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Effect of Increases in Heart Rate and Arterial Pressure on Coronary Flow Reserve in Humans

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Objectives. The objective of this study was to determine the effect of increases in heart rate and arterial pressure on maximal pharmacologic coronary blood flow reserve.

Background. Coronary flow reserve measurements are useful in assessment of the physiologic significance of coronary lesions. However, animal studies suggest that alterations in hemodynamic status may influence coronary flow reserve independent of coronary stenosis.

Methods. Coronary flow reserve was measured during cardiac catheterization with the use of a 3F coronary Doppler catheter and intracoronary papaverine. Flow reserve was measured under control conditions and during increases in heart rate produced by atrial pacing (18 patients) or during elevation of arterial pressure by intravenous phenylephrine infusion (9 patients) with intracoronary alpha-adrenergic blockade by phentolamine.

Results. Coronary flow reserve progressively decreased from 3.7 ± 0.9 (mean ± SD) at the rate of 71 ± 8 beats/min at rest to 3.0 ± 0.6 during pacing at 100 beats/min and to 2.6 ± 0.5 during pacing at 120 beats/min. Flow reserve decreased because of a progressive increase in rest coronary flow velocity during pacing (122 ± 16% of control value at 100 beats/min, 139 ± 16% of control value at 120 beats/min), whereas papaverine hyperemia peak velocity remained unchanged. Flow reserve decreased with pacing tachycardia whether the initial flow reserve was normal or depressed. Mean arterial pressure increased from 95 ± 12 mm Hg to 130 ± 8 mm Hg during intravenous phenylephrine infusion and to 123 ± 10 mm Hg during combined intravenous phenylephrine and intracoronary phentolamine infusions. Coronary flow reserve was not affected by the blood pressure increases (control value 4.3 ± 1.0, phenylephrine 4.4 ± 1.5, phenylephrine and phentolamine 4.4 ± 2.0).

Conclusions. Sudden increases in heart rate but not mean arterial pressure lead to a substantial reduction in maximal coronary blood flow reserve. These data suggest that the diagnostic utility of all flow reserve measurement techniques might be improved by standardization of heart rate during measurement or extrapolation of the measured flow reserve to that expected at a reference heart rate.

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The measurement of coronary blood flow reserve using maximal pharmacologic vasodilation has been employed to assess the physiologic significance of coronary stenoses (1), as well as evaluate the results of coronary angioplasty (2) and coronary bypass surgery (3). A limitation to the use of coronary flow reserve in these settings is that factors altering rest or maximal coronary flow independent of coronary stenosis may affect measured flow reserve (4–6). Hemodynamic status (heart rate [7,8], arterial pressure [9–11] contractility [12] and preload [13]), left ventricular hypertrophy (14), myocardial infarction (15) and pharmacologic agents (16) have been demonstrated to influence indexes of coronary flow reserve in animals.

Coronary flow reserve measurement in awake humans during cardiac catheterization with the use of a coronary Doppler catheter was pioneered by Wilson and associates (17,18). These investigators studied the effect of changes in heart rate and arterial pressure on coronary flow reserve in cardiac transplant recipients (19). Coronary flow reserve was reduced during pacing tachycardia but was unaffected by elevation in arterial pressure produced by isometric handgrip.

The applicability of these studies performed in patients with transplanted and largely uninervated hearts to other patients is uncertain. Significant alpha-adrenergic neural influences on the coronary reactive hyperemia response have been observed in animal studies (20). A number of morphologic and physiologic aonormalities are uniquely present in transplanted hearts. Cardiac allograft vasculopathy, a pervasive problem after transplantation, involves the small coronary arteries and arterioles, as well as large epicardial vessels. Coronary intimal proliferation is uniformly detectable by intravascular ultrasound 1 year after transplantation and may be severe when coronary arteries are angiographically normal (21). Graft rejection results in impairment of large artery and resistance vessel dilator

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responses (22,23). Endothelium-dependent coronary vasodilation, as assessed by acetylcholine infusion, is impaired in transplanted hearts (24) and sensitivity to beta-adrenergic agonists is increased (25). The current study was performed to assess the influence of increases in heart rate and arterial pressure on coronary flow reserve in patients who were routinely referred for diagnostic cardiac catheterization and were free of these potentially confounding factors.

Methods

Study group. Patients undergoing elective coronary arteriography for the evaluation of chest pain were considered for study if angiography revealed a nonstenotic coronary artery that was anatomically suitable for placement of a coronary Doppler catheter and there was no evidence of left ventricular dysfunction. The study group consisted of 20 men and 7 women with a mean age of 51 ± 11 years. Single-vessel coronary disease (diameter stenosis >50%) was present in two patients and two-vessel disease in one patient. The left anterior descending coronary artery was studied in 17 patients and the left circumflex coronary artery in 10. The research protocol was approved by the University of Iowa Institutional Review Board, and written informed consent for the research protocol was obtained from each subject before cardiac catheterization.

Coronary flow reserve measurement. A 7F or 8F coronary angioplasty guiding catheter was positioned at the coronary ostium, and a 0.014-in. (0.036 cm) coronary angioplasty guide wire was advanced into the coronary artery to be studied. A 3F 20-MHz coronary Doppler catheter (NuMed) was advanced over the guide wire into the proximal vessel and positioned to obtain a high quality phasic signal of blood flow velocity. The pulsed Doppler meter (Bioengineering Department, University of Iowa Hospitals and Clinics) was range-gated to maximize the amplitude of the mean coronary blood flow velocity signal. Phasic and mean coronary blood flow velocity (kHz shift), mean arterial pressure obtained from the guiding catheter, heart rate and the electrocardiogram (ECG) were continuously recorded on a multichannel recorder. After measurement of coronary blood flow velocity at rest, a bolus dose of 6 to 10 mg of papaverine hydrochloride (2 mg/ml of 0.9% saline solution) was injected through the guiding catheter into the coronary ostium, and the resultant increase in coronary blood flow velocity was recorded. To confirm that a dose of papaverine produced maximal hyperemia, coronary blood flow velocity was recorded during administration of an additional papaverine dose 2 to 4 mg larger than the prior dose. Flow velocity was allowed to return to baseline levels between doses of papaverine. Coronary flow reserve was calculated as the quotient of the peak mean flow velocity (kHz shift) after intracoronary papaverine and the rest mean flow velocity during the 15 to 30 s preceding papaverine administration. Coronary flow reserve measurement was repeated after hemodynamic interventions using the largest dose of intracoronary papaverine administered during baseline coronary flow reserve measurement.

Experimental protocol. Subjects were brought to the cardiac catheterization laboratory in a fasting state. Prescribed medications were continued on the day of the research study. Diazepam (5 to 10 mg intravenously or orally) was given for sedation. No subject received atropine premedication. The study was performed during intravenous infusion of nitroglycerin at 8 μg/min to avoid catheter-induced coronary artery spasm and obviate papaverine-induced dilation of the proximal coronary artery, which would influence the relation between changes in coronary flow velocity and coronary blood flow.

Alteration in heart rate. The effect of increases in heart rate on coronary flow reserve was assessed in 18 patients. A 6F bipolar pacemaker was positioned at the high right atrium. After measurement of coronary flow reserve and arterial pressure during sinus rhythm, these variables were remeasured after 2 min of atrial pacing at 120 beats/min in nine patients and after pacing at 100 and 120 beats/min in nine patients.

Alteration in arterial pressure. The effect of increases in arterial pressure on coronary flow reserve was assessed in nine patients. A 6F bipolar pacemaker was positioned in the high right atrium, and pacing was performed at 5 to 10 beats/min above the rest sinus rate to prevent reflex cardiac slowing during elevation of arterial pressure. Coronary flow reserve and arterial pressure were measured under control conditions and after elevation in blood pressure by intravenous infusion of phenylephrine. Phenylephrine was infused at an initial rate of 20 μg/min and adjusted upward over a period of 5 to 10 min to produce a target increase in mean arterial pressure of 30 mm Hg. In animal experiments assessing the effect of increased arterial pressure on coronary flow reserve, a smaller increase in coronary flow during maximal vasodilation was observed when arterial pressure was increased with methoxamine compared with aortic constriction (10). To minimize any limitation to coronary flow resulting from direct effects of alpha-adrenoceptor stimulation on the coronary circulation, measurements were repeated in seven patients after regional alpha-adrenergic blockade with intracoronary phentolamine, 1 to 2 mg given over 3 min while phenylephrine was continued.

Data analysis. Data are expressed as mean value ± SD. Study variables before and after interventions were compared by using a two-way analysis of variance for repeated measures with assessment of intergroup differences by Scheffé F test or the Student *t* test for paired measurements. Statistical significance was assumed at $p < 0.05$.

Results

Effect of increases in heart rate on coronary flow reserve. *Systemic hemodynamics.* The control heart rate averaged 71 ± 8 beats/min in the patients who underwent coronary flow reserve measurement during sinus rhythm and at paced

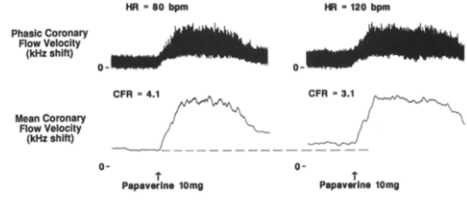


Figure 1. Recording of phasic and mean coronary blood flow velocity during measurement of coronary blood flow reserve (CFR) in sinus rhythm at a heart rate (HR) of 80 beats/min (bpm) and with atrial pacing at 120 beats/min. Coronary flow reserve was reduced during pacing tachycardia because of an increase in coronary flow velocity at rest, whereas papaverine hyperemia peak flow velocity was unchanged.

rates of 100 and 120 beats/min (n = 9). Mean arterial pressure was not affected by atrial pacing (97 ± 13 mm Hg at the control heart rate, 100 ± 14 mm Hg at 100 beats/min and 99 ± 14 mm Hg at 120 beats/min). The product of heart rate and mean arterial pressure (rate–mean pressure product) increased by 46 ± 21% and 74 ± 22% over the control value during pacing at 100 and 120 beats/min, respectively.

Coronary flow reserve. A representative recording of coronary blood flow velocity during measurement of coronary flow reserve under control conditions and during atrial pacing is shown in Figure 1. Coronary flow reserve decreased from 3.7 ± 0.9 at the control heart rate to 3.0 ± 0.6 during pacing at 100 beats/min ($p < 0.01$ vs. control value) and to 2.6 ± 0.5 during pacing at 120 beats/min ($p < 0.01$ vs. control value, Fig. 2). The decrease in coronary flow reserve resulted from an increase in coronary flow velocity at rest with increased heart rate. Coronary flow velocity at rest increased to 122 ± 16% of the control value at 100 beats/min ($p < 0.05$ vs. control) and to 139 ± 16% of the control value at 120 beats/min ($p < 0.001$ vs. control, $p < 0.05$ vs. 100 beats/min). Peak flow velocity with papaverine maximal hyperemia during atrial pacing was unchanged from the peak flow velocity under control conditions (Fig. 3). The control coronary flow reserve value was used to separate the patients who were studied during sinus rhythm and at the paced rates of 120 beats/min (n = 18) into two groups. Group 1 had flow reserve values within the normal range (18) (papaverine peak/rest velocity ratio >3.5), and Group 2 patients had depressed flow reserve. Coronary flow reserve decreased during atrial pacing in both Group 1 (4.5 ± 0.4 at baseline vs. 3.3 ± 0.4 at 120 beats/min, $p < 0.001$) and Group 2 (3.0 ± 0.3 at baseline vs. 2.5 ± 0.3 at 120 beats/min, $p < 0.001$, Fig. 4). The magnitude of reduction in coronary flow reserve tended to be greater in Group 1 than in Group 2 (−27 ± 10% vs. −17 ± 10%, $p = 0.05$).

Effect of increase in arterial pressure on coronary flow reserve. *Systemic hemodynamics.* Heart rate was maintained at 81 ± 12 beats/min by atrial pacing throughout the study. During infusion of phenylephrine (average dose 101 ± 53 μg/min), mean arterial pressure increased from 95 ± 12 mm Hg to 130 ± 8 mm Hg ($p < 0.01$ vs. control value, Fig. 5), and the rate-pressure product increased by 38 ± 10%. After intracoronary phentolamine (average dose 1.4 ± 0.5 mg, n = 7) was administered during the intravenous phenylephrine infusion, mean arterial pressure remained elevated at 123 ± 10 mm Hg ($p < 0.01$ vs. control value, p = NS vs. phenylephrine alone).

Coronary flow reserve. Coronary flow reserve averaged 4.3 ± 1.0 under control conditions. Flow reserve was unchanged during elevation of arterial pressure with intravenous phenylephrine (4.4 ± 1.5) and after intracoronary phentolamine during phenylephrine infusion (4.4 ± 2.0, Fig.

Figure 2. Effect of progressive increases in heart rate produced by atrial pacing on coronary flow reserve. bpm = beats per minute.

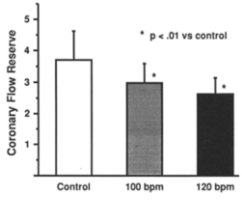
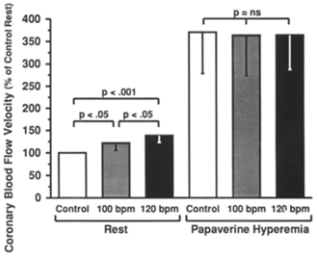


Figure 3. Effect of progressive increases in heart rate produced by atrial pacing on coronary blood flow velocity at rest and during papaverine-induced maximal hyperemia. Coronary blood flow velocity values are normalized to the control rest velocity. bpm = beats per minute.



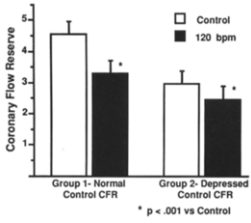


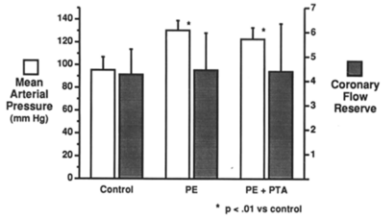
Figure 4. Effect of atrial pacing tachycardia on coronary flow reserve (CFR) in patients with normal control flow reserve (Group 1) and depressed control flow reserve (Group 2). Abbreviations as in Figure 1.

5). Both rest and papaverine maximal hyperemia coronary blood flow velocities tended to increase during elevation of arterial pressure (Fig. 6), but these values were not significantly different from the respective control values.

Discussion

Assessment of coronary flow reserve can provide clinically useful information in patients with known or suspected ischemic heart disease. However, as recently emphasized by Klocke (4) and Hoffman (6), interpretation of flow reserve measurements in individual patients is complicated by the fact that changes in flow reserve can be produced by several factors that alter rest or maximal coronary flow, including hemodynamic variables, left ventricular hypertrophy, myocardial infarction and microvascular disease. Because the most commonly used catheter-based methods for assessing coronary flow reserve, the coronary Doppler catheter and digital videodensitometry, measure *changes* in coronary flow, not *absolute* volumetric flow, it is impossible to determine with these techniques whether a reduction in coronary

Figure 5. Effect of intravenous phenylephrine (PE) infusion and phenylephrine combined with intracoronary phentolamine (PTA) on mean arterial pressure (left axis) and coronary flow reserve (right axis).



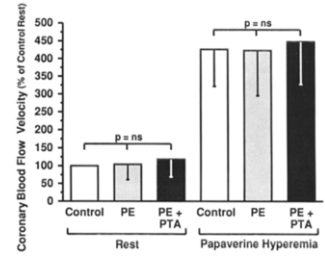


Figure 6. Effect of increases in arterial pressure produced by intravenous phenylephrine (PE) infusion and phenylephrine combined with intracoronary phentolamine (PTA) on coronary blood flow velocity at rest and during maximal papaverine-induced hyperemia. Coronary blood flow velocity values are normalized to the control rest velocity.

flow reserve represents a true limitation in maximal flow or an increase in rest flow.

In the present study we assessed the effect of increases in heart rate or arterial pressure on coronary flow reserve in conscious patients during cardiac catheterization. The hemodynamic interventions were relatively pure—mean arterial pressure was unchanged during heart rate increases and heart rate was held constant by atrial pacing during elevation of arterial pressure. Coronary flow reserve decreased progressively as heart rate was increased, and a significant reduction in flow reserve was observed with alterations in rate within the normal range. The reduction in coronary flow reserve during pacing was due entirely to an increase in coronary flow velocity at rest; maximal flow velocity was unchanged during pacing. In contrast, coronary flow reserve was not affected by elevations in arterial pressure that resulted in a similar increase in rate–mean pressure product observed during pacing. These findings are similar to those reported by McGinn et al. (19) in heart transplant recipients.

In that study, the increase in mean arterial pressure during isometric handgrip in transplant recipients was associated with an increase in both rest and hyperemic flow velocity. Because both velocities increased proportionally, coronary flow reserve was unchanged. In the present study there was no significant change in rest or maximal coronary flow velocity when arterial pressure was increased by phenylephrine.

There are several possible explanations for these findings. The dose of phentolamine used in the present study may have incompletely reversed adrenergically mediated coronary vasoconstriction that prevented the expected increase in coronary flow. An intracoronary dose of phentolamine of 2 to 3 mg has been shown to reverse exercise-induced coronary vasoconstriction (26), constriction of coronary resistance vessels by intracoronary phenylephrine (27) and

cocaine-induced epicardial vasoconstriction (28). In our study phentolamine was discontinued if arterial pressure began to decrease and the average dose was 1.4 ± 0.5 mg. We cannot exclude the possibility that a higher dose may have been necessary to completely reverse coronary vasoconstriction during phenylephrine infusion. In the study of McGinn et al. (19), performed in recipients of a denervated heart, circulating norepinephrine levels did not rise during isometric handgrip, and neither reflex nor humoral sympathetic vasoconstriction would be expected.

Enlargement of the coronary artery at the site of Doppler flow velocity measurement during phenylephrine-induced hypertension may have resulted in an underestimation of changes in volumetric coronary blood flow by flow velocity measurements. If the 38% increase in arterial pressure during phenylephrine infusion caused just a 5% increase in coronary diameter, coronary blood flow could have increased by 10% with *no change* in flow velocity. In fact, cyclic changes in coronary diameter of 5% to 10% occur with phasic changes in aortic pressure during the cardiac cycle (29,30). It is possible that smaller changes in arterial caliber during blood pressure elevation occurred in the transplant recipients studied by McGinn et al. (19) because of decreased arterial compliance related to the intimal thickening that accompanies cardiac allograft vasculopathy.

Limitations of the study. The present study has several limitations. 1) The elevations in heart rate and arterial pressure were brief in duration. More sustained alterations in these variables could produce different effects on coronary flow reserve. For example, chronic systemic hypertension can result in left ventricular hypertrophy and coronary arteriolar changes, or both, that reduce coronary flow reserve (31). 2) Changes in rest heart rate or arterial pressure caused by the direct and reflex effects of cardiac medications might influence coronary flow reserve to a greater or lesser degree than changes due to atrial pacing or phenylephrine. For example, antianginal agents with negative inotropic effects could lower myocardial oxygen demand, with a resultant reduction in flow at rest, and could decrease transmural compressive forces with a consequent increase in maximal hyperemic flow. The quantitative effect of these influences on coronary flow reserve at any given heart rate is unknown. 3) The highest arterial pressure achieved with phenylephrine infusion (130 ± 8 mm Hg) is still within the range of autoregulation; greater elevations may have a different effect on coronary flow reserve. When the upper limit of autoregulation is exceeded in dogs, flow at rest increases more than maximal flow and flow reserve begins to decrease (10). 4) We cannot predict from our study the quantitative effect of *reductions* in heart rate or arterial pressure on flow reserve.

Implications. Our findings and those of McGinn et al. (19) indicate that the "normal" range of coronary flow reserve will vary, depending on the heart rate at the time of flow reserve measurement. McGinn et al. (19) suggested measuring flow reserve at a paced rate of 100 beats/min to eliminate this source of variability. When flow reserve is measured by noninvasive techniques, such as positron emission tomography, control of heart rate is less feasible. Extrapolation of the measured flow reserve to that expected at a standardized heart rate might improve the usefulness of these measurements. Even if the effect of heart rate could be eliminated or corrected, the influence of other hemodynamic factors such as contractility (12) and preload (13,19) on coronary flow reserve would still limit the interpretation of flow reserve measurements in individual patients. With further advances in technology, it may eventually be possible to measure indexes of coronary vascular reserve that are independent of hemodynamic variables (11).

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