Coronary Artery Constriction Caused by the Cold Pressor Test in Human Hypertension

Isabelle Antony, Eduardo Aptecar, Guy Lerebours, Alain Nitenberg

Abstract Hypertensive patients with angiographically normal coronary arteries may have myocardial ischemia when metabolic demand increases. Abnormal epicardial coronary artery vasomotion in response to sympathetic stimulation may contribute to ischemia in such patients. We studied the vasomotor response of smooth coronary arteries to a cold pressor test in 10 hypertensive patients without other risk factors and in 9 control subjects. Vessel dimensions were measured by quantitative angiography, and blood flow was calculated using an intracoronary Doppler catheter in the left anterior descending coronary artery. In response to cold pressor stimulation, arteries of control subjects dilated 13.0±5.9% (P<.001), and they constricted 8.2±8.5% in hypertensive patients (P<.001). Rate-pressure product increased from 9466±1677 to 12 547±2367 beats per minute (bpm) · mm Hg in control subjects (P<.001) and from 13 720±1823 to 17 353±2037 bpm · mm Hg in hypertensive patients (P<.001). Coronary blood flow velocity and blood flow increased 51±26% (P<.05) and 87±27% (P<.001), respectively, in control subjects and 86±52% (P<.05) and 36±33% (P<.01) in hypertensive patients. At peak cold pressor test, despite a significant higher rate-pressure product in hypertensive patients, blood flow was similar in both groups, suggesting an uncoupling between myocardial metabolic demand and supply. Thus, hypertension impairs the vasodilator response of angiographically normal coronary arteries to a cold pressor test. This abnormal response may be due to enhanced catecholamine reactivity and/or impairment of endothelial function.

Key Words • vasomotor system • sympathetic nervous system • hypertension • cold pressor test • coronary arteries

Angina-like chest pain or thallium defects consistent with myocardial ischemia can occur in patients with hypertension and angiographically normal coronary arteries.1,2 Abnormal maximal coronary vasodilator reserve1-3 and/or disturbances of coronary vasomotion4,5 may constitute mechanisms responsible for myocardial ischemia in these patients. The vascular endothelium, by releasing relaxing and constricting factors,6,7 and the sympathetic nervous system are major regulators of vascular tone. Furthermore, endothelium is a modulator of the contractile agonist effects of sympathetic activation. In experimental hypertension, morphological changes develop in arterial endothelial cells.8 In hypertensive rats, endothelial destruction is associated with increased constriction of large vessels in response to norepinephrine infusion.9,10 In isolated pig and dog coronary arteries, norepinephrine is a more powerful vasoconstrictor in the absence of endothelium.11 In hypertensive patients (HTN patients), impairment of endothelium-dependent dilation of coronary epicardial and resistance vessels has been evidenced.4,12 and increased reactivity of forearm vessels to sympathetic stimulation has been demonstrated.13,14

The aim of the present study was to assess the effects of sympathetic stimulation on vasomotion of epicardial coronary arteries in HTN patients with angiographically normal coronary arteries. We studied the response to a cold pressor test, which activates the sympathetic nervous system and induces dilation of angiographically normal coronary arteries in control subjects.15 We measured coronary artery diameters by quantitative angiography and used intracoronary Doppler to measure blood flow velocity.

Methods

Patient Selection

Ten HTN patients and 9 control normotensive subjects undergoing diagnostic coronary angiography for evaluation of chest pain were studied. Control subjects had a supine systolic blood pressure lower than 140 mm Hg and a diastolic blood pressure lower than 90 mm Hg. All HTN patients had a well-established history of elevated blood pressure higher than 140/90 mm Hg, with at least four sets of readings taken at 1-week intervals. Hypertension had been recently diagnosed in 6 patients, who had never been treated, and less than 1 year earlier in the 4 others, in whom antihypertensive therapy was discontinued at least 3 weeks before cardiac catheterization. Thallium stress tests showed reversible defects consistent with ischemia in 3 HTN patients and nonreversible defects in 4; tests were normal in 3 patients. Patients who had a history of smoking more than five cigarettes a day or diabetes mellitus and patients with hypercholesterolemia (total cholesterol serum level >5.70 mmol/L [220 mg/dL] or low-density lipoprotein [LDL] cholesterol >3.70 mmol/L [143 mg/dL]) were excluded. None of the patients had a family history of coronary artery disease. Left ventricular systolic function assessed by two-dimensional and M-mode echocardiography was normal in all control subjects and HTN patients. Left ventricular dimensions and septal and posterior wall thicknesses were

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Coronary angiograms were made at the peak of the cold pressor test. The patient's hands were immersed in water for 4 minutes after intracoronary infusion of 2 mg isosorbide dinitrate (ISDN) to obtain maximal epicardial coronary vasodilation. Serial injections of the left coronary artery with contrast medium were performed at intervals of at least 5 minutes to exclude contrast-induced coronary vasodilation. Intracoronary blood flow velocity was measured prior to the tip of the Doppler catheter just before each coronary angiogram to avoid the hyperemic effects of the contrast medium. Five minutes after intracoronary injection of ISDN, coronary reserve was evaluated by injection of 10 mg papaverine hydrochloride through the proximal lumen of the coronary Doppler catheter (8 mg papaverine/mL, 0.9% saline). Coronary flow reserve was calculated as the ratio of peak blood flow velocity (maximum kilohertz shift after papaverine) to resting blood flow velocity (average of two successive measures, the second of which was performed after return to baseline coronary flow velocity).

**Quantitative Coronary Arteriography**

Left coronary arteriograms were obtained by electrocardiogram-triggered digital subtraction at a rate of six frames per second on a 512-pixel matrix (General Electric CGR DG 300). The angiographic system was set up in the right anterior oblique position with adequate cranial or caudal angulation allowing optimal view of the CX, LAD 1, and LAD 2 segments on end-diastolic frames without overlap by side branches. Relations between focal spot, patient, and height of image tube were kept constant throughout the procedure.

The reliability and accuracy of the method have been previously established on seven empty catheters ranging from 3F to 9F whose outer diameters were accurately measured with a 0.01-mm micrometer as well as on nine calibrated contrast medium–filled catheters ranging from 1 to 5 mm inner diameter. A calibrated catheter filled with saline positioned close to the center of the image was used as a scaling device for calibration. The procedure began with the operator's choice of two points inside the catheter that limited the segment to be analyzed by automated border detection of the catheter. A monodimensional median filter was applied row by row to reduce noise without affecting the signal. All the pixels of the region of interest were taken into account to search the densitometric axis of the catheter between the two limiting points. This axis was defined as the continuous path between the two points and was searched row by row by dynamic programming. For detection of one of the segment edges, a monodimensional asymmetric linear combination was computed for each pixel of all successive half-rows starting at the axis level. The combination was a weighted sum of the current pixel and three neighboring pixels, which produced a maximal amplitude response at the actual edge of a semicircular profile blurred by a Gaussian point spread function. The whole segment border was defined as the continuous path connecting the two limiting points whose combination overall sum was maximal. It was also searched by dynamic programming. Diameters (in pixels) were measured perpendicularly to the center line. About three diameters were determined per coronary arteriogram to avoid the hyperemic effects of the contrast medium.

All geometric diameter measurements were corrected by a magnification factor taking into account the spread function blurring and image intensifier pincushion distortion. Mean, maximal, and minimal diameters and standard deviation were automatically computed along the selected segment and compared with the actual values using linear regression analysis. The accuracy of the technique was 3.6±0.5% (mean±SD) and the precision 2.4±0.5%. The maximal error between the actual and calculated diameters was equal to ±5.7% ($R^2 = 0.984$).

In this study, a segment of the guiding catheter positioned in the left main coronary artery and filled with saline was placed...
close to the center of the image and used as a scaling device for calibration before the procedure was begun. Six- to 10-mm-long segments of the LAD 1, LAD 2, and CX were analyzed as described above, and the mean diameter was calculated for each coronary segment from a series of diameter measurements (18 to 30). Each segment was defined with two anatomic references to reproducibly measure the same segment after each injection. Each angiogram was analyzed at random without knowledge of the sequence of the procedure (base 1, cold pressor test, base 2, and ISDN). All diameter measurements were corrected by a magnification factor taking into account the distance of the segment from the center of the image. A change in vessel diameter was defined as a minimum 6% variation, which corresponded to the highest error reported using the quantitative angiography validation technique (5.7%).

Estimates of Coronary Blood Flow Changes

Blood flow in LAD 2 (F) was calculated from measurements of mean coronary flow velocity in LAD 2 (v) and LAD 2 cross-sectional area (CSA): \( F = v \times CSA \). The cross-sectional area was calculated from measurements of LAD 2 diameter (d) assuming a circular model: \( CSA = \pi d^2/4 \).

Statistical Analysis

All data are expressed as mean±SD. Differences between the two patient groups for clinical and biological characteristics, basal hemodynamic and echocardiographic parameters, and coronary reserve were compared by the nonparametric Mann-Whitney test. Statistical comparisons of hemodynamic parameters, coronary vessel diameters, and coronary velocity and flow under control, peak cold pressor test, recontrol, and post-ISDN conditions were made using two-way ANOVA with repeated measures for experimental condition factor, followed by the Fisher protected least significant difference test. Statistical significance was assumed if the null hypothesis could be rejected at the .05 probability level.

Results

Patient Characteristics

The Table shows patient characteristics. The mean ages of normotensive control subjects and HTN patients were comparable. On the basis of selection, mean aortic pressure was significantly higher in HTN patients (\( P<.001 \)) when resting heart rate was similar in the two groups. The total cholesterol serum levels and high density lipoprotein and LDL fractions were not statistically different in normotensive control subjects and HTN patients. One control subject was included in the study despite a slightly increased serum LDL cholesterol level (3.85 mmol/L [149 mg/dL]). The two groups were similar with respect to left ventricular end-diastolic diameter and fractional shortening. Septal thickness was slightly higher in HTN patients than in control subjects (\( P<.05 \)), and posterior wall thickness was comparable in the two groups. Left ventricular mass index was comparable in the two groups and was within 2 SD above the mean value reported previously for a healthy population in all control subjects and in seven HTN patients. It was slightly elevated in two HTN women and one HTN man.

Hemodynamic Effects of the Cold Pressor Test and Intracoronary ISDN Infusion

During the cold pressor test, heart rate and aortic pressures increased in control subjects and HTN patients (Fig 2). In control subjects, heart rate and systolic blood pressure significantly increased from 74±10 to 80±11 beats per minute and from 127±9 to 156±17 mm Hg, respectively. In HTN patients, heart rate and systolic blood pressure significantly rose from 78±10 to 85±8 beats per minute and from 176±9 to 203±15 mm Hg, respectively.

In both control and HTN groups, heart rate and aortic pressure values recorded after the recovery period (base 2) were comparable to those obtained at base 1 (Fig 2). After ISDN infusion, heart rate significantly increased in both groups, and aortic pressures significantly fell.

Vasomotor Responses of Epicardial Coronary Arteries to the Cold Pressor Test and Intracoronary ISDN Infusion

Twenty-seven and 30 segments of angiographically normal coronary arteries were analyzed, respectively, in normotensive subjects and HTN patients. Mean basal diameters of LAD 1, LAD 2, and CX were comparable in the two groups (Fig 3).

In control subjects, cold pressor stimulation caused dilation of all 27 segments studied (Fig 4). Mean vessel diameter of LAD 1, LAD 2, and CX significantly increased from 3.57±0.88 to 3.95±0.93 mm, from 2.60±0.50 to 2.95±0.48 mm, and from 2.91±0.52 to 3.31±0.61 mm, respectively (\( P<.001 \) for all). The mean base 1 vessel diameter for all segments increased 13.0±5.9%, from 3.03±0.75 to 3.40±0.79 mm (\( P<.001 \))

In HTN patients, no segment dilated in response to the cold pressor test. Nineteen segments constricted, and 11 segments did not change according to the change in vessel diameter defined in "Methods" (Fig 4). Mean vessel diameter of LAD 1 and LAD 2 significantly decreased from 3.71±0.53 to 3.32±0.55 mm and from 2.42±0.60 to

Clinical Characteristics of Control Subjects and Hypertensive Patients

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HR indicates heart rate; MAP, mean aortic pressure; t-Chol, total cholesterol serum level; HDL-C, high-density lipoprotein cholesterol serum level; LDL-C, low-density lipoprotein cholesterol serum level; LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening; ST, septal thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; and CFR, coronary reserve. Values are mean±SD. Probability values are for comparison with control group.
Fig 2. Line graphs show changes in heart rate, systolic pressure, and mean aortic pressure in control subjects and hypertensive patients (mean±SD). In both groups, significant changes were observed during cold pressor test (CPT) and after intracoronary isosorbide dinitrate (ISDN). Probability values are given for comparison with base 1.

2.21±0.56 mm, respectively (P<.001 and P<.01, respectively). No significant variation was observed in mean vessel diameter of the CX (2.59±0.75 to 2.44±0.70 mm). For all segments, a significant 8.2±8.5% decrease in mean base 1 vessel diameter was observed, from 2.91±0.84 to 2.66±0.76 mm. No coronary artery spasm was induced by the cold pressor test.

At base 2, mean vessel diameter for all segments was comparable to that of base 1 in both groups (Fig 4).

Fig 3. Bar graphs show coronary segment diameters (mean±SD) measured at base 1 and after intracoronary isosorbide dinitrate (ISDN) in both groups. No significant differences were observed between the two patient groups. LAD indicates left anterior descending coronary artery; CX, proximal circumflex artery.

In normotensive subjects, all 27 segments dilated in response to ISDN infusion (Fig 4). Mean vessel diameter of LAD 1, LAD 2, and CX significantly increased from 3.56±0.79 to 4.57±0.91 mm, from 2.61±0.50 to 3.42±0.57 mm, and from 2.87±0.52 to 3.77±0.60 mm, respectively (all P<.001), representing a 30.9±13.1% total mean increase (P<.001) (Fig 4). In HTN patients, all 30 segments also significantly dilated (Fig 4). Mean vessel diameter of LAD 1, LAD 2, and CX significantly increased from 3.63±0.53 to 4.53±0.67 mm, from 2.39±0.61 to 3.07±0.65 mm, and from 2.61±0.72 to 3.33±0.99 mm, respectively (all P<.001). The mean increase in vessel diameter was 26.6±12.6% for all segments (P<.001) and was comparable to that observed in the normotensive control group, demonstrating a similar vasodilative capability. After ISDN infusion, actual diameters of LAD 1, LAD 2, and CX were similar in the two groups.

Coronary Blood Flow Study

Coronary flow reserve was defined as normal when the mean coronary flow velocity after papaverine was at least 3.6 times the baseline flow velocity. The coronary flow reserve was normal in all control subjects and in eight HTN patients and was slightly reduced in two HTN patients. However, the mean value of coronary flow reserve was significantly lower in HTN patients than in normotensive subjects (P<.05) (Table).

Estimates of blood flow in LAD 2 (Fig 5) were calculated at base 1, during the cold pressor test, at base 2, and after ISDN infusion in all patients. At base 1, the
Discussion

This study demonstrates abnormal vasomotion in recently diagnosed HTN patients with angiographically normal large conduit coronary arteries, which constricted in response to cold pressor stimulation but dilated in normotensive control subjects. In contrast, coronary arteries of HTN patients kept their ability to dilate in response to the endothelium-independent vasodilator ISDN.

Cold Pressor Test in Normotensive Subjects and Hypertensive Patients

Although some studies have reported that cold pressor stimulation induced constriction of normal coronary arteries, the control subjects were not selected to have completely smooth coronary arteries without intraluminal irregularities. It has since been demonstrated that the cold pressor test dilates the epicardial coronary arteries in the absence of stenosis or luminal irregularities. Conversely, coronary atherosclerosis is associated with coronary constriction during cold pressor stimulation. The magnitude of dilation we observed in the coronary arteries of normotensive subjects was comparable to that reported in other studies. Conversely, in HTN patients, cold pressor stimulation induced constriction of epicardial coronary arteries early in the course of hypertension. The duration of hypertension was short in all patients studied. Among them, 7 had a normal left ventricular mass and 3 had minimal left ventricular hypertrophy; coronary flow reserve was preserved in 8 HTN patients and slightly reduced in 2.

Mechanisms of Dilation of Normal Coronary Arteries in Response to the Cold Pressor Test

Cold pressor stimulation induces sympathetic release of norepinephrine and epinephrine, which evokes an increase in heart rate, arterial blood pressure, and myocardial oxygen demand. This increase in myocardial metabolic demand has been shown to cause an increase in coronary blood flow and to dilate epicardial coronary arteries, despite the α-mediated coronary constriction induced by sympathetic stimulation. The endothelium modulates coronary vasomotion, facilitating vasodilation of resistance vessels and flow-dependent dilation in large vessels, the overall effect being a dilation of large coronary arteries in healthy subjects.

Mechanisms of Constriction of Angiographically Normal Coronary Arteries in Response to the Cold Pressor Test in Patients With Hypertension

Sympathetic-Mediated Vasomotion

The constriction of coronary arteries we observed in HTN patients in response to the cold pressor test may be due to an exaggerated response to sympathetic α-mediated stimulation that may restrain coronary vasodilation that occurs in response to increased myocardial metabolic demand. Indeed, epicardial coronary arteries are innervated with sympathetic nerve fibers and have α1- and α2-adrenergic receptors. Baran et al demonstrated in dogs that epicardial coronary arteries dilated further during exercise after intracoronary infusion of an α2-adrenergic blocking agent, suggesting an α1-adrenergic vasoconstriction that limits coronary va-
sodilation. A role for postsynaptic $\alpha_2$-adrenergic coronary vasoconstriction during exercise has not been documented. Increased sympathetic nerve activity occurs in some patients with essential hypertension. Furthermore, an enhanced reactivity of forearm vessels to intra-arterial norepinephrine has been evidenced in HTN patients. This increase in vascular reactivity may be the consequence of vascular structural changes. Human postmortem studies of HTN patients documented wall thickening in large arteries. The recent in vivo study of Gariepy et al showed carotid and femoral artery diameters similar to those of normotensive subjects and associated with wall thickening, providing evidence for vascular growth. Although the lumen diameters of coronary arteries we measured by quantitative angiography were comparable to those of control subjects, we were not able to assess the wall thickness and determine whether vascular growth or remodeling had developed.

Although it has been shown that stimulation of $\beta$-adrenergic receptors dilated large coronary arteries in conscious animals, Zeiler et al demonstrated that it is not an important determinant of the coronary vasomotor response during cold pressor stimulation.

**Endothelial-Mediated Vasomotion**

The resistance of coronary arteries to relax in response to cold pressor stimulation demonstrated in HTN patients could also be caused by impaired endothelium cell function so that flow-dependent dilation is blunted and unmasks adrenergic vasoconstriction. Increased in flow through arteries induces dilation. Flow-dependent vasodilation has been shown in normal human coronary arteries. Flow-mediated vasodilation is endothelium dependent, leading to the release of an endothelium-derived relaxing factor (EDRF), nitric oxide. In the present study, despite an increase in coronary blood flow secondary to the increase in myocardial metabolic demand evoked by the cold pressor test, we did not observe any dilation of the coronary arteries in HTN patients, suggesting an impaired flow-induced vasodilation. Impaired endothelium-dependent dilation of the forearm vasculature has been demonstrated in HTN patients (assessed by the responses to acetylcholine, an endothelium-dependent vasodilator), related to decreased EDRF release. Abnormal endothelium-dependent coronary vasomotor response to acetylcholine was also demonstrated in both large conduit and resistance vessels. In addition, although at the peak of cold pressor stimulation the rate-pressure product was significantly higher in HTN patients, coronary blood flow was similar in the two groups. The failure of coronary blood flow to adequately increase may suggest either endothelial dysfunction or exaggerated sympathetic constriction at the level of resistance vessels, leading to uncoupling between increased metabolic demand and coronary flow.

**Endothelial Modulation of Sympathetic Stimulation**

The importance of the endothelium-mediated vasodilator function when the sympathetic nervous system is activated has been evidenced in both experimental studies and humans. Endothelium removal enhances the constrictor response to catecholamines in rat arteries. $\alpha_2$-Adrenergic activation is potentiated by inhibition of nitric oxide synthesis in dog and human large and resistance coronary arteries. In humans, the coronary vasomotion induced by the cold pressor test has been shown to be related to the integrity of endothelial function, and coronary segments showing endothelial dysfunction were hypersensitive to constrictor effects of catecholamines. The modulation role of the endothelium on sympathetic activity may partly be due to the release of EDRF secondary to the stimulation of $\alpha_2$-adrenergic receptors located on endothelial cells. Sympathetic stimulation of platelet $\alpha_2$-adrenergic receptors also induces the release of vasoconstrictors, serotonin, histamine, and thromboxane A$_2$. The response to serotonin depends on the integrity of the endothelium, mediating dilation in coronary arteries when the endothelium is healthy and constriction when endothelial dysfunction is present secondary to atherosclerosis.

It has also been demonstrated that serotonin decreases coronary blood flow in spontaneously hypertensive rats, an effect that is inhibited by indomethacin, suggesting the release of a cyclooxygenase-dependent, contracting factor, which may be prostaglandin E$_2$. This may explain the increased sensitivity of coronary resistance vessels to ergonovine, reported in hypertensive humans, because ergonovine is a serotonin receptor agonist. Endothelin may also take part in the pathogenesis of the coronary constriction observed in the present study, by sensitizing the coronary vasculature to sympathetic vasoconstrictor stimuli. The endothelin production could be augmented by shear stress or by reduced local formation of EDRF.

**Study Limitations**

Although hypertension is a risk factor for atherosclerosis, the HTN patients we studied had no other risk factors or angiographic sign of atherosclerosis elsewhere in the coronary vasculature. However, intravascular ultrasound studies have shown that despite angiographically normal-appearing vessels, early coronary atherosclerosis can be present, and we cannot absolutely exclude angiographically undetectable atherosclerosis; however, it is unlikely that early atherosclerosis can completely explain the coronary constriction caused in HTN patients.

The method of quantification of coronary artery diameters assumes that the reference catheter (the segment of the guiding catheter near the coronary ostium) and vessel segments were located in the same plane parallel to the detector. This assumption may not be absolutely true. It has also been assumed that the section of the LAD 2 was circular. However, these points could have influenced only the absolute values of coronary blood flow and not the relative variations of coronary artery dimensions used in this study.

In this study, it is suggested that there was an inappropriate increase in coronary blood flow with regard to the increase in myocardial metabolic demand in HTN patients. However, the rate-pressure product is a rather rough estimate of myocardial oxygen demand, and coronary arteriovenous oxygen difference measurements should have been a better indicator of a mismatch between the increase in oxygen demand and flow. Coronary sinus catheterization was not used because of
ethical considerations. Also, simultaneous measurements of aortic and coronary sinus norepinephrine concentrations could have assessed whether increased norepinephrine release has a role in the abnormal coronary constriction secondary to a cold pressor test.

Last, the use of a crystal end-mounted catheter with a zero-crossing detector Doppler velocimeter might not have provided accurate measurements of coronary flow velocity. However, this limitation has been raised for measurements of flow velocity in stenosed coronary arteries. In addition, it has been demonstrated that velocities recorded simultaneously by the former method and by a spectral Doppler guidewire technique were not significantly different. Thus, the major results of our study should be valid.

Clinical Implications

Atherosclerotic coronary arteries constrict during common activities of daily life that stimulate the sympathetic nervous system, such as exercise, cold exposure, and mental stress. This abnormal vasoconstriction of coronary arteries may facilitate myocardial ischemia. In the present study, the decrease in coronary diameter observed during sympathetic stimulation (−8.2%) is quite substantial. By reducing the conductance of epicardial vessels, it may contribute, when the myocardial metabolic demand increases, to the myocardial ischemia reported in HTN patients with angiographically normal coronary arteries. This mechanism may further reduce the coronary flow reserve in the presence of coronary stenosis. Moreover, an inadequate increase in coronary flow during the cold pressor test, indicative of disturbances at the level of the resistance vessels, may also participate in the mismatch between myocardial metabolic demand and supply.

Conclusions

This study demonstrates that angiographically normal epicardial coronary arteries constricted in response to the cold pressor test in patients with hypertension and no other coronary risk factors. This abnormal coronary vasomotion occurs early in the course of hypertension and may have important implications regarding the myocardial perfusion abnormalities reported in HTN patients. However, the present study does not provide any direct information about the determinants of the abnormal response to the cold pressor test in HTN patients, and further investigations should be undertaken to elucidate the mechanisms involved.

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Coronary artery constriction caused by the cold pressor test in human hypertension.
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