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Coronary Blood Flow Reserve in Acute Aortic Regurgitation

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Objectives. **This study sought to determine the impact of acute aortic regurgitation on coronary blood flow reserve and phasic epicardial coronary blood flow in closed-chest dogs.**

Background. **Hemodynamic changes in acute aortic regurgitation are known to precipitate myocardial ischemia. Coronary blood flow reserve has not been studied in closed-chest experimental preparations with acute aortic regurgitation.**

Methods. **Graded temporary acute aortic regurgitation was produced in 11 mongrel dogs. Phasic coronary blood flow velocities were measured using a Doppler guide wire. Coronary flow reserve was defined as the ratio of the time average of spectral peak velocity after administration of papaverine to that of the baseline state.**

Results. **Under control conditions (mean [±SEM] diastolic blood pressure 82.2 ± 4.5 mm Hg), coronary flow reserve was 3.51 ± 0.27 with predominantly diastolic epicardial coronary blood flow. With mild acute aortic regurgitation (diastolic blood pressure 61.8 ± 3.0 mm Hg), coronary flow reserve decreased to 2.38 ± 0.27, with an increase in phasic systolic epicardial coronary blood flow. At the onset of moderate acute aortic regurgitation (diastolic blood pressure 42.1 ± 0.9 mm Hg), coronary flow reserve declined further to 1.46 ± 0.12, and the phasic systolic epicardial coronary blood flow became more prominent. With severe aortic regurgitation (diastolic blood pressure 29.2 ± 2.2 mm Hg), coronary flow reserve reached 1.20 ± 0.05, and the phasic epicardial coronary blood flow pattern was found to be predominantly systolic with retrograde diastolic flow. The ratio of diastolic to systolic pressure-time indexes with severe aortic regurgitation suggested subendocardial underperfusion.**

Conclusions. **This study demonstrates a marked decline in coronary blood flow reserve and documents a progressive change in the phasic epicardial blood flow to a predominantly systolic pattern with increasing degrees of acute aortic regurgitation.**

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Acute aortic regurgitation constitutes a true medical emergency. Arrhythmia and possibly sudden death, presumably related to myocardial ischemia, have been reported in patients with acute aortic regurgitation (1). Experimental studies have shown a slight increase in mean coronary blood flow per unit of weight of myocardium in dogs with acute aortic regurgitation (2). In view of the possibly increased mean coronary blood flow and in the absence of coronary artery disease, the mechanism of myocardial ischemia in this group of patients remains speculative.

Acute aortic regurgitation affects both myocardial oxygen supply and demand. Tachycardia and increased wall stress augment the metabolic requirements of the heart and baseline coronary blood flow. The increase in wall stress in acute aortic regurgitation is related to the elevation in left ventricular diastolic pressure and to the acute enlargement of the left ventricle (3). Concomitantly, the myocardial blood supply may be compromised because of reduced aortic root diastolic pressure and tachycardia. The interplay between these opposing forces may yield a smaller coronary blood flow reserve (defined as the ratio of maximal coronary blood flow to baseline blood flow) in acute aortic regurgitation.

Assessment of coronary blood flow reserve in closed-chest animal preparations of acute aortic regurgitation has been hampered because of methodologic limitations. Using a percutaneous approach for producing acute aortic regurgitation and a Doppler guidewire, we investigated the impact of graded temporary acute aortic regurgitation on coronary blood flow reserve and on phasic coronary blood flow in dogs.

Methods

Cage catheter device for producing acute aortic regurgitation. The device used for producing acute aortic regurgitation was a modification of the valve-spreading catheter reported by Spring and Rowe (4). It is composed of six struts of 0.127-mm stainless steel, 0.5 cm wide and 5 cm in length, glued on one end to the distal portion of a single-lumen woven Dacron 7F catheter and on the other end to a 1.5-mm needle shank. A smooth sphere was mounted permanently 2.5 cm from the distal tip of a removable core guide wire. The guide wire was then passed through the distal end of the struts and the catheter. Pulling the guide wire retracted the sphere against

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the needle shank and opened the cage. Markings on the distal end of the guide wire correlated with the extent of cage expansion and the severity of acute aortic regurgitation.

Pulsed-wave Doppler coronary guide wire. All velocity measurements were performed using a newly designed Doppler guide wire (Cardiometrics, Inc.). This device was constructed of a 150-cm, 0.018-in. flexible steerable guide wire with a 0.018-in. 12-MHz transducer mounted on its tip. A pulsed-wave Doppler velocimeter with a real-time spectral analysis system and a scrolling gray-scale display was used to compute instantaneous spectral peak velocities.

All data, including electrocardiogram and instantaneous pressure waveforms, were recorded along with simultaneous Doppler velocity data using a video recorder and video page printer. This Doppler guide wire system has been validated previously against an electromagnetic flowmeter both in vitro in a blood perfusion model and in vivo (5).

Animal experiment. Eleven healthy mongrel dogs (weight 18 to 28 kg) were anesthetized with sodium pentobarbital (20 mg/kg body weight) and intubated and ventilated with room air and oxygen (Harvard Apparatus). Fentanyl (0.05 mg/kg) and droperidol (0.5 mg/kg) were administered intramuscularly as premedications and every hour during the experiment to maintain anesthesia. Arterial blood gases were monitored intermittently to maintain pH between 7.25 and 7.40 and arterial partial pressure of oxygen >100 mm Hg. Introducer sheaths were placed percutaneously in the right and left femoral arteries. A 7F pigtail catheter was advanced into the left ventricle through the left femoral artery sheath for continuous monitoring of left ventricular pressure. An 8F guiding catheter was inserted fluoroscopically in the ostium of the left main coronary artery. A 3F infusion catheter was advanced through the guiding catheter into the left main coronary artery, and the guiding catheter was retracted from the coronary ostium. This infusion catheter was used for administration of papaverine. The pulsed Doppler coronary guide wire was steered through the 3F infusion catheter and guided fluoroscopically to an optimal position in the mid-left circumflex coronary artery. Electrocardiographic, femoral arterial pressure and left ventricular pressure tracings were recorded using a multichannel cardiac monitor/recorder (PPG Biomedical Systems). Phasic coronary blood flow velocity waveforms were recorded at baseline and after administration of 8 mg of intracoronary papaverine. The velocity waveforms at baseline and after the administration of papaverine were recorded twice for each grade of aortic regurgitation.

A 9F percutaneous sheath was inserted in the right common carotid artery, previously dissected free from the surrounding tissue. The removable core guide wire of the cage catheter was advanced fluoroscopically through the right common carotid artery sheath into the left ventricle. The cage catheter in the collapsed position was advanced over the guide wire into the left ventricle. The guide wire then was retracted, and the cage was opened to the desired degree. The position of the guide wire relative to the cage catheter was stabilized using a clamp. The complete apparatus was then pulled back into the aortic valve area to open the aortic valve cusps.

Three grades of acute aortic regurgitation were produced randomly based on the decrease in diastolic blood pressure (3). Each animal was allowed 5 min to achieve hemodynamic stability before hemodynamic and blood flow velocity measurements. The presence of aortic regurgitation was verified angiographically, without grading of valvular regurgitation, by injection of 4 to 5 ml of Renografin-76 (Squibb Diagnostics) in the ascending aorta. Aortic regurgitation was then reversed, and the animals were allowed ~20 min to stabilize at baseline hemodynamic function before the next measurement.

At the end of the experiment the animals were killed with an injection of potassium chloride. The heart was excised and examined for damage to the aorta, aortic valve, left ventricle and coronary arteries. The dogs used in this project were studied in accordance with the guidelines of "Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Council (Department of Health and Human Services publication no. [NIH] 85-23, revised 1985).

Data analysis. The spectral peak velocity waveforms for 2-s intervals were traced manually on a computer bit-pad. An average of eight 2-s intervals were analyzed for each set of hemodynamic conditions. A custom BASIC computer program calculated several parameters using the areas under the spectral peak velocity curves and the time base of these measurements. The calculated variables were time average of spectral peak velocity, time average of diastolic peak velocity and time average of systolic peak velocity. Diastole was defined as the beginning of the aortic dicrotic notch to the systolic aortic upstroke. Positive and negative peak velocity curves were traced separately.

The time average of spectral peak velocity is linearly related to the coronary blood flow rate in both an in vitro blood perfusion model and an animal model of coronary artery flow (r^2 = 0.93 to 0.99) (5). The ratio of time average of spectral peak velocity after administration of papaverine to that of the baseline state can therefore be used to estimate coronary blood flow reserve, provided vessel size remains unchanged. Intracoronary injection of papaverine has been shown not to affect vessel diameter (6). The time averages of systolic and diastolic peak velocities are also linearly related to systolic and diastolic coronary blood flow rates (5). The ratio of time average of diastolic peak velocity to time average of systolic peak velocity can therefore be used as an estimate of diastolic/systolic blood flow ratio, provided vessel size remains unchanged (6).

The systolic pressure-time index was determined by planimetry of the area under the aortic systolic pressure curve. The diastolic pressure-time index was estimated by planimetry of the area under the diastolic aortic pressure curve minus the planimetry of the area under the left ventricular diastolic pressure. Estimates of the systolic pressure-time index and diastolic pressure-time index may vary from their true measurements by 5% to 10% (7). The hemoglobin level in all experimental preparations varied from 10 to 14 g %.

Table 1. Hemodynamic Variables, Coronary Blood Flow Reserve and Diastolic/Systolic Blood Flow Ratio in Eight Dogs With Graded Acute Aortic Regurgitation

	Heart Rate (beats/min)	Pressure (mm Hg)			Coronary Blood Flow Reserve	Diastolic/Systolic Blood Flow
		Systolic	Diastolic	Left Ventricular End-Diastolic		
Control	108.4 ± 11.2*	125.9 ± 5.0	82.2 ± 4.5†	1.2 ± 1.8	3.51 ± 0.27†	5.45 ± 0.69*
Aortic regurgitation						
Mild	131.1 ± 7.2	118.1 ± 7.6	61.8 ± 3.0†	3.3 ± 3.0	2.38 ± 0.27†	1.93 ± 0.23
Moderate	143.4 ± 7.1	101.2 ± 8.9	42.1 ± 0.9†	4.5 ± 2.4	1.46 ± 0.12†	1.22 ± 0.08
Severe	138.6 ± 15.6	96.2 ± 10.1	29.2 ± 2.2†	26.9 ± 4.6†	1.20 ± 0.05	

*$p < 0.05$ for each grade of aortic regurgitation. †$p < 0.05$ versus baseline and each grade of aortic regurgitation. Data presented are mean value ± SEM. Mild (Moderate, Severe) aortic regurgitation-diastolic blood pressure of 70 to 50 (49 to 40, 39 to 20) mm Hg (5).

Statistical analysis. Hemodynamic variables, coronary blood flow reserve, the ratio of time average of diastolic peak velocity to time average of systolic peak velocity, diastolic pressure-time index, systolic pressure-time index and diastolic pressure-time index/systolic pressure-time index at each grade of aortic regurgitation were subjected to repeated-measures analysis of variance with Tukey's post hoc test (8).

Results

Three animals died before completion of all studies and are therefore excluded from further analyses: one each because of severe pulmonary edema associated with open aortic regurgitation, refractory ventricular arrhythmia and technical errors (substantial blood loss). The data from the remaining eight animals constitute the basis for this report. Examination of the explanted hearts of these animals revealed no gross damage to the valvular apparatus. The hemodynamic effects of graded acute aortic regurgitation are shown in Table 1. All values are expressed as mean ± SEM. The degree of aortic regurgitation was based on diastolic blood pressure, which has been shown to correlate well with the severity of valvular regurgitation (3). Mild, moderate and severe grades of aortic regurgitation were chosen at diastolic blood pressures of 70 to 50, 49 to 40 and 39 to 20 mm Hg, respectively. The heart rate and pulse pressure increased significantly once mild acute aortic regurgitation was produced; however, no significant changes were observed as the severity of aortic regurgitation increased. Left ventricular end-diastolic pressure did not rise with mild and moderate acute aortic regurgitation. However, there was a statistically significant increase in left ventricular end-diastolic pressure with severe aortic regurgitation (Table 1). Table 2 presents the diastolic and systolic pressure-time indexes under control conditions and with varying degrees of acute aortic regurgitation. The diastolic pressure-time index/systolic pressure-time index ratio declined significantly with increasing degrees of acute aortic regurgitation; the ratio was 0.28 ± 0.08 with severe aortic regurgitation.

A representative example of simultaneous electrocardiography and phasic circumflex coronary artery flow velocity waveform under control conditions is illustrated in Figure 1A. The baseline coronary blood flow velocity waveform is characterized by diastolic predominance. Diastolic/systolic blood flow ratio (the ratio of time average of diastolic peak velocity to time average of systolic peak velocity) was 5.45 ± 0.69 under control conditions. On administration of intracoronary papaverine, there was a marked increase in total coronary blood flow (Fig. 1B). The coronary blood flow reserve in the absence of aortic regurgitation was 3.51 ± 0.27 (Table 1).

With the onset of mild acute aortic regurgitation, systolic coronary blood flow increased moderately (Fig. 2A). Diastolic/systolic coronary blood flow ratio (ratio of time average of diastolic peak velocity to time average of systolic peak velocity) with mild aortic regurgitation was 1.93 ± 0.23. Coronary blood flow reserve decreased to 2.38 ± 0.27, which was significantly less than the coronary blood flow reserve in the absence of aortic regurgitation ($p < 0.01$) (Fig. 2B).

Coronary blood flow with moderate aortic regurgitation showed a further increase in systolic flow. Diastolic/systolic coronary blood flow ratio was 1.22 ± 0.08. Coronary blood flow reserve in the presence of moderate aortic regurgitation was 1.46 ± 0.12, significantly less than coronary flow reserve in the absence of aortic regurgitation or with mild aortic regurgitation ($p < 0.01$).

With severe acute aortic regurgitation, the coronary blood flow velocity waveform was characterized by systolic predominance of blood flow and retrograde diastolic flow (Fig. 3A). Diastolic/systolic coronary blood flow ratio was not calculated for severe aortic regurgitation because diastolic blood flow was retrograde. In assessment of coronary blood flow reserve in severe aortic regurgitation, only the antegrade systolic compo-

Table 2. Diastolic and Systolic Pressure-Time Indexes in Graded Acute Aortic Regurgitation

	DPTI (mm Hg·s min^{-1})	SPTI (mm Hg·s min^{-1})	DPTI/SPTI
Control	3,576 ± 601	2,268 ± 390	1.57 ± 0.46
Aortic regurgitation			
Mild	2,762 ± 554	2,631 ± 740	1.22 ± 0.35
Moderate	1,640 ± 636*	2,786 ± 798	0.52 ± 0.15
Severe	603 ± 107*	2,929 ± 893	0.28 ± 0.08*

*$p < 0.05$ versus control. Data presented are mean value ± SEM. DPTI (SPTI) = diastolic (systolic) pressure-time index; aortic regurgitation as in Table 1.

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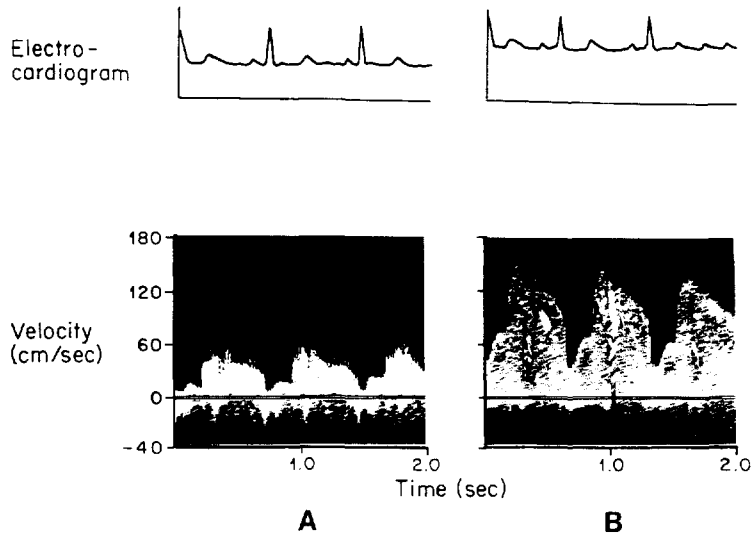

Figure 1. Representative example of simultaneous electrocardiography and left circumflex coronary artery velocity waveform under control conditions (**A**) and after administration of papaverine (**B**).

nents were compared. The time average of the retrograde diastolic peak velocity curve was <18% of the time average of the peak velocity waveform and was excluded in the calculation of coronary blood flow reserve. The coronary flow reserve with severe aortic regurgitation was 1.20 ± 0.05, which was also significantly different from the coronary flow reserve in the absence of aortic regurgitation or with mild aortic regurgitation ($p < 0.01$) (Fig. 3B).

Discussion

Coronary blood flow reserve decreased significantly with the induction of acute aortic regurgitation. There appeared to be a direct relation between the severity of acute aortic regurgitation and the decline in coronary blood flow reserve. Acute aortic regurgitation also changed the phasic epicardial coronary blood flow pattern: During severe acute aortic regurgitation the majority of anterograde epicardial coronary blood flow occurred in systole, and retrograde diastolic epicardial blood flow was noted.

Coronary blood flow reserve is a physiologic variable reflecting the ratio of maximal coronary blood flow to the rest level in a designated vessel at a given perfusion pressure. Coronary flow reserve is dependent on the factors influencing rest and maximal flow, such as heart rate, contractility, end-diastolic pressure and the presence of collateral channels (9). The magnitude of coronary blood flow reserve refers to the capacity of the coronary resistance vasculature to dilate to increase blood flow and oxygen delivery at the time of increased myocardial oxygen demand. A decline in coronary flow reserve beyond a threshold level may predispose the involved myocardium to ischemia. Although this threshold level has not been clearly established, it has been suggested that flow reserve less than twice the resting level may subject the myocardium to

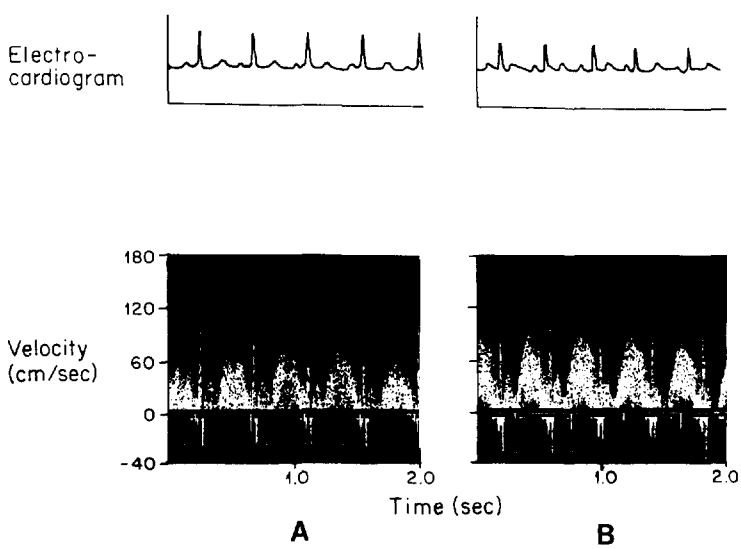

Figure 2. Representative example of simultaneous electrocardiography and left circumflex coronary artery velocity waveform with mild aortic regurgitation (**A**) and after administration of papaverine (**B**).

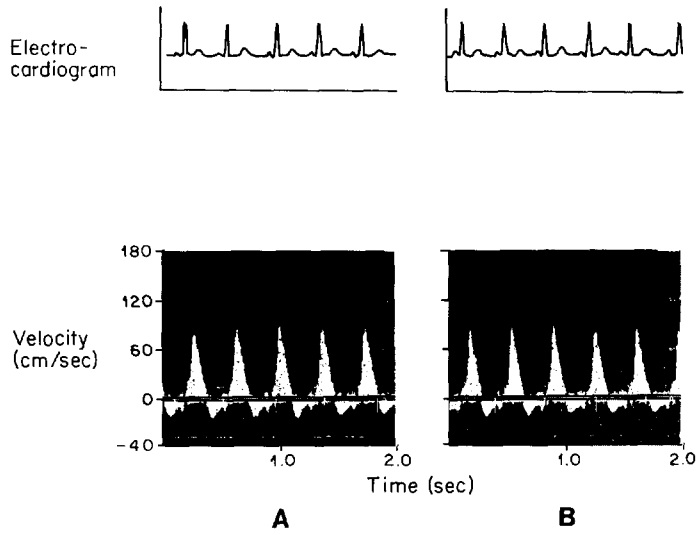

Figure 3. Representative example of simultaneous electrocardiography and left circumflex coronary artery velocity waveform with severe aortic regurgitation (**A**) and after administration of papaverine (**B**).

ischemia with moderate increases in myocardial oxygen demand (10). This hypothesis is based on the observation that moderate exercise or tachycardia can double myocardial oxygen demand and thereby flow requirements (11). Coronary blood flow reserves in moderate and severe acute aortic regurgitation in this study were 1.46 ± 0.12 and 1.20 ± 0.05, respectively. These findings suggest that coronary blood flow reserve in the presence of moderate and severe acute aortic regurgitation in this animal model may fail to satisfy the increased myocardial metabolic demand and therefore subject the involved myocardium to ischemia. In fact, studies have documented biochemical evidence of myocardial anaerobic metabolism after production of severe acute aortic regurgitation in experimental animal models (12). The present study further suggests a relation between the severity of valvular regurgitation and the decline in coronary blood flow reserve, emphasizing the greater vulnerability of the myocardium to ischemia when severe acute aortic regurgitation is present.

A reduced diastolic pressure-time index/systolic pressure-time index ratio is associated with a decreased proportion of blood flow to the subendocardial muscle and hence subendocardial ischemia. The critical value of the diastolic pressure-time index/systolic pressure-time index below which relative subendocardial underperfusion may occur has been estimated at 0.4 to 0.5 in dogs with normal levels of hemoglobin (13). The diastolic pressure-time index/systolic pressure-time index values in moderate and severe aortic regurgitation in this experimental study were 0.52 ± 0.15 and 0.28 ± 0.08, respectively. These values suggest that in this experimental model in the presence of normal coronary arteries, subendocardial blood flow is inadequate with severe acute aortic regurgitation and is marginal with moderate aortic regurgitation. In a previous study, creation of arteriovenous fistula (thus mimicking the volume overload of aortic regurgitation) was also associated with a marked decline in diastolic pressure-time index/systolic pressure-time index and subendocardial underperfusion (7). It is intriguing to speculate that arrhythmia and possible sudden death in patients with severe acute aortic regurgitation may be related to subendocardial ischemia.

Potential mechanisms of the diminished coronary blood flow reserve. Acute aortic regurgitation affects the coronary blood flow reserve through several mechanisms (9,14). There is an increased resting myocardial oxygen requirement and a decreased maximal coronary blood flow rate, leading to a net decline in coronary blood flow reserve. The increase in rest myocardial oxygen consumption is due to increased heart rate and systolic wall stress (15). Tachycardia is a major determinant of myocardial oxygen metabolism and a hallmark of acute aortic regurgitation. Systolic wall stress is also increased because of acute enlargement of the left ventricle secondary to regurgitation, which increases the left ventricular radius and thins the left ventricular wall. Concomitantly, the maximal coronary blood flow rate is compromised in the presence of acute aortic regurgitation because of the shortened total diastolic phase with tachycardia. Lowered aortic root perfusion pressure also decreases the maximal achievable coronary blood flow rate. The result of the interplay between augmented basal myocardial oxygen demand and compromised maximal coronary blood flow rate is a reduction in coronary blood flow reserve.

Alteration in phasic epicardial coronary blood flow in acute aortic regurgitation. Acute aortic regurgitation also produces a change in the phasic pattern of epicardial coronary blood flow. In the absence of valvular regurgitation epicardial coronary blood flow is characterized by predominance of diastolic blood flow. With increasing degrees of acute aortic regurgitation the ratio of diastolic to systolic blood flow decreases. In severe acute aortic regurgitation anterograde coronary blood flow occurs predominantly in systole, and there is retrograde flow during diastole. It has been postulated that the change in the phasic pattern of coronary blood flow in acute aortic regurgitation is due to the lowered diastolic coronary perfusion pressure (16). With a low diastolic pressure the coronary arteries are relatively underfilled during diastole and can

therefore store more blood during systole. Hence anterograde flow is detected in the epicardial arteries in systole. The retrograde diastolic epicardial coronary blood flow can be attributed to the combined effects of low diastolic aortic pressure and the Venturi effect of the regurgitant jet at the coronary ostia (17).

Strengths and limitations of the study. A strength of this study is the closed-chest experimental animal preparation. Using the percutaneous approach for producing acute aortic regurgitation and measuring coronary blood flow reserve, we conserved the physiologic effects of the pericardium during this experiment (18). Previous reports (2,12,15–17) studying coronary hemodynamic function with acute aortic regurgitation have used either open-chest or recently operated on animal preparations. It has been reported that during severe acute aortic regurgitation, the pericardium plays a role in limiting sudden left ventricular dilation (19). Application of the concept of coronary blood flow reserve and comparison of the values in the setting of acute aortic regurgitation deserve a word of caution. Coronary blood flow reserve, an index of maximal to baseline flow in a designated vessel, is critically dependent on coronary perfusion pressure (20,21). In acute aortic regurgitation coronary perfusion pressure (that is, diastolic blood pressure) decreases with increasing severity of regurgitation. Therefore comparison of coronary blood flow reserves at varying degrees of acute aortic regurgitation should be interpreted in the context of the decreasing perfusion pressure. A potential problem of the current study concerns the effect of intracoronary papaverine on coronary vessel diameter. An inherent assumption in using the ratio of the time averages of spectral peak velocity waveforms to represent coronary blood flow reserve is the constancy of vessel diameter. Previous studies have shown that normal epicardial coronary arteries dilate minimally after papaverine injection (6).

Conclusions. The present study suggests that moderate and severe acute aortic regurgitation in closed-chest anesthetized dogs predisposes the myocardium to ischemia due to the hemodynamic consequences of valvular regurgitation. This finding may have implications in the management of patients with acute aortic regurgitation. Further studies should define the precise contributions of the different variables lowering coronary blood flow reserve and the effects of certain pharmacologic agents on coronary flow reserve; the results may provide guidelines for the appropriate medical management of patients with acute aortic regurgitation.

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