertical line). PTCA, percutaneous transluminal coronary angioplasty.

Potential mechanisms for DTF increase after \( \alpha \)-blockade. Pharmacological agents can have a significant effect on dia-stolic duration \((3, 17)\). Urapidil is a selective \( \alpha_1 \)-antagonist, which has a central hypotensive effect without reflex tachycardia due to serotonergic activation \((2, 6, 29)\). Urapidil has a 90-fold larger preference for \( \alpha_1 \) than for \( \alpha_2 \)-receptors \((6)\). To some degree it causes presynaptic \( \alpha_2 \)-blockade and thereby \( \beta \)-receptor stimulation and increased norepinephrine release \((13, 28)\), which shortens the duration of systole and could allow for an increase in the duration of diastole at a given heart rate. However, all but one patient received \( \beta \)-blocking medication, which limits the effectiveness of this mechanism.

Merkus et al. \((24)\) demonstrated in an animal study an inverse nonlinear relation between DTF and intracoronary perfusion pressure and flow, suggesting a possible protective mechanism whereby DTF increases when coronary perfusion is impaired distal to a stenosis. However, this regulatory mechanism only takes action at perfusion pressure below 50–60 mmHg, whereas average distal pressure after PCI was >90 mmHg in our study group.

From the effect of urapidil on DTF\(_ C \) it is clear that urapidil influences the mechanical function of the heart. There is no reference in the literature directly relating \( \alpha \)-adrenoreceptors and DTF. A possible link exists via stimulation of myocardial \( \alpha_1 \)-adrenergic receptors, which has been shown to exert a positive inotropic effect in a large number of species including humans \((21, 26)\) and is associated with a prolongation of contraction \((15, 22)\). Hence, \( \alpha_1 \)-receptor blockade by urapidil may counteract this prolongation and thereby increase DTF. Interestingly, cardiac myocytes have been shown to release a substance that stimulates the production of the potent vasoconstrictor endothelin-1 in coronary microvessels in response to \( \alpha_1 \)-adrenergic stimulation, which is blocked by the administration of an \( \alpha \)-adrenergic antagonist \((33)\) and augmented by decreased bioavailability of nitric oxide \((25, 34)\), a hallmark of endothelial dysfunction associated with atherosclerotic coro-nary artery disease. Regulation of DTF may be an additional player in this scenario.

Methodological considerations. Because in the present study heart rate in individual patients did not change spontaneously by >20–25 beats/min throughout the protocol, we fitted the DTF-heart rate relations by a linear rather than a curvilinear relationship, which is obtained over a larger range of heart rates, usually achieved by pacing \((3, 4)\). Due to the pressure dependence of DTF \((24)\), we also did not use any measurements obtained in the presence of a stenosis for the DTF-heart rate regression lines before \( \alpha \)-blockade, to avoid mixing DTF values obtained at substantially lower perfusion pressures.

We defined systole as the period between the ECG R-peak and the dicrotic notch on the \( P_a \) signal. In that way systolic time includes both the isovolumic contraction phase and the left ventricular ejection period. It is possible that the beneficial effect of urapidil is partly the result of improved relaxation after the occurrence the dicrotic notch. However, although the absolute magnitudes of DTF might have been different for a different definition of systolic duration, it is unlikely that the relative changes in DTF would have been affected \((24)\).

 epicardial vessel dilation after urapidil could cause an in-crease in flow to be underestimated when assessed by flow velocity. Coronary blood flow was not determined in the present study since its estimation from angiographic vessel...
dimensions and velocity is subject to simplifying assumptions and prone to errors, especially for angiograms obtained during adenosine-induced vasodilation. It also would have required additional contrast injections and radiation exposure, which we tried to limit in our study. All patients received intracoronary nitroglycerin before stent placement to relax large vessel tone and minimize active changes in vessel caliber. We therefore consider epicardial vessel dilation unlikely in our study group, in particular since observed hyperemic velocity changes were opposite to changes in HMR after urapidil for both pressure groups shown in Fig. 4.

Left ventricular pressure (LVP) was not measured, and a possible effect of changes in end-diastolic LVP on coronary hemodynamics could not be assessed. However, \( \alpha_1 \)-adrenergic stimulation has previously not been shown to alter end-diastolic LVP in humans (21), and changes induced by intracoronary urapidil administration are therefore rather unlikely.

Our choice for \( \alpha_1 \)-receptor blockade was prompted by the prominent vascular effect of this subtype observed in earlier studies on PCI-induced vasoconstriction (12, 27) and the demonstrated cardiac myocyte-mediated effects upon \( \alpha_1 \)-adrenergic stimulation (21, 26, 33). With the consideration of the preferential sensitivity of coronary arterioles to \( \alpha_2 \)-adrenergic stimulation, it would certainly be interesting to extend the investigation to \( \alpha_2 \)-blocking agents.

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The size of our study group was small, and although the effect of \( \alpha_1 \)-blockade on heart rate-independent DTFC was significant, with a marked reduction in HMR in the constant coronary pressure group, future studies using combined intracoronary pressure and flow velocity measurements should be carried out in a larger population to confirm the urapidil-related mechanisms and to further investigate potential implications for functional parameters.

Implications. Our data revealed interactive effects that occurred after \( \alpha_1 \)-receptor blockade. Administration of urapidil resulted in a significant elevation of the DTF-heart rate relationship, effectively prolonging diastolic perfusion time irrespective of heart rate. Additionally, coronary perfusion pressure, which has been shown to increase HMR in humans (34), was reduced after urapidil. Animal microsphere studies have shown a beneficial effect of prolonged DTF via an enhanced subendocardial perfusion (1, 8). The observed increase in DTFC in the present study, although small, may well be of clinical importance, since microsphere studies of myocardial perfusion (1) have shown that a 1% increase in DTF increases subendocardial flow by 2.6% to 6.1%, which for the present 3.1% prolongation in DTFC translates to a potential 18.3% increase in subendocardial perfusion. This effect would be on top of the HMR-reducing effect of urapidil by pharmacological pathways involving the relief of constricted resistance vessels.

Conclusion

We conclude that \( \alpha_1 \)-receptor blockade after coronary angioplasty produced an upward shift in the DTF-heart rate relationship, resulting in a modest but significant prolongation of DTF at a given heart rate. This suggests a possible adjunctive mechanism to the well-established beneficial effect of urapidil after PCI via an improvement in subendocardial perfusion, which is critically dependent on DTF.

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REFERENCES


