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Effects of left ventricular contractility and coronary vascular resistance on coronary dynamics

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[1]*Department of Medicine and Department of Physiology and Biophysics, University of Calgary, Calgary, Alberta, Canada T2N 4N1; and* [2]*Physiological Flow Studies Group, Department of Biological and Medical Systems, Imperial College of Science, Technology, and Medicine, London SW7 2AZ, United Kingdom*

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Sun, Yi-Hui, Todd J. Anderson, Kim H. Parker, and John V. Tyberg. Effects of left ventricular contractility and coronary vascular resistance on coronary dynamics. *Am J Physiol Heart Circ Physiol* 286: H1590–H1595, 2004. First published December 18, 2003; 10.1152/ajpheart.01100.2001.—Wave-intensity analysis, which separates upstream from downstream events and defines their interaction, has been used to study the effects of changes in left ventricular (LV) contractility (E_{max}) and left circumflex coronary artery resistance (R_{LCx}) on the coronary systolic flow impediment (CSFI). In 10 anesthetized, open-chest dogs, we measured coronary, aortic, and LV pressures, coronary velocity (Flowire), and flow. E_{max} was increased by paired pacing and R_{LCx} was modulated by intracoronary infusions of vasodilators (adenosine and nitroglycerin) and a vasoconstrictor (phenylephrine). When both E_{max} and R_{LCx} were varied, CSFI and the energy of the backward-going compression wave (I_{W-}) were greatest at the highest levels of E_{max} and the lowest levels of R_{LCx}. I_{W-} was proportional to the CSFI. We conclude that contractility and coronary resistance change CSFI by modulating the backward-going compression wave.

wave intensity analysis; coronary flow impediment

THE CORONARY CIRCULATION is particularly complicated because it passes through the beating heart. Coronary blood flow (CBF) is a function of the pressure difference across the vascular bed (i.e., the coronary driving pressure) and coronary resistance. Coronary driving pressure depends on ventricular function. Coronary resistance has two components: one intrinsically vascular and one extravascular. First, vascular resistance is determined by the tone of the smooth muscle in the coronary arterial wall, which is modulated by vasoactive agents and by autoregulatory mechanisms that, in turn, are affected by ventricular performance. Second, the extravascular component of resistance is due to the contraction of the myocardium, which creates mechanical stresses in the wall of the left ventricle (LV) that compress the coronary microcirculation during systole, thereby increasing its resistance to blood flow (5–8, 21). Those mechanical stresses are increased by increased contractility, which has been shown to increase intramyocardial pressure and coronary systolic flow impediment (CSFI; i.e., the decrease in coronary blood flow during systole) when the coronary arterial circulation is maximally dilated (13, 14).

In a recent study, we (25) used wave-intensity analysis (WIA) to study the effects of LV contraction and relaxation on the dynamics of coronary flow. At the beginning of isovolumic contraction, a backward-going compression wave (BCW) is generated, which continues until peak LV pressure (P_{LV}) is achieved. When contractility is increased by paired pacing, the BCW becomes larger, which suggests that the BCW may be caused by the systolic compression of coronary vessels and that it may be directly responsible for the CSFI. However, the effects of the interaction of vasodilation or vasoconstriction and changing contractility on the BCW and the CSFI are unknown.

Therefore, the goals of the present study were to define the effects of vasodilation or vasoconstriction and contractility on the early systolic BCW and on the CSFI and to define the interaction of coronary resistance and contractility when both were manipulated. We hypothesized that the greatest values of the BCW and CSFI would be found when coronary resistance was minimal and contractility was maximal.

METHODS

Animal preparation. This study was performed on 10 mongrel dogs (18–20 kg) of either sex, according to a protocol approved by the faculty animal care committee. All animal experiments conformed to the "Guiding Principles of Research Involving Animals and Human Beings" of the American Physiological Society. Anesthesia was induced with thiopental sodium (25 mg/kg iv) and maintained with fentanyl citrate (20–50 $mg \cdot kg^{-1} \cdot h^{-1}$ iv). The dogs were intubated and ventilated (70% nitrous oxide-30% oxygen mixture) using a constant-volume ventilator (model 607, Harvard Apparatus; Millis, MA) and a closed rebreathing system. Arterial P_{O_2}, P_{CO_2}, and pH were monitored and maintained at 90–120 mmHg, 30–40 mmHg, and 7.3–7.4, respectively, by adjustment of the tidal volume. Body temperature was maintained between 36.5 and 37.5°C using a warming blanket and a heating lamp. A large-bore cannula was introduced into the external jugular vein for administration of fluids, and the ECG was monitored.

With the dog in the supine position, a midline sternotomy was performed and the ventral surface of the pericardium was incised transversely along the base of the heart. P_{LV} and aortic pressure (P_{Ao}) were measured using 8-Fr catheter-tip manometers with fluid-filled reference lumens (model SPC-485A, Millar Instruments; Houston, TX) so that absolute values of pressure could be ascertained. Left circumflex coronary artery (LCx) pressure (P_{LCx}) was measured using a 2.5-Fr catheter-tip manometer (Millar), which was introduced into a 1.0- to 1.5-mm branch and was advanced retrogradely 3 mm into the artery. Because the LCx branch was too small to accommodate a manometer-tipped catheter with a lumen, the absolute value of P_{LCx} could not be ascertained in the same manner as P_{LV}. However, in a series of three dogs, we recorded P_{LCx} using a fine plastic tube and a conventional pressure transducer that demonstrated that P_{LCx} was equal to P_{Ao} during the midportion of diastole. Thereafter, P_{LCx} was matched to P_{Ao} during that interval. Under fluoroscopic observation, a JL2.5 Judkins catheter was advanced into the LCx from the left

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femoral artery through which a Doppler Flowire (Endosonic; Mountain View, CA) was introduced to measure LCx velocity (U_{LCx}) at the same location as pressure was measured. LCx flow (Q_{LCx}) was measured using an ultrasonic flow probe (Transonic Systems; Ithaca, NY) placed at the same location as the Doppler Flowire. A pair of ultrasonic crystals was implanted in the anterior midwall of the LV to measure the circumferential segment length (L_{LV}). Pacing wires were attached to the right ventricular free wall for the control of heart rate and to effect paired pacing to increase contractility (17). A pneumatic constrictor (In Vivo Metrics; Healdsburg, CA) was placed around the inferior vena cava. After cardiac instrumentation, the pericardium was reapproximated using single interrupted sutures (19). All pressures were referenced to the midplane of the LV.

Protocol. After instrumentation and a 15- to 20-min stabilization interval, all hemodynamic data (P_{LV}, P_{LCx}, P_{Ao}, U_{LCx}, Q_{LCx}, and L_{LV}) were recorded while the heart was paced from the right ventricle. Coronary resistance was then modified by a LCx infusion (via the Judkins catheter) of vasodilators (adenosine and nitroglycerin) or a vasoconstrictor (phenylephrine). First, adenosine (0.022, 0.22, and 2.2 $mg \cdot ml^{-1} \cdot min^{-1}$), then phenylephrine (20 and 60 $\mu g \cdot ml^{-1} \cdot min^{-1}$) and finally nitroglycerin (20 and 60 $\mu g \cdot ml^{-1} \cdot min^{-1}$) were infused. Paired pacing was instituted before and after each drug infusion. After each drug effect was recorded, a 10- to 15-min recovery interval was allowed to regain hemodynamic stability. Immediately before a new drug was infused, all the hemodynamic data were recorded again. During each drug infusion and its preceding control run, the inferior vena cava was constricted transiently to describe the LV end-systolic pressure-length relation and to determine length-based maximum elasticity (E_{max}) to assess contractility (3, 18). (Linear regression was applied to the end-systolic pressure-length points and the slope was defined as E_{max}.) Individual hearts were paced at the same rate during control and during each drug infusion condition. Hearts were paced from 85 to 100 beats/min, rates that just exceeded each dog's natural heart rate.

Data collection. All the data (P_{LV}, P_{Ao}, P_{LCx}, U_{LCx}, L_{LV}, and the ECG) were sampled at a constant rate (~200 Hz) and recorded using a data-acquisition system (Sonometrics; London, Ontario, Canada). During each recording, the ventilator was turned off at end-expiration for ~20 s.

Data analysis and statistics. WIA was used to identify and quantitate the effects of changing coronary resistance and LV contractility on the BCW and CSFI. As described in detail previously (10, 11, 15, 16, 25), intensities (in W/m^2) of forward- and backward-going waves are termed dI_{W+} and dI_{W-}. At any instant, the algebraic sum of dI_{W+} and dI_{W-} equals the net intensity (dI_W). They are calculated as follows

$$dI_{W+} = (1/4\rho c)(dP + \rho c dU)^2$$

$$dI_{W-} = (-1/4\rho c)(dP - \rho c dU)^2$$

$$dI_W = (dI_{W+}) + (dI_{W-}) = dP dU$$

where ρ is the density of blood, c is the wave speed, dP is the incremental difference in P_{LCx}, and dU is the incremental difference in U_{LCx} during a sampling interval (~0.005 s). The energy (in J/m^2) of the wave, I_{W+} (forward) or I_{W-} (backward), was obtained by integrating the area under the respective intensity waveform with respect to time (t) over the duration of the wave

$$I_{W+} = \int (dI_{W+}) dt$$

$$I_{W-} = \int (dI_{W-}) dt$$

Using specialized software (CVSOFT, Odessa Computer Systems; Calgary, Alberta, Canada), we calculated dI_{W+}, dI_{W-}, dI_W, I_{W+}, and I_{W-}. On the basis of Doppler delay measurements (25) and as confirmed by the manufacturer, we advanced all the Doppler Flowire data 20 ms in time.

Coronary resistance (R_{LCx}) was calculated as the ratio of mean coronary pressure ($\bar{P}_{LCx}$) and flow ($\bar{Q}_{LCx}$) ($R_{LCx} = \bar{P}_{LCx}/\bar{Q}_{LCx}$). The CSFI was calculated as the difference between end-diastolic and minimum systolic coronary blood flow ($CSFI = Q_{LCx\text{-}ED} - Q_{LCx\text{-}min}$) (12). The energy of the BCW (I_{W-}) was measured. To define the combined effects of changing coronary resistance and changing contractility on CSFI, CSFI and I_{W-} were plotted as functions of E_{max} and R_{LCx} in three-dimensional plots. Only the first beat of paired-pacing data was used to minimize the contribution of secondary metabolic changes. To understand the implications of calculating CSFI in absolute terms (i.e., ml/min), $Q_{LCx\text{-}ED}$ and $Q_{LCx\text{-}min}$ were plotted as a function of R_{LCx} (i.e., $1/R_{LCx}$). For this analysis, all the data were randomly chosen from control and vasoactive agent infusion runs (i.e., paired-pacing data were not included).

Regression analyses were performed using linear equations (SigmaPlot 8.0, Regression Wizard, 3D). Student's paired t-test was used to identify statistically significant differences; a value of $P < 0.05$ was considered significant.

RESULTS

Figure 1 demonstrates typical changes in coronary pressure and wave intensity during systole and before and after intracoronary infusion of vasodilators (adenosine and nitroglycerin) and a vasoconstrictor (phenylephrine). During each beat, a BCW was generated immediately after mitral valve closure. After the aortic valve opened, a forward-going compression wave was observed. dI_{W-} started to increase in magnitude immediately after end diastole, achieved its peak absolute magnitude during early LV ejection, and returned to zero at approximately the time P_{LV} reached its peak. dI_{W+} started to increase at the beginning of ejection, but only after ~30 ms did its absolute magnitude become greater than that of dI_{W-}. dI_{W+} also returned to zero when P_{LV} reached its maximum value. As illustrated, decreasing R_{LCx} by vasodilators increased the CSFI and dI_{W-}; increasing R_{LCx} by a vasoconstrictor had the opposite effects.

Figure 2 illustrates the increases in dI_{W-} and I_{W-} and in CSFI due to ventricular paired pacing.

Figure 3*A* is a plot of CSFI as a function of both R_{LCx} and E_{max} ($CSFI = -15 + 0.89E_{max} - 2.08R_{LCx}$; $R = 0.82$, $P < 0.001$). When E_{max} is low, decreasing R_{LCx} increases CSFI slightly but not so much as when E_{max} is high. When R_{LCx} is high, increasing E_{max} increases CSFI but not so much as when R_{LCx} is low. Figure 3*B* is a plot of I_{W-} as a function of both R_{LCx} and E_{max}, which reveals a surface of a similar shape ($I_{W-} = -0.23 + 0.02E_{max} - 0.14R_{LCx}$; $R = 0.90$, $P < 0.001$). It suggests that, at any value of E_{max}, reducing R_{LCx} increases I_{W-}; at any value of R_{LCx}, I_{W-} is contractility dependent; I_{W-} is greatest at the highest values of E_{max} and the lowest values of R_{LCx}. Statistical analysis indicated that I_{W-} varied inversely and linearly with E_{max} and R_{LCx}.

In Fig. 4 we plotted the changes in I_{W-} versus the changes in CSFI (because there was less measurement error in CSFI) and found that the changes in I_{W-} were proportional to the changes in CSFI ($I_{W-} = -0.17 + 0.02CSFI$; $R = 0.85$, $P < 0.001$). As CSFI increased, I_{W-} also increased. Although the highest values of CSFI and I_{W-} were associated with adeno-

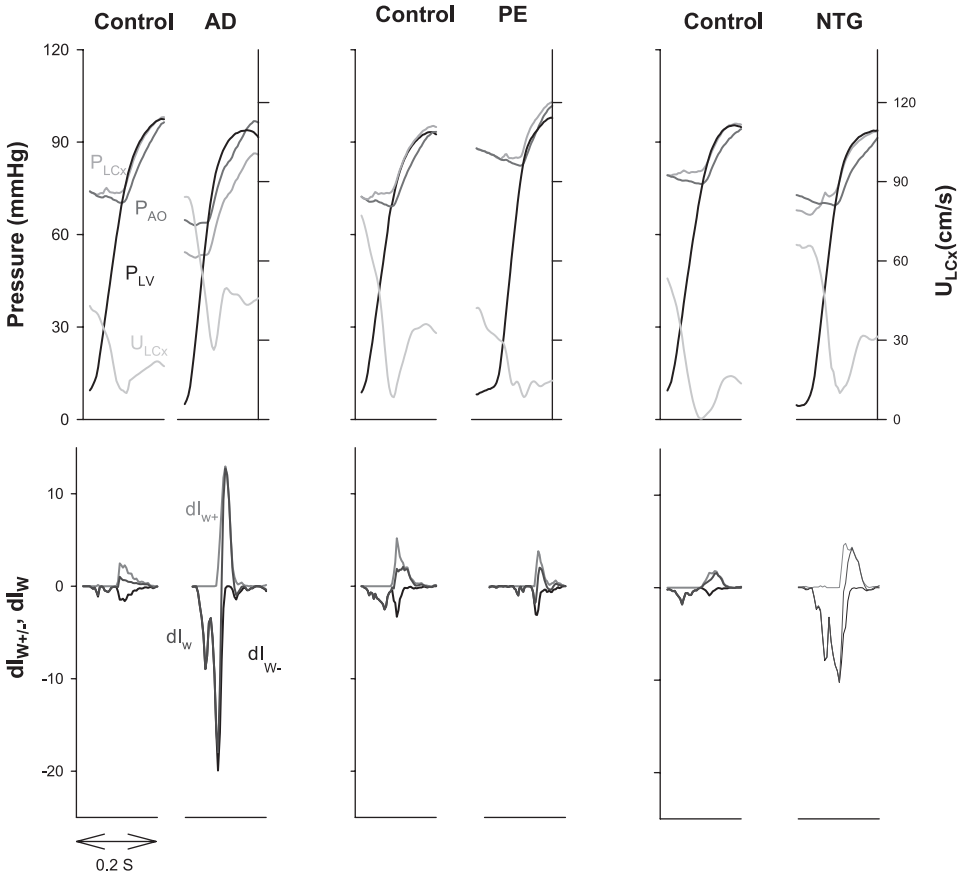

Fig. 1. Hemodynamic measurements and calculated coronary wave intensities showing the effects of infusions of adenosine (AD), phenylephrine (PE), and nitroglycerin (NTG). *Top*: left circumflex (P_{LCx}), left ventricular (P_{LV}), and aortic (P_{Ao}) pressures and left circumflex blood velocity (U_{LCx}); *bottom*: intensity of the forward- (dI_{W+}; positive values) and backward-going waves (dI_{W-}; negative values) and the net intensity (dI_W). Note that the vasodilators increased and the vasoconstrictor decreased dI_{W-}.

sine administration, each drug regimen was associated with a wide range of values.

Figure 5 is a plot of $Q_{LCx\text{-}ED}$ and $Q_{LCx\text{-}min}$ as functions of $1/R_{LCx}$ ($Q_{LCx\text{-}ED} = 8.9 + 87.8/R_{LCx}$; $R = -0.75$, $P < 0.001$; and $Q_{LCx\text{-}min} = 1.4 + 43.5/R_{LCx}$; $R = -0.65$, $P < 0.001$). Decreasing R_{LCx} (i.e., increasing $1/R_{LCx}$) increased both $Q_{LCx\text{-}ED}$ and $Q_{LCx\text{-}min}$ proportionally. As the slopes of the two regressions were different ($P < 0.001$), CSFI, which equals the (vertical) difference between $Q_{LCx\text{-}ED}$ and $Q_{LCx\text{-}min}$, must have also increased as R_{LCx} decreased.

DISCUSSION

There have been many investigations of the phenomenon known as the CSFI. The vascular waterfall, the intramyocardial pump, and the time-varying elastance model have all been used to explain how coronary systolic flow is impeded by changes in extravascular force. The intramyocardial pump model was proposed by Spaan et al. (22, 23) and assumes that compression of the coronary microvessels squeezes blood out of the microvessels into both arteries and veins, transiently decreasing coronary arterial flow and increasing venous flow. The increase in intramyocardial pressure during systole is a measure of the force of the pumping action. The time-varying elastance model proposed by Krams et al. (12–14) considers the intramyocardial vascular space to be an additional chamber of the heart. Using the time-varying elastance concept as developed from the pressure-volume relation of the LV by Suga and Sagawa (24), this model relates increasing coronary pressure and decreasing coronary flow during systole to increasing coronary elastance (13, 14).

Our analysis of wave intensity may not seem to be compatible with either of these models. As both intramyocardial pressure and elastance continue to increase until near the end of systole, one would not expect coronary flow to start increasing before then. In reality, however, it starts to increase much earlier. These apparent contradictions are resolved by the fact that WIA can separate simultaneously occurring forward- and backward-going waves. The backward compression wave continues until late in systole, entirely consistent with the predictions of the intramyocardial pump and elastance models. However, after the opening of the aortic valve, there is also a forward-going compression wave whose intensity exceeds the magnitude of the backward one from the moment coronary flow begins to increase until the end of systole. Thus WIA is consistent with the predictions of both models (i.e., that the backward compression wave should continue until the end of systole) but also provides the explanation for the early increase in flow (i.e., flow increases because net wave intensity becomes positive, indicating that the intensity of the forward compression wave has become greater than that of the backward compression wave), which neither model was capable of providing in themselves. The intramyocardial pump model and the elastance model are two similar expressions of the effects of the compression of the contracting myocardium on its intramural vasculature. Using coronary arterial WIA, we can look at the dynamic effects of that compression and compare them with the effects of increasing P_{Ao}.

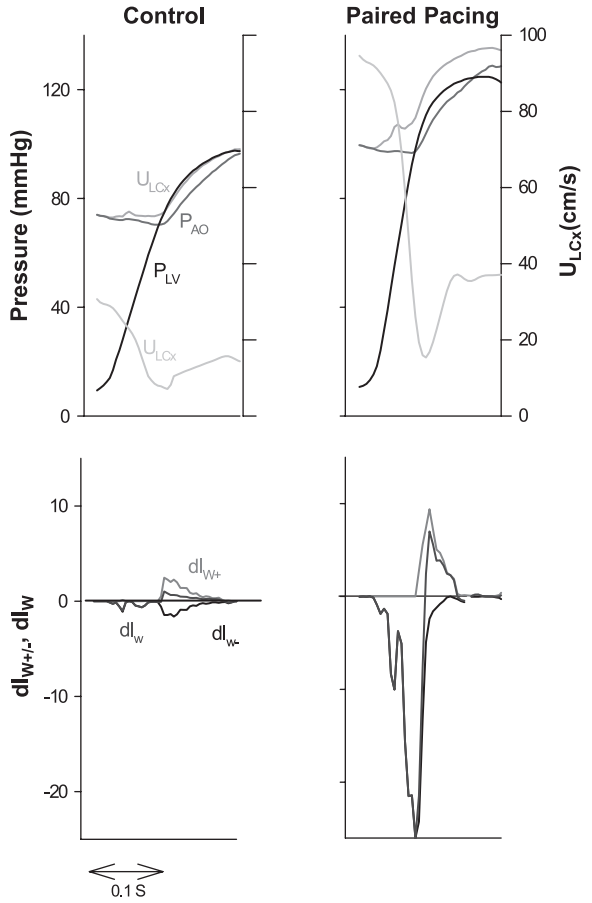

Fig. 2. Hemodynamic measurements and calculated coronary wave intensities showing the effects of increased contractility (paired pacing). Abbreviations are as in Fig. 1.

The present study using WIA shows that the energy of the BCW, which is generated by contracting myocardium and represents coronary microcirculatory effects, is directly related to CSFI. Thus this study conducted under physiological conditions provides direct evidence of the effect of the intramyocardial force generator and how that effect accounts for the CSFI. In our previous study (25), we were the first to study coronary dynamics using WIA. We showed that increases and decreases in coronary velocity were the result of the combined effects of forward- and backward-going waves. The present study relates the BCW to CSFI.

Under normal physiological conditions, coronary vascular resistance and contractility may change, spontaneously and independently. To assess the effects of changing contractility on CSFI at different levels of coronary resistance, paired pacing was used to increase contractility before and after the intracoronary infusions of vasoactive agents. To avoid complicating the effect of the increase in contractility with the additive effect of the resultant metabolic vasodilation, we selected only the first beat of the paired-pacing run for analysis. We found that increased contractility and decreased coronary vascular resistance interact to increase the magnitude of the BCW and CSFI.

We used WIA to clarify the mechanisms by which changes in coronary vascular resistance and contractility affect the CSFI. As anticipated by the results of the previous study (25),

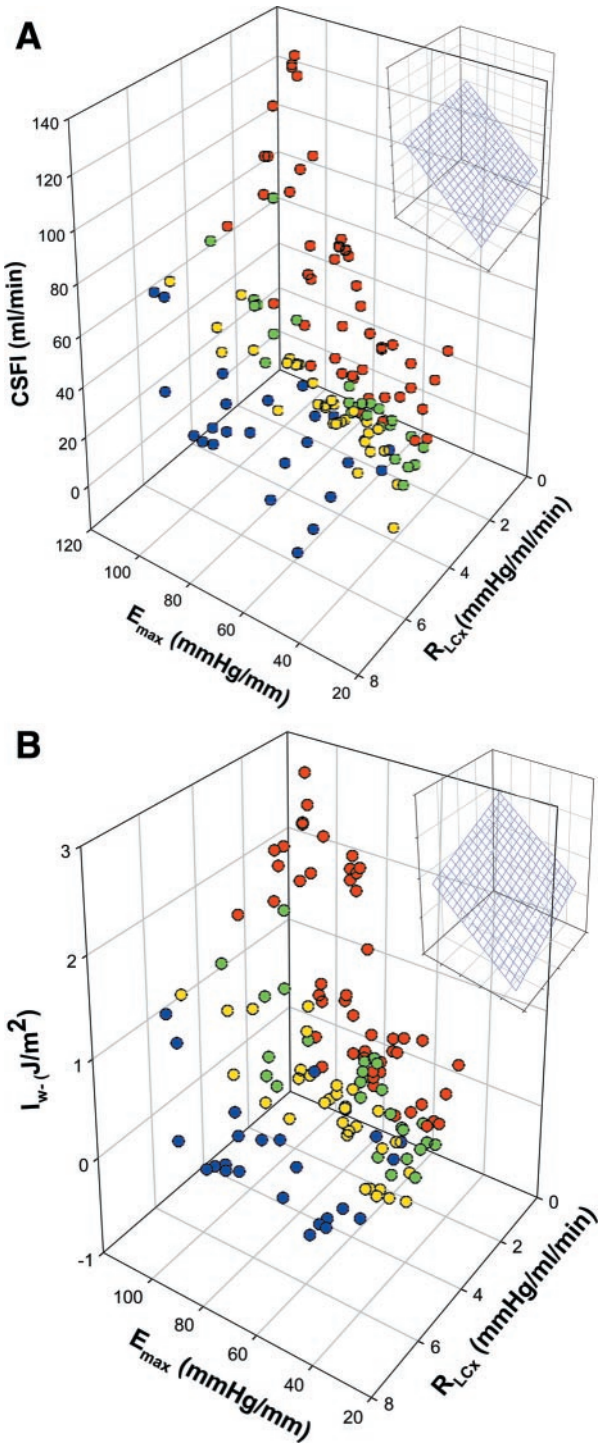

Fig. 3. *A*: three-dimensional (3-D) plot of coronary systolic flow impediment (CSFI) as a function of contractility (E_{max}) and coronary resistance (R_{LCx}). There is an inverse relationship between CSFI and both contractility and coronary resistance. *B*: 3-D plot of the energy of the systolic backward-going compression wave (BCW) (I_{W-}) as a function of E_{max} and R_{LCx}. There is an inverse relationship between the energy of the BCW and both contractility and coronary resistance. Data recorded during the control period are plotted in yellow, during administration of adenosine in red, of nitroglycerin in green, and of phenylephrine in blue. *Inset*: meshed plane. Pooled data are from 10 dogs.

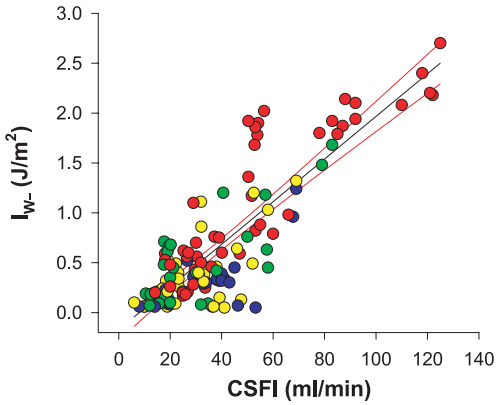

Fig. 4. I_{W-} plotted as a function of CSFI. Color conventions as in Fig. 3. Pooled data are from 10 dogs. The black solid line shows the regression and the gray solid lines represent the 95% confidence intervals for the regression.

we find that increasing contractility increases both the BCW and CSFI. The energy of the BCW (I_{W-}) is directly related to the CSFI, which supports the conclusion that I_{W-} determines CSFI. In addition, we demonstrated that decreasing coronary resistance also increases both I_{W-} and the CSFI. Changes in I_{W-} (and thus in CSFI) are shown to represent the interaction of coronary resistance and contractility. When contractility is constant, changes in I_{W-} reflect changes in coronary resistance, and, when coronary vascular resistance is constant, changes in I_{W-} reflect changes in contractility. When both contractility and coronary vascular resistance change, changes in I_{W-} represent their combined effects.

To study the effects of coronary vascular resistance on CSFI, vasodilators (adenosine and nitroglycerin) and a constrictor (phenylephrine) were infused into the LCx to change vascular resistance. When coronary vascular resistance was decreased by vasodilators, CSFI was increased, and when coronary resistance was increased by vasoconstrictors, CSFI was decreased; thus changes in CSFI were inversely related to the changes of coronary vascular resistance. This implies that dilating the coronary system increases its response to myocardial contraction. In other words, the same extravascular compression causes a larger coronary flow reduction when the coronary vessels are dilated and increasing coronary resistance minimizes the coronary flow reduction caused by extravascular compression.

CSFI is a measure of absolute flow reduction (in ml/min), and, therefore, it is difficult to interpret equal values of CSFI observed before and after vasodilation. Infusions of vasodilators increased CSFI by increasing the end-diastolic flow more than the minimum systolic flow, as shown in Fig. 5. Infusion of the vasoconstrictor decreased CSFI by decreasing the end-diastolic flow more than the minimum systolic flow. Vasodilators increased both diastolic and systolic flow in approximately the same proportion; thus it was inevitable that the difference (i.e., the CSFI) should increase in absolute magnitude. Vasoconstriction had exactly the opposite effect. A previous study (1) found different results: that increasing contractility did not affect diastolic flow but increased the systolic flow impediment mainly by decreasing coronary systolic flow. This difference may be due to the fact that they used a maximally dilated, isolated, perfused papillary muscle preparation.

Theoretically, there are at least two possible mechanisms by which vasodilation might increase the BCW and CSFI, at any level of contractility. First, vasodilation increases microvascular blood volume so that more blood might be displaced during myocardial contraction, resulting in a larger BCW at its source. Second, vasodilation might reduce the attenuation that the BCW sustains before it reaches the proximal coronary artery, also resulting in a larger measured BCW. Obviously, these mechanisms might exist in some combination.

We used adenosine, which acts primarily on the resistance vessels of the microcirculation (4), and nitroglycerin, which acts primarily on the larger vessels (20). Our results clearly show that adenosine reduced R_{LCx} more than nitroglycerin did and that adenosine was associated with higher values of CSFI and I_{W-}. This might suggest that the increasing blood volume displacement mechanism is more important than the attenuation mechanism. It also might suggest that the greater effect of adenosine is because it acts by both the displacement and the attenuation mechanism, whereas nitroglycerin might act only by the latter. Further experiments need to be designed to determine which mechanism is more important. In the present study, the relative effects of each of these mechanisms cannot be ascertained from our observations because we cannot rule out the possible contributions of changes in venous resistance or of microvascular compliance. The energy of the BCW simply represents the summation of all these factors.

Han et al. have shown that the sensitivity of lymph pressure to a change in P_{LV} is much larger during diastole than during systole (9), and they suggested that the increased elastance of myocardium "protects" intramyocardial lymph vessels from the effects of P_{LV}. This concept is somewhat similar to our interpretation of the effects of vasoconstrictors: vasoconstric-

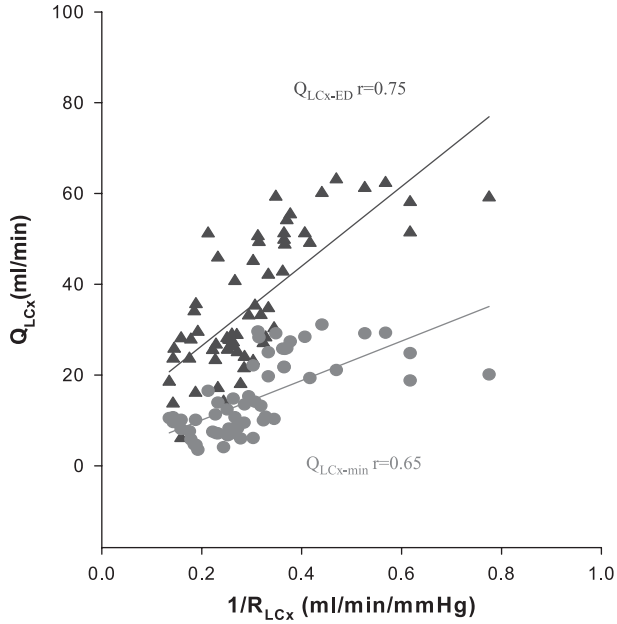

Fig. 5. End-diastolic ($Q_{LCx\text{-}ED}$) and minimum systolic coronary blood flows ($Q_{LCx\text{-}min}$) as a function of the change in the reciprocal of coronary resistance ($1/R_{LCx}$). Because changes in both $Q_{LCx\text{-}ED}$ and $Q_{LCx\text{-}min}$ are proportional to changes in $1/R_{LCx}$, the data indicate that CSFI (i.e., the vertical distance between the two lines) must also change in proportion to changes in $1/R_{LCx}$. Pooled data are from 10 dogs as in Fig. 3 except no paired-pacing data were included.

tors, which increase the elastance of coronary vessels, decrease the effects of myocardial contraction on coronary flow.

Although our method allows us to separate forward and backward waves in the artery, our measurements at a single site do not allow us to differentiate between waves generated in different regions of the myocardium. However, our methodology of separating waves, combined with simultaneous measurements at different sites in the coronary arteries, does offer the theoretical potential for deducing both the magnitude and the timing of the effects of myocardial contraction in different parts of the myocardium. This, as-yet-unrealized, potential of the method could be one of its greatest advantages. WIA integrates all upstream and all downstream effects acting on a single cross-sectional plane of the vessel; theoretically, it should be possible to assess the transmural difference and vessel size dependency of myocardial contraction vessel coupling if it were technically feasible to make measurements at different sites along the coronary arterial tree. However, it was not our intent in the present study to investigate such inhomogeneous effects.

We used a simple approach to the calculation of coronary vascular resistance, ignoring the possibility of a significant zero flow-pressure intercept (2), which, in any case, was not evident in these experiments.

Coronary resistance and LV contractility both play important roles in modulating CBF. A better understanding of the mechanisms whereby the coronary microcirculation and LV contractility interact to modulate coronary flow dynamics may ultimately be helpful for patient management. β-Blocker therapy has been shown to be effective in treating ischemic heart disease and the results of this study, that decreasing contractility may increase systolic blood flow, may provide another partial rationale for their use.

In conclusion, using WIA, we demonstrated that both contractility and coronary vascular resistance modulate the energy of the early systolic backward compression wave and thus the CSFI. By increasing myocardial compression, increased contractility increases the backward wave directly and vasodilation increases the sensitivity of the coronary microcirculation to myocardial compression, thus augmenting the wave. The close association between the energy of the backward wave and CSFI supports our hypothesis that the backward compression wave is the mechanistic cause of the CSFI.

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