Distension of urinary bladder induces exaggerated coronary constriction in smokers with early atherosclerosis

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Received 1 February 2000; accepted in final form 18 July 2000

DISTENSION OF THE URINARY bladder has been shown to cause the reflex response of an increase in sympathetic activity (10, 34). The regulation of coronary blood flow by activated sympathetic nerves depends on status of coronary endothelial function (24). When the endothelium is impaired by atherosclerosis (12) or exhaustion of autoregulation (25), adrenergic-mediated vasoconstriction becomes unrestricted and sufficiently powerful to reduce coronary blood flow and initiate myocardial ischemia (23). Different maneuvers to elicit sympathetic activities, e.g., mental stress (48), handgrip (6), cold pressor test (1), and supine exercise (28), may differ in their recruitment of adrenergic-mediated coronary vasoconstriction. No studies have demonstrated the vasoconstriction reflex of the coronary arteries caused by the distension of the urinary bladder.

Smoking, a well-established risk factor for atherosclerosis (37), induces early impairment of endothelial function. Previous studies revealed the importance of endothelial function in both basal and stimulated control of vasomotor tone in large conduit and resistance vessels (27). Smoking has been shown to impair endothelial function in response to sympathetic activation in patients with coronary atherosclerosis (27). However, no previous data in smokers has been reported on the effect of urine bladder distension on coronary circulation. In addition, when coronary flow was determined by the coronary sinus thermodilution method, the effects of interventions on regional myocardial flow cannot be assessed. To study the acute effects of urinary bladder distension on regional coronary circulation, we measured coronary blood flow by intracoronary Doppler flow-wire during such distension. The report describes clinical studies designed to test the hypothesis that there is an abnormal response of coronary conduit and resistance vessels during distension of the urinary bladder especially in smokers, by a combined intracoronary Doppler flow and quantitative coronary angiography.

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Distension of urinary bladder induces exaggerated coronary constriction in smokers with early atherosclerosis. Smoking, a well-established risk factor for atherosclerosis (37), induces early impairment of endothelial function. Previous studies revealed the importance of endothelial function in both basal and stimulated control of vasomotor tone in large conduit and resistance vessels (27). Smoking has been shown to impair endothelial function in response to sympathetic activation in patients with coronary atherosclerosis (27). However, no previous data in smokers has been reported on the effect of urine bladder distension on coronary circulation. In addition, when coronary flow was determined by the coronary sinus thermodilution method, the effects of interventions on regional myocardial flow cannot be assessed. To study the acute effects of urinary bladder distension on regional coronary circulation, we measured coronary blood flow by intracoronary Doppler flow-wire during such distension. The report describes clinical studies designed to test the hypothesis that there is an abnormal response of coronary conduit and resistance vessels during distension of the urinary bladder especially in smokers, by a combined intracoronary Doppler flow and quantitative coronary angiography.

H2838 0363-6135/00 $5.00 Copyright © 2000 the American Physiological Society http://www.ajpheart.org
METHODS

Patients

The study was conducted prospectively. Potential candidates were eligible for the present study if they had a single non-flow-limiting stenosis (<50% diameter stenosis) in the proximal or middle portion of one major coronary artery. Because severe atherosclerotic lesions of epicardial coronary artery may induce limited vasodilation and reflex vasoconstriction (6), only patients with mild stenosis were included. Exclusion criteria included prior myocardial infarction, unstable angina pectoris, uncontrolled hypertension, ejection fraction <55% by catheterization study, valvular heart disease, diabetes mellitus, and echocardiographic left ventricular mass index >117 g/m² for men and 104 g/m² for women (15). Because of influence of smoking on autonomic function (40), we excluded patients with autonomic dysfunction to make baseline autonomic system of our study subjects homogenous by autonomic reflex evaluation (44). A total of 117 g/m² for men and 104 g/m² for women (15). Because of influence of smoking on autonomic function (40), we excluded patients with autonomic dysfunction to make baseline autonomic system of our study subjects homogenous by autonomic reflex evaluation (44). A total of consecutive 24 patients were included. Patients were classified into habitual smokers (group 1, n = 14) and nonsmokers (group 2, n = 10, individuals who had never smoked). Habitual smokers were randomized into two subgroups on the basis of the use of doxazosin, as follows: subgroup 1A (n = 7), without administration of doxazosin before catheterization; subgroup 1B (n = 7), with dosing doxazosin. A habitual smoker was defined as someone who had regularly smoked each day for the previous 10 years regardless of the amount smoked. The clinical characteristics of patients were given in Table 1. The study was approved by the National Taiwan University Hospital Review Board, and all subjects provided informed written consent before participation. Medications, including calcium channel blockers and β-adrenergic blockers, and caffeine-containing drinks were held for 48 h before the procedure, except doxazosin for subgroup 1B patients. Any patients who had taken nitroglycerin within 4 h of catheterization were excluded from this study. All subjects refrained from smoking for more than 12 h before the study.

Table 1. Clinical and angiographic characteristics in the three groups

<table>
<thead>
<tr>
<th>Smokers</th>
<th>Nonsmokers (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/1</td>
</tr>
<tr>
<td>Age, y</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>2(29)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>187 ± 42</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>40 ± 8</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>119 ± 21</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>231 ± 72</td>
</tr>
<tr>
<td>Coronary lesions</td>
<td></td>
</tr>
<tr>
<td>LAD, %</td>
<td>5(71)</td>
</tr>
<tr>
<td>LCX, %</td>
<td>0(0)</td>
</tr>
<tr>
<td>RCA, %</td>
<td>2(29)</td>
</tr>
</tbody>
</table>

Values are means ± SD, and nos. in parentheses are %values as indicated. Subgroup 1A, smokers without pretreatment with 2 mg doxazosin; subgroup 1B, smokers with pretreatment with doxazosin; group 2, nonsmokers. HDL, high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; and RCA, right coronary artery.

Catheterization procedures. Diagnostic left catheterization and angiography were performed from a femoral approach. After completion of the diagnostic catheterization, intravenous heparin was supplemented to maintain activated clotting time at 300 to 350 s, and a 7-French Judkins catheter was advanced to the ostium of the left or right coronary artery. A 0.014-in. Doppler wire (FloWire, Cardiometrics, Mountain View, CA) was first introduced through a standard angioplasty-type Y-connector attached to the angiographic catheter into the proximal coronary artery that had nonobstructive lesions (<50%). The wire tip was positioned such that a characteristic and stable flow velocity waveform was obtained. Three pairs of perpendicular views (90°) of the left and right coronary arteries were obtained. The precise angle, skew rotation, and table height of each projection were recorded so that the projection could be duplicated. Serial hand injections of contrast medium were performed at baseline and during urinary bladder distension. At each time interval, intracoronary Doppler flow was recorded, followed by coronary angiography.

Intervention procedures. All study subjects underwent a post-voiding residual catheterization to empty the bladder. An 8-French transurethral catheter was used to fill the bladder with normal saline at room temperature and was then attached to a water-filled line and pressure transducer, which was zeroed to atmospheric pressure. This line measured intravesical pressure. Aortic blood pressure, heart rate, coronary angiograms, intravesical pressure, and intracoronary Doppler velocity were obtained at baseline. Normal saline was then installed slowly from two 50-ml syringes through the catheter while the intravesical pressure was constantly monitored. If the intravesical pressure reached 20 mmHg or increased such that there was a risk of leakage into the urethra, then normal saline was withdrawn. The pressure level (20 mmHg) was chosen because the intravesical pressures were at least 17 mmHg in subjects with normal bladder function during micturition (14). The technique allows distension of the bladder to be maintained at a steady urinary bladder pressure in terms of maximal variation in bladder pressure of less than 10%. Because rate of filling influences the bladder’s ability to accommodate an increasing volume and test results (8), the filling rate was controlled at 50–100 ml/min. The same measurements were obtained 5 min after the stable conditions of distension of the urinary bladder. To examine the mechanism of the coronary flow response to distension of the urinary bladder, the patients in subgroup 1B were pretreated with the selective α1-blocker doxazosin (2 mg po) 4 h before cardiac catheterization. The dose was selected because previous studies used the dose to obtain α-adrenergic block (7).

Parameter Measurements

Angiography measurements. Digital coronary angiograms were recorded in three orthogonal projections before and after each procedure. For each lesion, the view showing the best demonstrated stenosis with minimal foreshortening was used for analysis. The minimal lumen diameter and proximal angiographically normal segment were measured. Quantitative measurements of coronary artery dimensions were made using a computer-based edge enhancement technique (DCI System; Philips, Best, The Netherlands), as previously described (32). The Doppler catheter was positioned at a distance of 5–10 mm proximal to the stenosis, far from any large branching vessel. To determine cross-sectional area of the artery, a 5-mm segment was measured immediately distal to the tip of the
Doppler catheter. All injections and projections throughout a given study were performed by the same operator (T.-M. Lee) to minimize variability in angiographic technique. Three electrocardiographic leads were continuously recorded. These were selected to reflect leads showing electrocardiographic S-T segment changes during bladder distension. Ischemic electrocardiographic changes were defined as a horizontal or down-sloping S-T segment deviation of 0.1 mV or greater at 60 ms after the J point in any lead. Transient electrocardiogram (ECG) changes that were observed shortly after coronary arteriography were not taken to be a positive. During bladder distension, patients were asked to characterize the nature of chest pain and abdominal sensation. The degree of segmental vasoactivity to bladder distention and nitroglycerin was expressed as the absolute vessel diameters and change percent. For angiographic normal reference vessel caliber in our laboratory, the intraobserver and interobserver differences for quantitative coronary angiography were 0.18 ± 0.15 mm (5.7 ± 6.2%) and 0.21 ± 0.23 mm (6.7 ± 6.8%), respectively.

Lactate measurements. To confirm myocardial ischemia during urinary bladder distension, selective catheterization of coronary sinus was successfully attempted in the last 10 patients (3 in subgroup 1A, 3 in subgroup 1B, and 4 in group 2). Simultaneous samples of aortic root and coronary sinus at the same speed were obtained for measurements of lactate contents. Myocardial lactate extraction ratio (MLE, %) was calculated by the following formula: MLE = [(LAO - LCS)/LAO] × 100, where LAO and LCS represent plasma lactate concentrations in the aortic root and in the coronary sinus, respectively.

Calculation of volumetric coronary blood flow and coronary resistance. The coronary flow velocity measurements were obtained with a Doppler ultrasound 0.014-in. guide wire. Digitized spectral peak velocity waveforms were averaged to compute the average peak velocity (APV). The monitor display was continuously recorded on Super VHS videotape for off-line analysis. Volumetric coronary blood flow (CBF, ml/min) was calculated as CBF (ml/min) = CSA (mm²) × APV (cm/s) × 0.5 × 0.6 as validated by Doucette et al. (18), where CSA is cross-sectional area (mm²). The factor of 0.5 has been empirically validated and corresponds to the correction for a parabolic velocity profile by compensating for the ratio of spectral peak velocity as measured by the Doppler system and the spatial average velocity required for the calculation of volumetric flow. The factor of 0.6 was for the unit change. Coronary resistance was derived as mean blood pressure divided by coronary blood flow.

Statistics

The continuous variables are expressed as means ± SD. Paired t-tests were used to search for possible effects of bladder distension within the groups. Unpaired t-tests were used to compare the effect of doxazosin on vascular responses between the 2 subgroups (subgroups 1A and 1B) and to compare the differences in groups of patients with or without smoking (subgroup 1A and group 2). Probability values are two-tailed, and a value of P < 0.05 is considered to be statistically significant.

RESULTS

There were no baseline characteristic differences among these three groups shown in Table 1. These groups were comparable in terms of gender, age, lipid profile, heart rate, and blood pressure. Coronary risk factors for coronary artery disease were evenly distributed among the three groups. Blood pressure was significantly decreased from 113 ± 8 to 95 ± 7 mmHg after dosing doxazosin (P < 0.001) in subgroup 1B. The reduction of blood pressure was compatible with α₁-receptor blockade after doxazosin administration. The baseline MLE ratios were positive and similar in the three groups (20 ± 7% in subgroup 1A, 19 ± 8% in subgroup 1B, and 23 ± 12% in group 2). The MLE ratio during urinaly bladder distension was decreased significantly in subgroup 1A patients (3 ± 8% vs. baseline, P = 0.05) but remained unchanged in subgroup 1B and group 2 (17 ± 12%, 10 ± 9%) compared with baseline (not significant, both). During bladder distension, neither chest pain nor ST changes on the surface ECG occurred. Bladder distension used in the present study elicited fullness sensations in the suprapubic and perineal regions.

Bladder Distension and Hemodynamic Data

The intravesical pressure was similar in the three groups, namely, 21.5 ± 2.3 mmHg in subgroup 1A (range: 17–23 mmHg, filling 250–550 ml of normal saline), 20.6 ± 1.3 mmHg in subgroup 1B (range 18–23 mmHg, filling 250–550 ml of normal saline), and 21.8 ± 1.9 mmHg in group 2 (range: 17–22 mmHg, filling 225–525 ml of normal saline).

An increase in intravesical pressure induced an increase in heart rate of 11 ± 7 beats/min (range: 4–21; P = 0.05) from baseline level of 68 ± 5 beats/min (range: 63–78) in subgroup 1A (Table 2). Changes in heart rate, mean blood pressure, and double product (systolic pressure × heart rate) at rest, and during bladder distension were also comparable in the three groups.

Epicardial Vasomotor Response

In subgroup 1A, bladder distension significantly decreased epicardial coronary diameter by 24 ± 9% (from 1.88 ± 0.29 to 1.41 ± 0.11 mm, P = 0.0003) and decreased coronary blood flow by 29 ± 12% (from 50.5 ± 12.2 to 35.5 ± 8.9 ml/min, P = 0.003) compared with baseline values (Table 2; Fig. 1, A and C) in the stenotic vessel segments. In contrast to stenotic segments, normal vessel segments remained unchanged coronary diameters during bladder distension (Fig. 1B). In subgroup 1B, there were no significant changes in epicardial stenotic coronary diameter (Fig. 1A) and coronary blood flow (Fig. 1C) during bladder distension compared with baseline data. There were significant differences of coronary diameter (P = 0.008) and coronary blood flow (P = 0.002) between the two subgroups during bladder distension. Patients in subgroup 1A showed significant differences of coronary diameters at the stenotic segments (P < 0.0001) and coronary blood flow (P = 0.02) compared with patients in group 2 during bladder distension.
Resistance Vessel Response

In subgroup 1A, bladder distension significantly increased coronary resistance by $81 \pm 35\%$ (from $2.09 \pm 0.89$ to $3.83 \pm 2.15$ mmHg/min, $P = 0.01$), compared with baseline values (Table 2; Fig. 1D). In subgroup 1B, there were no significant changes of coronary resistance during bladder distension compared with baseline data. There were significant differences of changes of coronary resistance ($P < 0.0001$) between the two subgroups in response to bladder distension. Patients in subgroup 1A showed a significant difference of changes of microvascular vasomotor response to bladder distension at the stenotic segments compared with patients in group 2 ($81 \pm 35\%$ vs. $24 \pm 12\%$, $P < 0.0002$, Fig. 1D).

DISCUSSION

The present study demonstrated that distension of the urinary bladder decreases coronary diameter of the stenotic segments and coronary blood flow and increases coronary resistance in the homogenous patients with similar severities of coronary atherosclerosis.

Table 2. Changes in hemodynamic variables, angiographic variables and coronary blood flow in patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Subgroup 1A (n = 7)</th>
<th>Subgroup 1B (n = 7)</th>
<th>Group 2 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Bladder distension</td>
<td>Baseline</td>
</tr>
<tr>
<td>MBP, mmHg</td>
<td>97 ± 11</td>
<td>121 ± 16*</td>
<td>95 ± 7</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68 ± 5</td>
<td>78 ± 7*</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>SBP × HR, double product</td>
<td>9,256 ± 1,010</td>
<td>13,129 ± 1,129*</td>
<td>8,572 ± 1,399</td>
</tr>
<tr>
<td>Angiographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diam, mm</td>
<td>3.10 ± 0.26</td>
<td>2.90 ± 0.26</td>
<td>3.32 ± 0.46</td>
</tr>
<tr>
<td>Lesion diam, mm</td>
<td>1.88 ± 0.29</td>
<td>1.41 ± 0.11*</td>
<td>2.05 ± 0.45</td>
</tr>
<tr>
<td>Doppler APV, cm/s</td>
<td>22.3 ± 4.3</td>
<td>20.1 ± 5.5</td>
<td>19.4 ± 3.3</td>
</tr>
<tr>
<td>CBF, ml/min</td>
<td>50.5 ± 12.2</td>
<td>35.5 ± 8.9*</td>
<td>49.8 ± 8.6</td>
</tr>
<tr>
<td>MCR, mmHg·ml⁻¹·min</td>
<td>2.09 ± 0.89</td>
<td>3.83 ± 2.15*</td>
<td>1.97 ± 0.39</td>
</tr>
</tbody>
</table>

Values are means ± SD. *$P < 0.05$ compared with data from respective baseline. †$P < 0.05$ compared with data from subgroup 1A during bladder distension. ‡$P < 0.05$ compared with data from respective baseline and during bladder distension in subgroup 1A. APV, averaged peak velocity; HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; CBF, coronary blood flow; and MCR, mean coronary resistance.
sis. The intravesical pressure (17–23 mmHg) and volume (225–550 ml) used in this study were within the physiological range reached during normal filling, a physiological stimulus (22). Such abnormal vasomotor responses during urinary bladder distension are exaggerated in smokers. In smokers, distension of the urinary bladder induced an exaggerated decrease in coronary blood flow despite an increase in myocardial oxygen demand. These changes resulted in myocardial ischemia as assessed by lactate production. Doxazosin administration reversed the myocardial ischemia, reflecting the mechanism of coronary vasoconstriction, and concomitant increase in coronary vascular resistance is mediated by α1-adrenoceptors during bladder distension.

Conduit Vessel Vasoconstriction

Our results showed that vasoconstriction of conduit vessels evoked with urinary bladder distension was significantly higher in smokers. The constriction of coronary conduit vessels in response to bladder distension may be due to an exaggerated response to sympathetic activation and, in part, endothelial function. Sympathetic activation dilates normal coronary arteries but constricts atherosclerotic vessels in proportion to the severity of endothelial dysfunction (50).

Two factors are related to increased sympathetic activities in this study. First, distension of urinary bladder induces catecholamine release, which evokes an increase in heart rate, blood pressure, myocardial oxygen demand, and myocardial ischemia as assessed by sinus lactate production. Distension of hollow viscera has been shown to stimulate receptors located in their walls (10, 45), which may reflexly affect coronary circulation. For instance, distension of stomach has been reported to elicit reflex increases in heart rate and blood pressure and has been related to postprandial angina (46).

Second, habitual smoking induces complex alterations in autonomic cardiovascular control, including an increase in afferent impulses from the distended bladder (4) and in cardiac sympathetic efferent drive (20, 33). Previous studies have demonstrated that smoking significantly increases circulating norepinephrine release (47). The increased norepinephrine concentrations evoked nitric oxide release from the urinary bladder mucosa (4). Nitric oxide released in the bladder may modulate multiple functions by influencing the excitability of bladder afferents (29). Node et al. (41) have demonstrated that an α1-adrenergic antagonist attenuates the release of nitric oxide, which decreases afferent nerve activity and lessens adrenergic-mediated vasoconstriction. Besides, Grassi et al. (20) have demonstrated increased coronary sinus norepinephrine spillover in smokers, an indirect index of sympathetic traffic to the heart. Nicotine binds to acetylcholine receptors at autonomic ganglia, the adrenal medulla, and neuromuscular junction (3). As a consequence of receptor stimulation, nicotine evokes the release of catecholamines and facilitates the release of electrical stimulation-induced neurotransmitters from sympathetic nerves in cardiovascular system (3). The number of α-adrenergic receptors is increased in atherosclerotic blood vessels, which could augment vasoconstrictor response to bladder distension (39).

The mechanism of coronary vasoconstriction is mediated by α1-adrenoceptors. Epicardial coronary arteries are innervated with sympathetic nerve fibers and have α1- and α2-adrenoceptor (2). Baran et al. (2) showed that α1-receptors are involved in vasoconstriction of large coronary arteries during sympathetic activation, such as exercise. The increased vascular α1-tone can explain epicardial coronary vasoconstriction during bladder distension. Furthermore, α1-adrenergic antagonist has been shown in our study to limit coronary vasoconstriction during bladder distension, which was consistent with the finding of Collins and Sheridan (13) that indoramine, a selective α1-adrenergic antagonist, has been shown to limit exercise-induced angina pectoris.

Besides, vasoconstriction of coronary arteries in response to bladder distension could also be caused by impaired endothelial function. The importance of impaired endothelial function when the sympathetic nervous system is activated has been extensively investigated. Removal of endothelium by atherosclerosis has been shown to abolish the release of nitric oxide, which may permit adrenergic agonists to activate smooth muscle to cause vasoconstriction (49). Smoking may lead to endothelial dysfunction. The effect of smoking on endothelial function of conduit vessels was examined by Celemajer et al. (9), who found an impaired brachial artery dilation in response to increased flow. Nabel et al. (38) demonstrated that sympathetic stimulation dilates normal and constricts atherosclerotic coronary arteries, which was inconsistent with our finding that vasoconstriction was noted in stenotic segments but remained unchanged in “normal reference” segments. However, a “smooth” appearance of the luminal surface on the coronary angiogram does not exclude the presence of intimal involvement with atherosclerosis. The presence of functioning endothelium in “normal reference” segments may attenuate urinary bladder distension-induced vasoconstriction.

Resistance Vessel Constriction

Distension of the urinary bladder causes greater increase of coronary vascular resistance in smokers than nonsmokers. In patients with coronary disease, coronary resistance increases during sympathetic stimulation because vasodilatory reserve has been exhausted such that α-adrenoceptor-mediated vasoconstriction is unopposed (26). The failure of coronary blood flow to increase may suggest either endothelial dysfunction or exaggerated sympathetic vasoconstriction at the level of resistance, leading to uncoupling between increased metabolic demand and coronary flow. Although atherosclerotic lesions are confined to epicardial vessels, the functional consequences of atherosclerosis may extend into the microvessels. Minor
et al. (35) have demonstrated that smokers may have reduced coronary flow reserve. Heitzer et al. (27) showed that long-term smoking is associated with markedly reduced acetylcholine responses in forearm resistance vessels, which further supports impaired endothelial function of resistance vessels. Thus the failure of endothelial cells to produce or release adequate quantities of nitric oxide occurred in resistance vessels devoid of atheroma. Furthermore, because of a differential distribution of \( \alpha \)-adrenergic receptors in the canine coronary circulation, with \( \alpha_1 \)-adrenoceptors mediating epicardial vasoconstriction and \( \alpha_2 \)-adrenoceptors mediating vascular resistance, Heusch et al. (26) showed that this response of coronary vascular resistance can be partially blocked by \( \alpha_1 \)-adrenoceptor antagonists and nearly completely blocked by \( \alpha_2 \)-adrenoceptor antagonists. The finding was consistent with our results that \( \alpha_3 \)-adrenoceptor antagonist doxazosin reduced the increase in coronary resistance during sympathetic stimulation (urinary bladder distension).

**Study Limitations**

This study could be criticized on the basis that heart rate was uncontrolled by cardiac pacing and double product was not held constant during the study. Although the patients were not paced during bladder distension, this decrease in mean coronary blood flow could not be explained, since an increase in heart rate is known to increase blood flow (16). Controlling double product was important because the increased double product will increase the metabolic demand, which in turn may result in vasodilatation of resistance vessels. The degrees of changes of double product among the three groups were similar. However, there was a significant increase of double product during bladder distension, which was expected to have increased coronary diameters on the basis of increased metabolic requirement. Thus the changes of double product could not be a major factor of vasoconstriction during bladder distension.

Another limitation of the present study was lack of normal control for ethic reason. The need of the invasive study made it impractical to have a normal control group. Instead, each patient serves as his or her own control. Besides, there appears to be bias to the inclusion of males in this study (22 males and 2 females). Patients here were included for cardiac catheterization to rule out the possibility of coronary atherosclerosis, which is more prevalent in males than in females (31).

The third limitation was the possible change of threshold for angina depending on the intensity of afferent impulses from the distended bladder. Patients in this study experienced fullness sensation referred to perineum or suprapubic areas from the distended bladder, which was consistent with the finding of Szasz and Whyte (43), showing that pain can be elicited by distending pressures ranging from 12 to 19 mmHg. Bladder afferents in the hypogastric and pelvic nerves enter the spinal cord through the L2–L5 and S1–S4, respectively (5). These fibers are activated by noxious information from the distended bladder. Thoracic spinal tracts that receive cardiac input are strongly inhibited by afferent activity from distended urinary bladder (5). It could explain, at least in part, low incidence of chest pain (0%), although marked decreased coronary flow was noted during urinary bladder distension.

The fourth limitation was poor sensitivity of the surface electrocardiography to detect myocardial ischemia during bladder distension. Sutton et al. (42) reported the electrical focus caused the S-T changes to be a localized area of myocardium and therefore may not be apparent on the leads of a surface electrocardiography. Besides, the relatively short bladder distension time may not produce ischemia sufficient to develop S-T-segment changes. We did not measure intracoronary ECG and regional wall motion abnormality assessed by echocardiography, which have been proved to be more sensitive for detecting myocardial ischemia (19). Thus, although the supplied flow was less than one-half of the metabolic flow demand as indicated by the decrease of coronary flow (29%) and concomitant increase of metabolic demand (42%) compared with predistension values, none of the patients in subgroup 1A demonstrated S-T changes on surface electrocardiograms.

The fifth limitation refers to the possibility that the \( \alpha \)-adrenergic antagonist used in this study provided an insufficient dose. However, this is unlikely, because the mean blood pressure reduction after complete blockade of the \( \alpha \)-adrenergic pressor effects was 13 mmHg reported by Guth et al. (21), which is similar to our result of 18 mmHg.

Finally, although previous studies have used \( \alpha_2 \)-adrenergic blockers to demonstrate the role of adrenergic receptors in mediating coronary vasoconstriction effects, we did not use these, which will increase circulating norepinephrine and myocardial oxygen consumption (30). Such adverse myocardial effects will increase the complexity of effects of \( \alpha_2 \)-adrenergic blockers on coronary vasomotor function.

**Clinical Implication**

Urinary bladder distension performed in this study constitutes a physiological form of stress and therefore may have relevance to the clinical setting. Coronary artery vasomotor may have a significant role in the pathogenesis of ischemic myocardial disease. During bladder distension the reflex coronary vasoconstriction would limit the expected coronary vasodilatation, which is secondary to the concomitant reflex increases in heart rate and arterial blood pressure. Traditionally, relation of bladder distension to myocardial ischemia has been related to increased systolic pressure \( \times \) heart rate (double product), an index of myocardial oxygen requirement. From this study another potentially important contributing mechanism is the reflex coronary vasoconstriction. Such vasoconstriction response of resistance vessels distal to the stenosis could further
limit the blood supply to the myocardium and contribute to myocardial ischemia during bladder distension. Smoking can lower the angina threshold and increase the frequency of ischemic events by coronary vasoconstriction in the settings of high circulating catecholamine such as urinary bladder distension. Besides, focal constriction of epicardial vessels in patients with early atherosclerosis could lead to coronary spasm and further vascular endothelial damage and predispose to plaque rupture. The study suggested that the \( \alpha_1 \)-adrenoceptor blockade is unique among drugs for obstructive coronary artery disease in having a beneficial effect on coronary blood flow in smokers.

Conclusions

The present study showed that urinary bladder distension reflexly caused an abnormal vasomotor response of epicardial vasoconstriction and a concomitant increased coronary resistance even in patients with early coronary atherosclerosis. The abnormal vasomotor responses during urinary bladder distension are exaggerated in smokers. The response involved efferent and/or afferent sympathetic mechanisms related to \( \alpha_1 \)-adrenoceptors. Pretreated administration of doxazosin had reversed the decreased coronary blood flow during bladder distension toward baseline.

We thank our colleagues in the catheterization laboratory for technical assistance.

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