Tone-Dependent Coronary Arterial-Venous Pressure Differences at the Cessation of Venous Outflow During Long Diastoles

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Background. The origin and magnitude of the back pressure opposing diastolic coronary inflow remain controversial. The arterial pressure at which coronary inflow stops during a prolonged diastole, ie, "zero-flow pressure," is higher than coronary venous pressure. However, because of capacitive discharge as distending pressure falls, flow at the microcirculatory level exceeds inflow, and coronary outflow ceases later than inflow. If coronary arterial pressure continues to exceed venous pressure at the point of venous flow cessation, zero-flow pressure cannot be an artifact of capacitive discharge.

Methods and Results. Coronary inflow and outflow, arterial pressure, and right atrial pressure have been measured during long diastoles in closed-chest dogs chronically instrumented with volumetric flow probes on the great cardiac vein or coronary sinus as well as the circumflex artery. Although venous outflow continued for 1 to 4 seconds after arterial inflow ceased, coronary artery pressure at the point of venous flow cessation (P_{a-v}) always exceeded right atrial pressure (13±1.3 mm Hg [SEM] vs 6±0.7 mm Hg, P<.001). When vasomotor tone was augmented using vasopressin, the diastolic pressure-flow relation shifted to the right, with P_{a-v} increasing to 21±2.4 mm Hg despite an unchanged right atrial pressure (6±0.5 mm Hg).

Conclusions. Transcoronary pressure differences persist when venous outflow stops and are larger when vasomotor tone is increased. Measurements of zero-flow pressure that exceed venous pressure cannot be considered an artifact of continuing capacitive discharge after the cessation of arterial inflow. Diastolic coronary back pressure exceeds right atrial pressure and is tone dependent. (Circulation. 1993;88:1238-1244.)

Key Words • coronary pressure-flow relations • zero-flow pressure • coronary back pressure • coronary capacitance

The origin and magnitude of the back pressure opposing diastolic coronary inflow remain controversial. Calculations of coronary vascular resistance have most often taken this pressure to be right atrial pressure. However, a variety of studies have demonstrated that coronary inflow during a prolonged diastole stops at an arterial pressure that is systematically greater than coronary venous pressure.1-9 This finding has been interpreted as indicating that coronary back pressure, commonly referred to as "zero-flow pressure" (P_{a-v}), exceeds coronary venous pressure. Other studies have questioned this interpretation because of confounding effects of coronary vascular capacitance.10-14 Because of capacitive discharge as distending pressure falls, flow at the microcirculatory level exceeds arterial inflow during long diastoles. One consequence of this discharge is that venous outflow continues, for at least a brief period, after arterial inflow has ceased.11,13,15 The point at issue is whether values of P_{a-v} exceeding coronary venous pressure are due entirely to continuing capacitive discharge or whether coronary back pressure is indeed higher than coronary venous pressure.

If coronary back pressure does exceed coronary venous pressure, the difference between coronary arterial and venous pressures during a long diastole might be expected to persist to the point of venous as well as arterial flow cessation. The present study was undertaken to test this hypothesis by measuring coronary inflow and outflow pressures at the points of arterial and venous flow cessation during long diastoles. Flows were quantified using ultrasonic probes that measure transit times across the entire vessel and therefore provide values for flow in absolute terms, ie, milliliters per minute. These probes have been shown to be suitable for chronic implantation on the great cardiac vein and coronary sinus as well as the circumflex coronary artery.10 Studies were therefore conducted in chronically instrumented dogs to exclude effects of thoracotomy and acute instrumentation.17

Methods

Studies were performed using procedures and protocols concordant with institutional guidelines for the care and use of experimental animals.

Experimental Preparation

Eleven mongrel dogs of both sexes weighing 23 to 28 kg (average, 25 kg) were studied. After an overnight
fast, general anesthesia was induced with sodium thi-amyll (20 mg/kg IV), and an endotracheal tube was inserted. Using a mechanical ventilator, anesthesia was maintained using a mixture of nitrous oxide (≈60%), halothane (1% to 2%), and oxygen (≈40%). A left thoracotomy was performed under sterile conditions.

Instrumentation was performed using procedures previously described. Tygon catheters were inserted into the aorta and both atria for pressure measurement. After attachment of bipolar pacing wires to the surface of the right ventricle, complete heart block was induced by injection of formalin into the AV node. Heart rate was controlled for the remainder of the surgical period and after surgery using a battery-operated external pacemaker (model 5840, Medtronic Co). The circumflex artery was dissected free in its proximal portion and instrumented with a 3-mm ultrasonic transit time probe (type 3R, Transonics Systems Inc, Ithaca, NY). In five animals, an arterial occluder was also implanted immediately beyond the flow probe. The coronary sinus or great cardiac vein was dissected free in the posterolateral area of the left atrium and ventricle and instrumented with a 4-mm ultrasonic transit time probe (Transonics 4R).

The chest was closed, and intrapulmonary air was evacuated. Antibiotics (procaine penicillin 300 000 U and streptomycin 300 mg IM) were given daily for 3 to 5 days. All catheters were flushed daily with heparin (1000 U/mL). Enteric-coated aspirin (325 mg daily) was given from the fourth day postoperatively. Animals were allowed to recover for at least 1 week before study.

Study Protocol

Dogs were fasted on the day of study and premedicated with Innovar-Vet (fentanyl 0.4 mg/mL and droperidol 20 mg/mL, 1 to 3 mL IM). To avoid any excitement and/or transient loss of consciousness during prolonged diastoles, we performed experimental protocols under general anesthesia. After induction with sodium thiamyll (20 mg/kg IV), animals were intubated and ventilated with a piston-type respirator, again using a nitrous oxide (≈60%), halothane (1% to 2%), and oxygen (≈40%) mixture. Coronary arterial and venous flows were monitored using a two-channel ultrasonic flowmeter (Transonic, model T-201). Intravascular pressures were measured using strain gauges (Statham P33B) zeroed to the level of the right atrium. Arterial pH, PO2 and PCO2 averaged 7.41±0.02 mm Hg (SEM), 107±11 mm Hg, and 28±1.4 mm Hg. Hematocrits were 32±1.5.

Prolonged diastoles were induced by sudden cessation of ventricular pacing at 100 to 120 beats per minute. In some cases, postponing diastoles were lengthened by prior administration of lidocaine (10 mg IV). Observations were made in the initial anesthetized state (n=10), during augmentation of vasomotor tone by intravenously administered arginine vasopressin (1 to 5 mU · min⁻¹ · kg⁻¹, n=9), and during coronary vasodilation (carbocromen 7.5 mg/kg IV, n=5). Between two and four long diastoles were obtained under each condition, and the mean values of individual parameters were used for further analysis. At the completion of studies, animals were euthanized with intravenous thiamyll followed by KCl. In situ ultrasonic flow probe zero signals were recorded after cardiac arrest with the chest still closed in seven animals; zero-flow levels obtained in this setting agreed with the electronic zero-flow setting of the flowmeter within 1.9±0.5 mL/min. When ultrasonic flow probes were suspended in a beaker of unstirred saline after having been removed from the hearts, probe outputs agreed with the flowmeter electronic zero-flow setting within 1.4±0.6 mL/min.

Data Analysis

Data were recorded on a multichannel direct-writing recorder and, in 10 of the 11 animals, were digitized on line before and during long diastoles. For venous flow probes, zero was taken as the signal recorded in situ immediately after euthanasia; when this recording was not available, the signal recorded in postmortem unstirred saline was used. For arterial flow probes in animals with arterial occluders in place, zero was taken as the signal recorded during occluder inflation at the time of study; when occluders were not available, we used the signal recorded in situ after euthanasia or in postmortem unstirred saline. Instantaneous arterial pressures and arterial and venous flows in the latter portions of long diastoles were fitted to quadratic equations using the least squares method. The arterial pressures at which arterial and venous flows ceased were designated as P FA,VA  and P FVA,VA; the pressures at which flows were 10% and 20% of their mean values just before the long diastole were also compared (P FA,VA 10% and P FVA,VA 20%). The volume of venous outflow occurring between P FVA,VA  and P FVA,VA  was calculated from the average venous flow during this interval and the length of the interval.

Data are given as mean±SEM. Initial values of P FVA,VA  and right atrial pressure and changes in the magnitude of the differences between these pressures in response to vasopressin and carbocromen were evaluated using paired t tests, with P<.05 taken as significant.

Results

Hemodynamic parameters before long diastoles are summarized in Table 1. Mean aortic pressure increased from 82±6.7 to 122±5.6 mm Hg during administration of vasopressin and was unchanged (82±7.5 mm Hg) after carbocromen. Analog recordings of arterial and venous flows are illustrated in Fig 1. Values of P FVA,VA  (10% and 20%), P FVA,VA  (10% and 20%) , and right atrial pressure at P FVA,VA  and P FVA,VA  are given in Table 2.

Aortic pressure at the point of venous flow cessation (P FVA,VA) was higher than the simultaneous value of right atrial pressure in every case. As shown in Fig 2, P FVA averaged 13±1.3 mm Hg in the initial anesthetized state

### Table 1. Hemodynamic Parameters Before Long Diastoles

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<td>GCV-CS flow (mL/min)</td>
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Values are mean±1 SEM. LC indicates left circumflex artery; GCV-CS, great cardiac vein to coronary sinus; RA, right atrium; LA, left atrium.
and exceeded right atrial pressure at $P_{\text{f}=0}$ ($6 \pm 0.7$ mm Hg) by $7.5 \pm 1.4$ mm Hg ($P < .001$). During vasopressin administration, $P_{\text{f}}$ rose to $21 \pm 2.4$ mm Hg, exceeding right atrial pressure by $12 \pm 1.8$ mm Hg ($P < .005$). Corresponding values after vasodilation with carbocromen were $10 \pm 1.7$ and $3.8 \pm 1.4$ mm Hg ($P < .05$).

Aortic pressure at the point of arterial flow cessation ($P_{\text{a}=0}$) exceeded $P_{\text{f}=0}$ by $2.1 \pm 1.0$ mm Hg in the initial anesthetized state and $6.3 \pm 1.2$ mm Hg during vasopressin administration. $P_{\text{a}=0}$ and $P_{\text{f}=0}$ did not differ measurably during carbocromen-induced vasodilation. Venous outflow continued for $1.1 \pm 0.8$ seconds after the cessation of arterial inflow in the initial anesthetized state and for $3.8 \pm 0.7$ seconds during vasopressin. Total volumes of venous outflow averaged $0.15 \pm 0.07$ and $0.31 \pm 0.08$ mL, respectively.

Fig 3 summarizes pressure-flow data for flows of 10% and 20% of those at the onset of long diastoles as well as at the cessation of flow. Venous and arterial diastolic pressure-flow relations both shift to the right when tone is augmented and to the left under vasodilation.

Discussion

This study indicates that values of zero-flow pressure ($P_{\text{f}=0}$) that exceed coronary venous pressure cannot be considered an artifact of continuing capacitive discharge after the cessation of arterial inflow. Although venous discharge does continue for a brief period after arterial flow stops during a long diastole, arterial pressure falls only a few millimeters of mercury during this period and remains above right atrial pressure when venous flow has also ceased. The magnitude of the transcoronary pressure gradient is increased when vasomotor tone is augmented.

Several features of the experimental preparation merit comment. The fact that studies were conducted in chronically instrumented animals avoided potential complicating factors in acute, open-chest, and/or isolated heart preparations. The transit-time ultrasonic venous flow probes provided a measurement of volumetric flow rather than flow velocity, thereby avoiding difficulties related to changes in cross-sectional area of the coronary sinus or great cardiac vein during experimental measurements. In our experience, these probes have a stable zero-flow signal that corresponds closely to zero determinations based on vessel occlusion and recordings made in situ after euthanasia or in postmortem unstirred saline. In addition, because the probes provided measurements of absolute flow, we were able to evaluate pressure-axis intercepts from continuous data as flow approached zero during long diastoles (Table 2 and Fig 3). Since only coronary sinus outflow was measured, we are unable to directly assess the possibility that drainage through other venous channels continued after coronary sinus flow ceased. In the absence of abnormal venous obstruction, we know of no data suggesting this might have been the case. Moreover, in the canine heart, coronary sinus outflow includes essentially all drainage from the left ventricular free wall.

In a study using citrate-arrested isolated swine hearts, Bellamy and O’Bena asked whether the findings in this preparation would apply under more physiological conditions.
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\( n \) = number of long diastoles. \( P_{fa=0,10\%,20\%} \) = arterial pressure at the cessation of arterial inflow and when inflow had decreased to 10% and 20% of its mean value just before the long diastole; \( P_{fa=0,10\%,20\%} \) = arterial pressure at the cessation of venous outflow and when outflow had decreased to 10% and 20% of its mean value just before the long diastole; \( P_{fa=0} \), \( P_{fa=10\%} \), \( P_{fa=20\%} \) = right atrial pressures at the cessation of arterial inflow and venous outflow; values are in millimeters of mercury.

Studying long diastoles in an open-chest canine preparation, Chilian and Marcus reported that \( P_{fa=0} \) exceeded right atrial pressure by "only a few mm Hg," i.e., 10 to 14 mm Hg vs 5 to 9 mm Hg (series 1 and 2 in their Table 2, \( n = 6 \)). Venous outflow continued for 2.5 ± 1.0 seconds after the cessation of arterial inflow; the volume of coronary sinus outflow occurring after \( fa = 0 \) averaged 0.23 ± 0.31 mL/100 g (of entire left ventricle) (\( n = 4 \)). Effects of vasodilation in this study are difficult to compare with the present and other previous studies, since long diastoles were assessed at peak reactive hyperemia or during systemic asphyxia rather than during sustained pharmacological vasodilation. Responses to vasoconstrictors were not evaluated.

The present findings demonstrate that transcoronary pressure gradients persist when coronary outflow ceases in chronically instrumented closed-chest dogs. The magnitude of these gradients was tone dependent, averaging 7.5 ± 1.4 mm Hg under initial conditions, increasing to 12 ± 1.8 mm Hg during vasopressin, and decreasing to 3.8 ± 1.4 mm Hg after maximum vasodilation. Although the presence of a substantial intramyocardial capacitance is not at issue, the differences between \( P_{fa=0} \) and right atrial pressure are not explained by continuing.
These plots show arterial and right atrial pressures at cessation of venous outflow ($f_V=0$). Average values are shown as mean±1 SEM.

Capacitive discharge. The actual back pressure to flow in these studies must have been higher than $P_{VA}$, ie, between $P_{VA}$ and $P_{VA}$, since discharge beyond the locus of $P_{VA}$ would be expected to continue until equilibration with outflow pressure was achieved. Back pressure may also have been underestimated in non-dilated beds because of autoregulatory vasodilation as pressure fell during long diastoles.

The fact that $P_{VA}$ exceeded $P_{VA}$ by relatively small amounts in the present studies probably reflected the small rate of change of arterial pressure (and therefore limited capacitive effects) as inflow approached zero. These differences (2.1±1.0 mm Hg under initial conditions, 6.3±1.2 mm Hg during vasopressin, and negligible during vasodilation) are comparable to those observed by Bellamy and O’Benar (4±3 mm Hg in the arrested vasodilated state, 9±4 mm Hg after acetylcholine, and 0±3 mm Hg during barium contracture). Chilian and Marcus did not report direct comparisons of $P_{VA}$ and $P_{VA}$ in the six animals in which both parameters were measured under control conditions.

The present findings are also consistent with a study from our laboratory demonstrating so-called “waterfall behavior” in isolated canine hearts. In that study, venous pressure was measured in the great cardiac vein (whereas that has not been possible in chronically instrumented animals in our hands). Elevations in great cardiac vein pressure did not affect coronary flow until a threshold value was reached. The magnitude of this threshold value was affected by vascular tone and mechanical activity. Coronary venous waterfall behavior was originally described by Scharf et al in 1971. More recently, Uhlig et al have demonstrated that large coronary veins running in the atrioventricular groove can behave as collapsible tubes in at least some experimental settings and have postulated that waterfalls occur in superficial epicardial veins as well. However, while studying effects of extracardiac pressure on pressure-flow relations in vasodilated beds, Satoh et al found that $P_{VA}$ always remained higher than both surrounding heart pressure and directly measured epicardial venous pressure; therefore, they concluded that $P_{VA}$ could not be explained solely on the basis of waterfall behavior in epicardial veins. This conclusion is compatible with the absence of transients in coronary inflow recordings after a step change in coronary artery pressure during a long diastole ($f_V$) (Fig 3). Were pressure not regulated proximal to the large capillary and venous capacitance of the heart, a transient change in inflow might be expected as the capacitive compartment was charged or discharged in response to the change in inflow pressure. Braakman, Sipkema, and Westerhof have demonstrated two levels of waterfall behavior in skeletal muscle in response to venous pressure elevation. Their lower value of $P_{VA}$ (8.8±2.2 mm Hg [SD]) was shown to be tone independent and was postulated to be located at a venular or venous level; the higher, tone-dependent value (28.5±9.5 mm Hg) was thought to be located in arterioles. The close agreement between $P_{VA}$ and $P_{VA}$ during maximum vasodilation in...
the present studies could reflect a more distal location of a tone-independent vascular waterfall in the coronary bed as well as in skeletal muscle.

The question of whether microvascular closure occurs during long diastoles remains unsettled. Kanatsuka and colleagues have measured internal diameters and red cell velocities during long diastoles in subepicardial microvessels during pharmacological vasodilation. Zero-flow pressure (13.6 ± 1.7 mm Hg [SD]) was systematically higher than right atrial (3.2 ± 4.4) and left ventricular diastolic (8.6 ± 2.7) pressures, but vascular closure was never observed. Arterial microvessel diameters decreased by 20% to 25% during long diastoles, indicating substantial increments in arteriolar resistance as distending pressure decreased. A preliminary report from Hirama et al. indicates a similar finding in subendocardial arterioles. Arteriolar closure has been visualized in some circumstances, however, and could be quite localized. In addition, vasoconstriction probably involves inolding of the vascular wall, which may be difficult to appreciate during intravital microscopy. Microvascular rheological effects have been suggested as an explanation for waterfall behavior in the absence of vascular closure. As pointed out by Braakman et al., waterfll behavior also might result from the nonlinear pressure-volume behavior of microvessels.

We continue to interpret available studies as indicating that coronary back pressure is greater than right atrial and/or coronary sinus pressure and potentially influenced by several factors. As discussed previously, blood vessels within the myocardial wall are subject to a number of forces able to cause local intravascular pressure to vary independently of changes in outflow pressure. These include transmitted intracavitary or extravascular pressure, contractile activity, t sniffing effects, and interstitial fluid pressure. Effects of intracavitary and extracardiac pressure and contractile activity are known to vary transmurally. Changes in intramyocardial blood volume during long diastoles also may alter pervascular strains. Rheological effects within microvessels may be especially important at low levels of flow.

The tension generated by vascular smooth muscle, which ordinarily includes active as well as passive components, remains of particular interest in assessing factors underlying coronary back pressure. To avoid possible autoregulatory effects during long diastoles, many studies of coronary pressure-flow relations in the 1980s dealt only with pharmacologically vasodilated beds. The present findings support the view that coronary back pressure is normally influenced by vascular smooth muscle tone as well as factors demonstrated in vasodilated beds. Although loci of waterfall-like behavior remain to be defined, we believe that arterioles are likely to be involved in tone-dependent effects. Changes in tone at the level of smaller arterioles play a pivotal role in coronary autoregulation, which has been suggested to involve changes in coronary back pressure as well as conductance. Changes in arteriolar tone could also serve to adjust for effects of other factors influencing coronary back pressure, i.e., in maintaining an appropriate level of intravascular pressure at the level of microcirculatory exchange.

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