Coronary Pressure-Flow Relationships
Controversial Issues and Probable Implications

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Background

In studies in which impedance flow through a vascular bed is calculated, driving pressure has traditionally been taken as the difference between inflow and outflow pressures, with the latter often assumed to be equal to right atrial pressure and, therefore, negligible in magnitude. In the coronary bed, ventricular diastolic pressure has sometimes been substituted for right atrial pressure, and has been taken as an index of intramyocardial forces presumed to influence the "back pressure" opposing coronary inflow.

These approximations have continued, despite publications dating back at least 50 years which suggest that inflow in several vascular beds ceases at pressures considerably in excess of right atrial or ventricular diastolic pressure. Values of this so-called "zero-flow pressure" (Pf_o) as high as 45 mm Hg were reported in the isolated hindlimb of dogs in the 1930's (Whittaker and Winton, 1933; Gomez and Veil, 1936). Influences of vasomotor tone, viscosity, and vessel distention and recruitment were addressed in the 1940's, and nonlinear pressure-flow relationships were identified experimentally (Pappeheimer and Maes, 1942; Green et al. 1944). A possible causative role of active tension in vascular smooth muscle was further emphasized in the early 1950's (Burton, 1951; Nichol et al., 1951). Permutt and colleagues' classical studies of pulmonary pressure-flow relationships in the early 1960's called attention to extravascular compressive forces, as well as vasomotor tone, and proposed a "vascular waterfall" as another explanation for higher-than-expected minimum pressures for forward flow (Permutt et al., 1962; Permutt and Riley, 1963).

Mosher et al. (1964) were among the first to describe pressure-flow relations in the coronary circulation. Steady state relationships obtained in five beating hearts by reducing perfusion pressure in step-wise fashion and measuring inflow 30 seconds to 2 minutes later indicated that inflow ceased at an average pressure of 23 mm Hg. Instantaneous relationships obtained by abruptly reducing pressure and measuring flow after only 1-2 seconds (presumably before autoregulatory changes could occur) showed higher values, suggesting in retrospect that Pf_o varied with inflow pressure and that changes in Pf_o were involved in autoregulatory adjustments of flow to changes in pressure. Later, a systolic waterfall was suggested by Downey and Kirk (1975).

Recent Coronary Studies

Interest in coronary pressure-flow relationships was rekindled by Bellamy's retrospective analysis of records of phasic coronary pressure and inflow in conscious dogs in the laboratory of the late Dr. Donald Gregg (Bellamy, 1978). During prolonged diastoles related to marked sinus arrhythmia, coronary inflow ceased at coronary arterial pressures as high as 40-50 mm Hg. For individual diastoles, flow was considered a linear function of inflow pressure. Pf_o was taken as the pressure-axis intercept of the extrapolated relationship, and resistance as the reciprocal of its slope. Interventions associated with coronary vasodilation (e.g., reactive hyperemia postocclusion, adenosine administration) resulted in substantial decreases in both estimated Pf_o and resistance.

Bellamy's report (1978) prompted a number of related studies of pressure-flow relationships. Pf_o derived from measurements during single long diastoles remained higher than right atrial or left ventricular diastolic pressure, even when possible over-estimates related to extrapolation of data terminating at pressures higher than Pf_o were obviated (Klocke et al., 1981). On the basis of apparent shifts in Pf_o following coronary sinus occlusion, Bellamy and colleagues (1980) suggested that Pf_o results from a "modified" waterfall influenced by extravascular forces and vasomotor tone, with venous pressure being a determinant of perivascular tissue pressure. Inconsistencies in the use of coronary outflow pressure (rather than Pf_o) in calculations of driving pressure and resistance were pointed out (Bellamy, 1980). Other groups agreed that diastolic Pf_o was less during vasodilation than with tone intact, and varied directly with inflow pressure when tone was operative (Klocke et al., 1981; Dole and Bishop, 1982a). In a study pertinent to viscous effects, it was found that conductance increased substantially, but that Pf_o decreased insignificantly, in response to hemodilution during maximum vasodilation (Baer et al., 1981). Ventricular systole was reported by three laboratories to increase Pf_o above diastolic values (Panerai et al., 1979; Bellamy and Lowensohn, 1980; Taylor et al., 1981).
Currently Controversial Issues

Although implications of these studies have been discussed widely, there remains controversy as to whether the effective back pressure opposing coronary flow is greater than coronary outflow or left ventricular diastolic pressure and, if so, by how much. The relative magnitude of $P_{r-o}$ within the myocardium, and increasing appreciation of the need to deal with the contour as well as the pressure-axis intercept of pressure-flow relationships. Among the important points underlying these issues are the effects of reactive (i.e., nonresistive) components of coronary impedance and the differences among— and/or vagaries of— individual experimental preparations used to study pressure-flow relationships. Effects of reactive components relate importantly to the magnitude and distribution of coronary capacitance, and, in particular, to the question of what portion of total intravascular capacitance affects diastolic pressure-flow relationships. The present discussion will attempt to clarify the implications of currently available studies by addressing four topics: reactive components of coronary input impedance, construction and interpretation of diastolic pressure-flow relationships which are free of reactive effects, persisting complexities in studies in nonvasodilated beds, and models of coronary pressure-flow behavior.

Reactive Components of Impedance

When discussions of $P_{r-o}$ in the coronary bed intensified in the late 1970’s and early 1980’s, Eng et al. (1982) called attention to reactive elements of impedance, particularly capacitance. Because of capacitive effects, inflow measured in a proximal artery necessarily underestimates flow in more distal portions of a vascular bed as inflow pressure falls (e.g., Hochberger and Zweifach, 1968). Conversely, measured inflow exceeds more distal flow when inflow pressure is increasing. The important questions in the coronary bed are the magnitude of this capacitive flow and its effects on the intercept and contour of experimentally determined pressure-flow relationships.

Characteristics of Coronary Input Impedance

Recent attempts to elucidate effects of capacitive flow on diastolic pressure-flow relationships identified a need for information about in vivo coronary input impedance. In a system with reactive as well as resistive components, input impedance is frequency-dependent and normally expressed in terms of modulus of impedance and phase angle. At zero frequency, the modulus of impedance is the vascular resistance calculated from mean flow and mean pressure gradient. At higher frequencies, the modulus falls, due to interactions of elastic, viscous, and inertial elements.

The conventional technique for determining input impedance involves resolving pulsatile pressure and flow waveforms into sinusoidal components by Fourier transformation. The coronary circulation is complex, not only in that pressure and flow are pulsatile, but also in that impedance may vary during the cardiac cycle. Systolic increases in resistance and/or $P_{r-o}$ related to mechanical effects of cardiac contraction are suggested by the reductions in mean coronary flow observed when heart rate is increased during pharmacological vasodilation (Raff et al., 1972; Domenech and Goich, 1976; Bache and Cobb, 1977). Such variations in impedance preclude the determination of coronary input impedance by Fourier transformation of pressure and flow waveforms taken over the entire cardiac cycle (Canty et al., 1985).

Using a programmable pressure control system (Canty and Mates, 1982), our laboratory has introduced sinusoidal pressure oscillations of constant amplitude and varying frequency at constant mean pressure levels during prolonged diastoles produced by cessation of pacing in heart-blocked dogs (Canty et al., 1985). The findings are qualitatively similar to those observed in other peripheral vascular beds: (1) as frequency is increased, the modulus of input impedance falls due to elastic properties of the coronary vessels; (2) at higher frequencies, the modulus of impedance levels off, probably due to inertia of the blood and viscoelastic effects; (3) the modulus of impedance decreases more rapidly with frequency as distending pressure decreases, both before and during vasodilation; (4) at any given pressure and frequency, input impedance modulus is smaller during vasodilation than with vasomotor tone active; (5) phase angles are negative, with flow leading pressure. Thus, in vivo diastolic coronary input impedance is a function of both distending pressure and vasomotor tone.

Reported Values of Coronary Capacitance

Coronary capacitance in this discussion is defined as a change in volume for a given change in pressure, i.e., $\Delta V/\Delta P$. The derivation of values of capacitance from impedance data requires some form of impedance modeling. As reflected by the numerous models of the coronary circulation proposed in recent years, the possibilities are virtually limitless!

Our initial approach to impedance modeling has been to examine systematically a number of lumped parameter models, incorporating viscoelastic and inertial elements, as well as resistance and capacitance, and using a standard optimization technique to determine the best least-squares fit to the measured impedance data (Mates et al., 1983). Over the frequency range 1–5 Hz, which includes the pressure decay rates encountered during long diastoles, a simple lumped RC parallel model has been surprisingly adequate. Above 5 Hz, data fits have been improved by adding a Voigt viscoelastic element.
TABLE 1
Quantitative Estimates of Coronary Capacitance

<table>
<thead>
<tr>
<th>Study</th>
<th>Preparation</th>
<th>Model</th>
<th>Mean distending pressure (mm Hg)</th>
<th>$10^6$ Capacitance (ml/mm Hg per 100 g)</th>
<th>Tone present</th>
<th>Tone absent</th>
<th>Pressure-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lewi and Schaper, 1971</td>
<td>In vivo: inflow pressure perturbation</td>
<td>RC</td>
<td>NS</td>
<td>0.4, 3*</td>
<td>0.9, 12*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Canty et al., 1985</td>
<td>In vivo: inflow pressure perturbation</td>
<td>RC</td>
<td>30-110</td>
<td>1.6-6.0</td>
<td>2.7-14</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3. Downey et al., 1983</td>
<td>In vivo: inflow pressure perturbation</td>
<td>RCR</td>
<td>NS</td>
<td>12*</td>
<td>59*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Eng and Kirk, 1983</td>
<td>In vivo: 25-μm emboli</td>
<td>None</td>
<td>&lt;73*</td>
<td>14-17</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Douglas and Greenfield, 1970</td>
<td>In vitro: 200-μm emboli</td>
<td>RC</td>
<td>90-150*</td>
<td>1.1-1.6*</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Spaan et al., 1981</td>
<td>Arterial pressure decay following inflow occlusion</td>
<td>Pump</td>
<td>90</td>
<td>70*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Spaan, 1982</td>
<td>Venous outflow following arterial occlusion</td>
<td>NS</td>
<td>100-250*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = not stated.

* Values have been calculated for the two animals illustrated in Figures 3 and 4. Capacitance was taken as the reciprocal of the modulus of volume elasticity, with pressure expressed as mm Hg rather than dynes/cm². Since weights of the perfused circumflex segments were not given, these two sets of values are expressed as ml/mm Hg rather than ml/mm per 100g.

Whereas these values are noticeably higher than those in studies 1 and 2, it should be noted that capacitance was calculated from a different model.

1. The cannulated artery of a bed occluded with 25-μm spheres was opened to a preselected back pressure. Capacitive flow was taken as the amount by which backflow during the first 30 seconds exceeded flow during subsequent 30-second periods (with the latter presumed to represent steady state collateral flow).

2. Distending pressures averaged 73 ± 10 (so) mm Hg prior to 11-90 mm Hg step reductions produced by opening the embolized anterior descending artery to preselected back pressures.

3. 0.1-ml increments in volume were superimposed on initial distending pressures of 60-120 mm Hg. From the data in Figure 2 and Table 1, we estimate pressure increments associated with the volume increments to have averaged 60 mm Hg. Mean distending pressure has therefore been taken as 30 mm Hg greater than initial distending pressure.

4. Calculated from the data in Table 1, assuming the left main, anterior descending, and circumflex beds to constitute 83, 32, and 39%, respectively, of total cardiac mass (Marcus, 1983, p. 7).

5. Estimate based on time constant of 3 seconds derived from the pattern of arterial pressure decay following inflow occlusion in a bed with vasomotor tone operative (Fig. 7). As discussed in the present text and by Downey et al. (1982), autoregulatory vasodilation probably occurred during the pressure decay, causing the reported time constant to reflect variations in resistance as well as capacitive effects. In addition, the model used to calculate capacitance appears to assume that resistance is constant throughout the cardiac cycle. As noted in the present text, systolic increases in resistance related to mechanical effects of cardiac contraction seem likely on the basis of the reductions in mean coronary flow observed when heart rate is increased during pharmacological vasodilation (Raff et al., 1972; Domenech and Goich, 1976; Bache and Cobb, 1977).

6. Great cardiac vein outflow was collected for 5-10 seconds after left main coronary occlusion in an autoregulating bed and related to the mass of the left anterior descending bed. Anterior descending drainage reaching the coronary sinus through marginal veins rather than the great cardiac vein (Nakazawa et al., 1978) was presumably not included.

(Canty et al., 1983a, 1985). Table 1 summarizes our studies and six other reports from which quantitative estimates of capacitance have been, or can be, derived. Three points are of interest:

1. Two of three studies (nos. 2 and 5) in which capacitance was examined at different levels of distending pressure find capacitance to vary inversely with pressure. The lack of such variation in the third study (no. 4) may relate to technical limitations of the experimental procedure (see third and fourth footnotes in Table 1). In our own laboratory, the degree of variation of capacitance was 3- to 4-fold over the pressure range ordinarily encountered during long diastoles.

2. Studies in which measurements were made before and during pharmacological vasodilation (nos. 1, 2, and 3) indicate that capacitance at any given pressure is at least twice as large in the vasodilated bed as in the bed with tone intact.

3. Values of capacitance reported by studies employing inflow pressure perturbation (nos. 1, 2, and 3) are of the same order of magnitude as those measured in a model-independent fashion by opening the cannulated artery of a bed occluded with 25-μm spheres to predetermined back pressures (no. 4). However, these values are 1-2 orders of magnitude smaller than those derived from measurements of venous outflow following arterial occlusion (no. 7). The values in studies 1-4 also reflect only a small fraction of the heart's total intravascular volume, which has most frequently been estimated at 6-15 ml/100 g (Marcus, 1983, p. 17).

The last of these points bears importantly on the question of what portion of total capacitance influencing...
ences diastolic pressure-flow relationships. We shall come back to this question in our consideration of models of pressure-flow behavior.

Effects of Rate of Change of Inflow Pressure on Capacitive Flow

Capacitive flow (CF) during long diastoles depends on the instantaneous rate at which transmural pressure is changing (dP/dt), as well as on capacitance (C), i.e., \( CF = C \cdot \frac{dP}{dt} \). This point is illustrated in Figure 1, which shows instantaneous pressure-flow relationships in a vasodilated bed during a long diastole in which coronary inflow pressure was made to decline linearly at three constant rates. At any given pressure level, measured inflow varies inversely with the absolute value of dP/dt, i.e., capacitive flow increases as dP/dt increases. The figure supports the view that values of capacitance are pressure-dependent, since the separation between any two relationships increases as pressure falls. It also calls attention to the variability in intercept and contour of pressure-flow relationships that can result from differences in capacitive effects produced by different patterns of inflow pressure decay. This latter point will be discussed further.

Capacitance-Free Diastolic Relationships

Because of the potential importance of capacitive effects when changing pressure and flow are used to construct diastolic pressure-flow relationships, experimental approaches which can define and compensate for capacitive flow have been of interest. If a coronary artery in a vasodilated bed is perfused at a constant pressure during a long diastole, reactive effects should disappear after an initial transient, with the steady state flow level representing the purely resistive component of impedance. Flow during later stages of a long diastole in an autoregulating bed should be relatively free of reactive effects if the time constant for the initial transient is short in relation to the time constant for autoregulation. If flows are measured during several long diastoles in which the level of constant pressure is varied, data from the several diastoles can presumably be combined to obtain a capacitance- and inertia-free pressure-flow relationship (Fig. 1).

Capacitance-Free Values of \( P_{f_0} \)

We are aware of four comparisons of pressure-flow relationships constructed in the fashion just described with those obtained during declining inflow pressure (Klocke et al., 1981; Downey et al., 1981; Eng et al., 1982; Dole and Bishop, 1982a). All four studies confirm that coronary capacitance results in an overestimate of \( P_{f_0} \) when the latter is taken as the pressure-axis intercept of a pressure-flow relationship constructed during a period of declining inflow pressure. Salient points of these studies, including capacitance-free values of \( P_{f_0} \), are summarized in Table 2.

Of particular interest (Table 2) is the fact that all three reports in which \( P_{f_0} \) was measured during pharmacologically induced maximum vasodilation (nos. 1, 2, and 3) find a back pressure to flow during long diastoles which is modestly but systematically greater than coronary outflow or diastolic intraventricular pressure. Average capacitance-free values of \( P_{f_0} \) in the three studies were 11-15 mm Hg. Values of right atrial and left ventricular diastolic pressures immediately prior to long diastoles averaged 3-5 and 7-9 mm Hg in the two studies in which they were reported (nos. 1 and 3). Using a different experimental approach to deal with capacitive effects, Kirkeeide et al. (1981) reported a similar effective back pressure during vasodilation, averaging 10 mm Hg. More recent studies in which pressure-flow relationships have been constructed during vasodilation from points measured during long diastoles a few seconds after onset of constant-pressure perfusion also report that \( P_{f_0} \) exceeds coronary outflow and ventricular intracavitary pressures by at least a few mm Hg (Canty et al., 1983; Messina et al., 1983; Uhlig et al., 1984*).

*In the study by Uhlig et al. (1984), the coronary sinus was cannulated and \( P_{f_0} \) at high coronary sinus pressures was less than coronary sinus pressure. However, uncanalulated coronary venous pathways remained at lower pressures during these measurements and values of \( P_{f_0} \) exceeded pressures in the uncanalulated pathways. Backflow into the coronary sinus was noted frequently at high coronary sinus pressures. Retrograde coronary sinus inflow presumably exited through the uncanalulated venous pathways, thereby interacting with normal antegrade flow and further complicating the interpretation of the pressures recorded at the point of arterial inflow cessation.
TABLE 2

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time of flow measurement (sec)</th>
<th>Tone present</th>
<th>Vasodilating agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>before long diastoles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after long diastoles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Klocke et al., 1981</td>
<td>Open&lt;sup&gt;a&lt;/sup&gt;</td>
<td>LC</td>
<td>1-4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Dole and Bishop, 1982a</td>
<td>Closed&lt;sup&gt;c&lt;/sup&gt;</td>
<td>LC</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>3. Eng et al., 1982</td>
<td>Open&lt;sup&gt;d&lt;/sup&gt;</td>
<td>LM, LC</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>4. Downey et al., 1981</td>
<td>Open&lt;sup&gt;e&lt;/sup&gt;</td>
<td>LM</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Average values are mean ± 1 SD. LC = left circumflex coronary artery. LM = left main coronary artery. P<sub>f0</sub> = pressure in perfused coronary artery. NS = not stated.

<sup>a</sup> These studies employed barbiturate anesthesia and acutely induced heart block, with long diastoles being produced by sudden cessation of ventricular pacing.

<sup>b</sup> This study employed chloralose anesthesia and produced long diastoles by vagal stimulation following intracoronary atropine.

<sup>c</sup> After establishment of each constant-pressure level.

<sup>d</sup> Eng and Kirk (1982) have called attention to Figure 9 in that report, pointing out that instantaneous inflow 1 second after a sudden reduction in inflow pressure was sometimes negative. As mentioned in the text of the report, such momentary backflow was felt to result from backward capacitive discharge from vessels downstream to the in-line electromagnetic flowmeter. The time course of the backward flow effect. A similar, somewhat briefer flow transient in a vasodilated bed is shown in Figure 3. In addition, Dole et al. have illustrated a negative flow transient in response to a sudden reduction of inflow pressure in an autoregulating bed (Dole et al., 1984, Fig. 4)

<sup>e</sup> Mean aortic pressures averaged 91 ± 14 mm Hg. However, Figure 3 shows a gradient of ~30 mm Hg across the coronary perfusion circuit in a nonvasodilated bed, indicating that coronary pressure was, at least in some cases, substantially less than aortic pressure.

Thus, all laboratories studying the point seem to agree that the back pressure to coronary flow during long diastoles is systematically greater than right atrial and/or left ventricular diastolic pressure during pharmacological vasodilation. The traditional formulation of coronary driving pressure is therefore inappropriate. Whereas the magnitude of the error involved in its use may be small under some experimental conditions, the need for improved definition and understanding of the mechanisms which govern coronary back pressure is apparent. A recent report from our laboratory indicates that capacitance-free values of P<sub>f0</sub> rise appreciably in the vasodilated bed when left ventricular preload is increased (Aversano et al., 1984). Bellamy’s coronary sinus occlusion study (in which capacitive effects were not evaluated directly and vasodilation was produced by temporarily occluding the coronary artery prior to diastolic arrest) suggested that P<sub>f0</sub> is also sensitive to elevations in coronary outflow pressure (Bellamy et al., 1980). Uhlig and co-workers (1984) have reported a vascular waterfall in the epicardial venous system of open-chest dogs which appears capable of influencing arterial as well as venous coronary flow, and have suggested that effects of increasing diastolic pressure may be mediated through such a waterfall.

Three of the four studies (1, 2, and 4) summarized in Table 2 report that the magnitude of capacitance-free values of P<sub>f0</sub> is influenced by vasomotor tone, as well as non-tone-dependent factors, and that P<sub>f0</sub> varies with coronary pressure prior to diastolic arrest when tone is operative. Average values of P<sub>f0</sub> were appreciably higher than during vasodilation, varying between 18 and 37 mm Hg. The lower values of P<sub>f0</sub> and absence of a demonstrable influence of vasomotor tone on P<sub>f0</sub> in study no. 3 may relate to factors such as relatively low levels of coronary pressure prior to long diastoles (see fifth footnote in Table 2). In addition, since constant-pressure perfusion data in this study were sometimes taken within 200 msec of the onset of diastole in autoregulating beds, constant-pressure flow measurements in such instances probably included the transient related to refilling of vessels emptied during the preceding systole described by Downey et al. (1983).

The quantitative implications of P<sub>f0</sub> levels of 20-40 mm Hg have caused the measurements of this magnitude with vasomotor tone operative to be regarded with particular skepticism. Concern has most frequently centered on effects of capacitive flow. As discussed earlier, capacitive flow—and, therefore, the degree of capacitance-related overestimate of P<sub>f0</sub> during declining pressure measurements—depends on the absolute value of capacitance and the instantaneous rate of change of transmural pressure. Depending on experimental conditions, substantial overestimates are clearly possible.
When flow is measured with an in-line flowmeter in an external perfusion circuit, the capacitance of the circuit between the flowmeter and the coronary artery is added to the capacitance of the coronary vessels themselves. Potential effects of dP/dt at the time of inflow cessation are illustrated in Figure 1, in which overestimates of $P_{f_o}$ exceed the capacitance-free value of 12 mm Hg by 83–150% as dP/dt at inflow cessation increases in magnitude from −35 to −125 mm Hg/sec. To our knowledge, values of dP/dt at the point of zero inflow have not been evaluated systematically in any published study of $P_{f_o}$ employing declining inflow pressure. Perfusion circuit capacitance and/or a high dP/dt at the time of inflow cessation could be involved in occasional marked discrepancies between the capacitance-free value of $P_{f_o}$ and $P_{f_o}$ derived from a declining pressure measurement (e.g., Eng et al., 1982).

On the other hand, even though absolute values of capacitance increase substantially over the range of spontaneous pressure decay during a typical long diastole, capacitive flow may be quite small at the time of inflow cessation because of large reductions in dP/dt as diastole proceeds. In our own experience to date, pressure-flow relationships recorded during a steady decline of inflow pressure at −3 mm Hg/sec have corresponded closely to capacitance-free relationships in vasodilated beds (Aversano et al., 1984, Fig. 4). An example of particular interest is Bellamy’s widely reproduced record of a diastole lasting ~2.5 seconds in a conscious dog with vasomotor tone intact (Bellamy, 1978, Fig. 1). Although the rate of decrease of circumflex inflow pressure was ~60 mm Hg/sec at the onset of diastole, it had fallen to ~3 mm Hg/sec at the point at which a $P_{f_o}$ of 45 mm Hg was recorded. Assuming capacitance to be 0.003–0.005 ml/mm Hg per 100 g at this pressure, capacitive flow at the point of inflow cessation would be estimated at <0.5 ml/min per g are sometimes recorded in the central core of myocardial segments a few minutes after regional inflow occlusion. Recent reports make two points about acute studies in previously unmanipulated canine coronary beds: (1) a minimum interarterial pressure gradient of 40–70 mm Hg is required before any collateral flow is detected (Messina et al., 1983; Messina et al., personal communication); (2) collateral flow within the low-pressure portion of the bed requires a minimum arterial pressure of ~20 mm Hg in the collateralized segment (Eng and Kirk, 1984).

The issue of $P_{f_o}$ in beds with vasomotor tone operative will be commented upon further when considering complexities in the experimental determination of the contour of pressure-flow relationships in beds with tone active, and when discussing pressure-flow modeling. On the basis of the capacitance-free values of $P_{f_o}$ in Table 2 and the considerations just discussed, the conclusion that $P_{f_o}$ is higher in autoregulating beds than vasodilated beds, and pressure-dependent when tone is operative, seems persuasive.

**Possible Effects of Collateral Flow on Measured Values of $P_{f_o}$**

As controversial points about coronary pressure-flow relationships have become more focused, questions have arisen about possible effects of collateral flow on even capacitance-free values of $P_{f_o}$. Of particular concern is the possibility that reported values of $P_{f_o}$ are artificially high in preparations in which the test coronary artery is cannulated because of unmeasured collateral flow into the cannulated bed. Concern about effects of collateral flow is heightened in canine preparations, in which flows as high as 0.1–0.2 ml/min per g are sometimes recorded in the central core of myocardial segments just discussed, the conclusion that $P_{f_o}$ is

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† Limitations of this model have been discussed by several workers (Dole and Bishop, 1982a; Hori, 1982; Hoki, 1982; Braakman et al., 1982) and acknowledged by its proponents (Eng and Kirk, 1982).
two before a pressure-flow data point is obtained (e.g., Mosher et al., 1964; Messina et al., 1983) rather than a few seconds before (e.g., Klocke et al., 1981; Canty et al., 1983; Aversano et al., 1984). Finally, pressure-flow relationships derived from measurements of arterial inflow in situations in which collateral flow is likely assume that the size of the bed perfused by the cannulated artery does not change as the pressure gradient between the cannulated and noncannulated beds is varied.

Despite these differences among experimental approaches, it remains noteworthy that laboratories recently studying coronary pressure-flow relationships—including one studying swine, in which collateral effects would be expected to be less prominent than in dogs (Pantely et al., 1984)—all report that \( P_{\text{ef}} \) in vasodilated beds normally exceeds coronary venous and left ventricular diastolic pressures by at least a few mm Hg. The studies discussed above indicating that \( P_{\text{ef}} \) is higher with tone operative than during vasodilation also seem difficult to "explain away" on the basis of collateral flow.

Possible Effects of Myocardial Ischemia on Measured Values of \( P_{\text{ef}} \)

Hoffman (1981) has called attention to possible effects of myocardial ischemia when determining the lower-pressure portion of pressure-flow relationships. Values of \( P_{\text{ef}} \) derived from measurements of full-cycle flow in the beating heart (which "cancel" reactive effects within the cardiac cycle) may include effects of ischemia-induced reductions in impedance caused by decreased myocardial contractility (Marzilli et al., 1979). If heart rate changes as perfusion pressure is lowered, additional changes in time-averaged impedance are possible. Although the critical level of pressure required to avoid myocardial ischemia is no doubt rate- and afterload-dependent, levels below 40 mm Hg—which are crucial in the determination of \( P_{\text{ef}} \)—may be a problem even in pharmacologically dilated beds when heart rate is rapid. Additionally, when measurements are made during a long diastole after a period of reduced pressure with the heart beating, it is possible that diastolic myocardial properties have been altered by the preceding period of reduced flow.

Contour of Capacitance-Free Relationships

It is apparent that capacitive flow can affect the contour as well as the intercept of diastolic pressure-flow relationships. This consideration is pertinent, not only to values of resistance (or conductance) derived from pressure-flow relationships, but also to disagreement among laboratories as to whether diastolic pressure-flow relationships are linear or nonlinear. The issue of curvilinearity was raised initially in regard to relationships constructed during periods of declining inflow pressure. Although our own laboratory's initial reports employed linear data fits (Ellis and Klocke, 1979; Canty and Klocke, 1979), we found as our experience increased (Klocke et al., 1981) that relationships were fit better by a second-than first-order process (despite linear correlation coefficients averaging 0.95–0.96), and became hesitant to infer specific values of resistance.

In retrospect, the contours of all diastolic pressure-flow relationships obtained during declining inflow pressure have been influenced by capacitive flow. The degree of influence no doubt varied from study to study, and is difficult to characterize quantitatively. Attempts to do so would have to deal with both instantaneous \( \Delta P/\Delta t \) (Fig. 1) and pressure-dependent changes in capacitance (Table 1). Apparent linearity of some previously reported relationships may reflect a combination of the effects of variations in \( \Delta P/\Delta t \) and capacitance. For example, in Figure 1, the capacitance-free relationship is curvilinear, whereas the relationships at high \( \Delta P/\Delta t \) levels are linear. Although there is no question that the changes in contour of pressure-flow relationships are independent of capacitive effects during interventions such as pharmacological vasodilation, modest changes in contour in studies employing declining inflow pressure need to be interpreted cautiously. Capacitive effects seem likely to limit the amount of new information that can be obtained in future studies of pressure-flow relationships in which inflow pressure is allowed to change in an undefined fashion.

More recent studies employing constant-pressure perfusion during several long diastoles, or other approaches for eliminating reactive effects, indicate that capacitance-free pressure-flow relationships in the vasodilated bed of open-chest dogs and isolated vented dog hearts are indeed curvilinear (Canty et al., 1983; Messina et al., 1983; Aversano et al., 1984; Hanley et al., 1984). Although, potentially, collateral flow can affect the contour of pressure-flow relationships, as well as their pressure-axis intercepts (Klocke et al., 1984), the curvilinearity of capacitance-free relationships has been equally apparent in left main (Messina et al., 1983; Hanley et al., 1984) and left circumflex (Canty et al., 1983; Aversano et al., 1984) preparations. The degree of curvilinearity can be substantial, particularly in the lower pressure range,† and appears to vary with preload and outflow pressure. As coronary arterial pressure was reduced from 65 to 20–30 mm Hg in an open-chest canine preparation, conductance decreased by ~30% at normal levels of left ventricular diastolic pressure, and by ~50% at left ventricular diastolic pressures of 30–35 mm Hg (Aversano et al., 1984). Similarly, in an isolated empty heart preparation, the slope of the relationship between flow and the logarithm of inflow pressure decreased

† Although extreme degrees of curvilinearity, with flow "hugging" the pressure axis, can be difficult to exclude experimentally (Aversano et al., 1984), they would have limited physiological meaning because of the very low flows associated with them.
by 35% as transcoronary driving pressure was reduced from 30 to 10 mm Hg (Hanley et al., 1984).

Dole and colleagues continue to find capacitance-free pressure-flow relationships to be linear in both vasoactive and pharmacologically dilated beds of closed-chest dogs (Dole and Bishop, 1982a; Dole et al., 1984). In their preparation, the circumflex artery is perfused through a metal cannula wedged in the proximal circumflex artery, and long diastoles are produced by vagal stimulation following intracoronary atropine. The basis for the difference in contour between their studies and those of other laboratories remains unclear, but could relate to differences between closed- and open-chest preparations or other experimental features just noted. Collateral flow effects at high coronary (and low aortic) pressures and other factors which may cancel curvature produced by changing resistance (Dole and Bishop, 1982; Hanley et al., 1984) also deserve consideration.

Whereas the basis for curvilinearity of pressure-flow relationships must involve pressure-dependent changes in the caliber of open vascular channels (Hanley et al., 1984), alterations in the number of perfused channels also seem likely. As pointed out by several groups, if \( P_f \) varies within the heart, the pressure-axis intercept of a pressure-flow relationship represents the minimum value of \( P_f \) associated with a measurable conductance in a distribution of \( P_f \) within the myocardial wall. In such a distribution, the number of open vascular channels increases with perfusion pressure and contributes to curvilinearity. Three studies have suggested that \( P_f \) varies transmurally (Archie, 1978; Rouleau et al., 1979; Ellis and Klocke, 1980), but each has experimental limitations. A preliminary report indicating that \( P_f \) does not vary transmurally (Firmin et al., 1982) involves assumptions that are difficult to validate. In our recent study of effects of preload (Aversano et al., 1984), pressure-axis intercepts exceed left ventricular diastolic pressure when the latter was 17 mm Hg or less, but were less than ventricular diastolic pressure at higher levels of preload. Increases in ventricular diastolic pressure were also accompanied by increases in coronary resistance at all levels of inflow pressure. These findings are compatible with a vascular waterfall in which higher values of \( P_f \) are concentrated in the inner myocardial layers. The preload-related increases in resistance may reflect not only a shift in minimum \( P_f \), but also a broadening of the overall distribution of \( P_f \) (and, therefore, a diminished number of functionally open channels at any inflow pressure). Although microsphere studies by Hanley et al. (1984) did not show a sequential dropout of vessels by transmural layer as inflow pressure was reduced, these workers were careful to note that their findings were directly applicable only to the isolated empty heart, and that transmural flow patterns would likely be altered in a working heart preparation.

In summary, the inherently nonlinear relationship between coronary pressure and flow needs to be taken into account in future attempts to quantify resistance and/or \( P_f \), and to identify changes in these parameters in response to interventions. The reductions in resistance which occur as inflow pressure is raised reflect increases in vessel radius, and probably vessel recruitment as well. More definitive studies of intramyocardial variations of \( P_f \) (both transmural and nontransmural) in working hearts are needed.

Confounding Effects in Nonvasodilated Beds

Autoregulatory effects remain a difficult confounding point in attempts to define \( P_f \) and/or the contour of diastolic pressure-flow relationships in beds that are not maximally dilated. Normal autoregulatory processes allow coronary flow to vary directly with myocardial metabolic demand at a constant coronary arterial pressure, and to remain relatively constant when inflow pressure is altered in the face of constant metabolic demand (Mosher et al., 1964). These metabolically induced and/or pressure-induced autoregulatory effects have long been agreed to involve changes in coronary vascular resistance, i.e., vasoconstriction and vasodilation. Three of the studies in Table 2 (1, 2, and 4) suggest that changes in \( P_f \) can also be involved, in that the values of \( P_f \) obtained from constant-pressure diastoles appear to vary with levels of diastolic pressure immediately prior to the determination of \( P_f \). Dole and Bishop (1982a) have studied the point most extensively, concluding that pressure-induced autoregulation involves important changes in \( P_f \), as well as coronary resistance.

Reports from at least five laboratories confirm that autoregulatory changes in flow occur during long diastoles in which the coronary bed is not diluted by pharmacological or other means. Our laboratory (Klocke et al., 1981) noted substantial time-dependent reductions in flow during long diastoles with constant inflow pressures \( \geq \)60 mm Hg. The time required for a 50% decrease in flow was \( \approx \)4 seconds and seemed consistent with the 10- to 15-second total autoregulatory time noted by Mosher et al. (1964) following abrupt changes in perfusion pressure at constant metabolic demand in beating hearts. Time-dependent changes in flow were smaller at pressures \( < \)60 mm Hg, suggesting that autoregulatory changes during long diastoles may affect the contour of a pressure-flow relationship to a greater degree than its intercept. Half-times of flow reduction similar to those reported by our laboratory were noted by Spaan and Laird (1981). Reductions in circumflex inflow of as much as 50 ml/min have been observed following a step increase in inflow pressure shortly after the onset of a long diastole (Klocke et al., 1984). In the constant-pressure perfusion experiments of Eng et al. (1982), the decision to use flow measurements taken within 200 msec of...
the onset of long diastoles in nondilated beds was based on reductions in flow as diastole proceeded. Dole and Bishop (1982) illustrated substantial changes in diastolic flow (at constant coronary pressure) in response to intracoronary adenosine injection, sudden cessation of pacing, and reactive hyperemia coupled with a marked reduction in heart rate at the moment of reflow. They felt it was possible, however, to maintain an essentially constant level of flow during long diastoles as long as such interventions were avoided (Dole and Bishop, 1982a). This assumption was importantly involved in their relatively detailed measurements of autoregulatory changes in resistance and $P_{f-o}$ (Dole and Bishop, 1982a).

Because of probable time-dependent changes in resistance and/or $P_{f-o}$ during long diastoles in nonvasodilated beds, we feel that the detailed interpretation of even pressure-flow relationships obtained using constant-pressure perfusion remains less clear than when vasodilation has been induced. Additional studies clarifying the nature of, and basis for, time-dependent changes in flow at constant pressure during long diastoles in autoregulating beds are highly desirable. As noted earlier, the conclusion that $P_{f-o}$ is higher in autoregulating than in vasodilated beds, and pressure-dependent when tone is operative, currently seems persuasive.

**Modeling Coronary Pressure-Flow Behavior**

The traditional concept of the coronary circulation as a resistive bed supplied by aortic pressure and drained at right atrial pressure is clearly not adequate to describe the pressure-flow relationships elucidated by experimental studies. Three findings must be reconciled in attempts to model coronary pressure-flow behavior:

1. The instantaneous pressure-flow relationship at any time during the cardiac cycle has a pressure-axis intercept greater than right atrial pressure. Studies during diastole discussed above indicate that the magnitude of $P_{f-o}$ depends on the level of smooth muscle tone in the vascular bed, as well as tone-independent factors. Studies during systole are more limited and less definitive. Recent reports suggesting that pressure-axis intercepts are higher during systole than diastole (Panerai et al., 1979; Bellamy and Lowensohn, 1980; Taylor et al., 1981) seem importantly limited by capacitive effects related to the two points listed below and/or by the magnitude of corrections applied to instantaneous recordings of coronary pressure and perfusion circuit flow to correct for reactive effects. Nevertheless, the possibility that $P_{f-o}$ is higher in systole than diastole requires consideration.

2. The phasic pattern of coronary venous outflow shows a peak related to systolic contraction while coronary inflow is reduced during systole and peaks during diastole. Capillary red cell velocity patterns appear to follow those in veins, rather than arterioles (at least in superficial vessels) (Tillmans et al., 1974). There is evidence that venous outflow persists after cessation of arterial inflow in at least some experimental circumstances (Chilian and Marcus, 1982; Spaan, 1982; Bellamy and O’Benar, 1984).

3. When inflow pressure is reduced, arterial backflow can occur during systole (Spaan et al., 1981; Chilian and Marcus, 1982).

Although various explanations of one or more of these phenomena have been proposed, two have received particular attention. Following earlier models of the pulmonary circulation (Permutt and Riley, 1963), several groups have considered a vascular waterfall a possible basis for experimentally observed pressure-flow relationships. Spaan and colleagues (1981) have proposed an intramyocardial pump, capacitively coupled to the circulation, as an explanation for patterns of phasic outflow and systolic backflow.

**Waterfall-Pump Model**

Figure 2 shows a model incorporating both the waterfall and the intramyocardial pump (Mates, 1984) which appears consistent with available experimental findings. Aortic pressure is represented by $P_a$ and coronary venous (right atrial) pressure by $P_v$. The intramyocardial or extravascular pressure, which drives the pump, is shown as $P_e$. $P_e$ represents an effective component of extravascular pressure due to vascular smooth muscle tone. $P_e$ is assumed to vary during the cardiac cycle as ventricular pressure rises and falls, as suggested by Spaan et al. (1981). $P_e$ is also time-varying, but with a longer time constant (several seconds). The waterfall (WF) regulates pressure under the influence of $P_e$ and $P_a$ (shown by dotted lines) by partial vascular collapse, producing an effective back pressure to coronary inflow ($P_f$). If pressures proximal and distal to the waterfall are above the effective back pressure, the waterfall has no effect. If distal pressure falls below the effective back pressure, the waterfall will produce whatever pressure drop is necessary to maintain the back pressure.

![Figure 2. "Waterfall-pump model" of the coronary bed. See text for explanation. (Reprinted with permission from Mates, 1984.)](image-url)
In this model, the resistance of the coronary bed is divided into two lumped components, $R_1$ and $R_2$. Similarly, capacitance is divided into a proximal component ($C_1$) and distal component ($C_2$). The lumped model is an obvious simplification, since, in reality, resistance and capacitance are distributed throughout the bed. The formulation in Figure 2 also ignores possible transmural variations in impedance which have been referred to above. Extravascular pressure is assumed to affect the waterfall. As mentioned earlier, changes in mean flow with heart rate in vasodilated beds suggest that $R_1$ may also be influenced by $P_c$. Smooth muscle tone appears to influence not only the waterfall pressure but also the proximal resistance and capacitance $R_1$ and $C_1$.

Let us examine the model in relation to the experimental findings cited above:

1. Experimentally observed diastolic pressure-flow relationships are consistent with the model as long as the waterfall pressure $P_b$ is considered to be tone-dependent. However, the distal capacitance $C_2$ also tends to regulate pressure between $R_1$ and $R_2$ during diastole. Spaan has suggested that a waterfall is not necessary (at least in the autoregulating bed) to explain the implication of diastolic pressure-flow relationships that pressure at some intermediate point in the circulation is regulated separately from venous pressure (Spaan and Laird, 1983). His hypothesis is that $C_2$ is sufficiently large so that the time constant for charging this capacitance ($R_2C_2$) is long compared to the time of diastole. Inflow recordings following step changes in inflow pressure during long diastoles in vasodilated beds in our own laboratory and in that of Downey show reactive time constants <100 msec, with no subsequent variation in inflow for at least 5–10 seconds (as long as coronary outflow and intraventricular pressures are kept constant) (Canty and Mates, 1982; Downey et al., 1982, 1983; Klocke et al., 1984). Figure 3 illustrates this type of response, with inflow remaining constant for 12 seconds after the initial transient following a reduction in inflow pressure. If one postulates a capacitance discharging at a sufficiently slow rate to be inapparent in this type of record, we find the capacitance required to be much larger than any reported values and inconsistent with estimates of total myocardial blood volume.

In a regulating bed, as noted above, it is more difficult to sort out the transient effects following a step change in pressure. However, unless some fundamental change occurs in the model during pharmacological vasodilation, it seems unlikely that the higher values of $P_{iso}$ observed with tone operative can be explained entirely on the basis of intramyocardial capacitance. Preliminary reports from Dole et al. (1982, 1983) indicate that the early diastolic overshoot in coronary flow during constant-pressure perfusion in dogs with vasomotor tone operative decays exponentially with a time constant of 55 msec (which is even less than during vasodilation). The short time constant would lead to the conclusion that reactive effects related to intramyocardial capacitance are completed early in diastole in beds with tone active, as well as in beds which have been dilated pharmacologically. In addition, Dole and colleagues have illustrated a 6-second period of apparent zero inflow in an autoregulating bed following a sudden reduction in inflow pressure from 125 to 27 mm Hg during a long diastole (Dole et al., 1984, Fig. 4).

As also noted above, it seems plausible that backflow pressures are higher during systole than during

![Figure 3](https://circres.ahajournals.org/external/fulltext/319/5/C319F3.jpg)

**Figure 3.** Response of coronary inflow to a reduction in inflow pressure during a long diastole in a heart-blocked dog in which the coronary bed was vasodilated with carbochromen. Following cessation of pacing, right, and left atrial reservoirs are opened, to keep coronary outflow and left ventricular pressures constant. The decay in inflow during the first second of diastole may relate to these initial adjustments in intracavitary pressures (see Aversano et al., 1984, Fig. 3), as well as to the effects of refilling of vessels compressed during the previous systole (see present text). When pressure in the cannulated left circumflex artery is subsequently reduced from 61 to 21 mm Hg, circumflex inflow stabilizes at 35 ml/min following an initial transient related to reactive effects and remains at this level for the next 12 seconds. (ECG = electrocardiogram; $P_{Ra}$, $P_{Rx}$, $P_{ccv}$, $P_{la}$, $P_{LC}$, $P_{LA}$ = pressures in the right atrium, aorta, left circumflex artery, left atrium, and great cardiac vein; EMF = phasic left circumflex inflow, measured with an electromagnetic flowmeter.)
diastole. This could be due to an influence of \( P_e \) on the waterfall back pressure \( P_b \).

2. The phasic pattern of venous outflow is explained by the intramyocardial pump. During systole, the extravascular pressure, \( P_v \), rises as left ventricular pressure increases. The resulting pressure difference across capacitor \( C_2 \) causes blood to be discharged through resistance \( R_3 \) into the right atrium. As the ventricle relaxes and \( P_v \) falls, venous outflow drops and the capacitor \( C_2 \) is recharged. If \( R_3 \) remains constant during the cardiac cycle, the pressure proximal to this resistance and to capacitance \( C_2 \) will rise during systole and fall during diastole in phase with the measured venous outflow. This explanation for venous outflow patterns would hold whether or not a waterfall is present upstream of \( C_2 \).

3. The intramyocardial pump also can explain systolic back flow. The original coronary waterfall model proposed by Downey and Kirk (1975) contained an electrical diode as part of the waterfall, preventing backflow. However, a collapsible tube will permit backflow if the distal pressure is higher than the effective backflow pressure. Thus, backflow is expected when the pressure proximal to \( R_3 \) exceeds inflow pressure. The observation of systolic backflow neither confirms nor precludes the existence of a waterfall.

Whereas Figure 2 provides a plausible model to explain a variety of experimental findings, the anatomic interpretation of model elements remains in question because it is presently possible to measure phasic pressures and flows only in the relatively proximal coronary arteries and distal coronary veins. Lacking detailed pressure and flow measurements at the microcirculatory level, one can only speculate on the anatomic location of individual lumped elements. The dependence of apparent back pressure on smooth muscle tone suggests that the waterfall, if it exists, lies upstream of the capillaries at the level at which primary flow regulation occurs. With this interpretation, \( R_1 \) would represent the lumped precapillary resistance and \( R_2 \) the resistance distal to this point. Similarly, \( C_1 \) would lump all of the precapillary capacitance, while \( C_2 \) would represent the capacitance of the capillary and venous beds. The fact that we were unable to identify two capacitive elements in perturbing inlet pressure and flow with a sine wave (Mates et al., 1983) is consistent with a location of \( C_2 \) distal to the major portion of coronary resistance. As indicated in Table 1, capacitance influenced by inflow pressure perturbation appears to increase 2-fold when the bed is pharmacologically vasodilated. This would be compatible with a significant portion of \( C_1 \) being located in the smaller precapillary vessels.

The anatomic distribution of capacitance bears importantly on the question of what portion of total capacitance influences diastolic pressure-inflow relationships. Since the capacitance \( C_2 \) is located downstream to the point of regulated pressure, it need not be involved in inflow regulation. Thus, persistence of coronary venous outflow beyond the point of inflow cessation during a long diastole (Chilian et al., 1982; Spaan, 1982; Bellamy and O'Benar, 1984) does not exclude a point of regulated pressure at the arteriolar-capillary level. The capacitance values in Table 1 estimated from inflow perturbation and arterial embolization (studies 1–5) presumably reflect \( C_1 \), whereas those obtained from venous outflow (study 7) represent primarily \( C_2 \).

Long Diastoles vs. Normal Cardiac Cycles

Although resistive components of coronary impedance can be separated from reactive ones in studies of pressure-flow relationships during long diastoles, the applicability of findings during long diastoles to the normal cardiac cycle remains to be demonstrated. Whereas the preponderance of coronary flow occurs during diastole, normal diastoles may not be quasi-steady. In the model shown in Figure 2, the vessels emptied during systole, represented by \( C_2 \), must be recharged during the early stage of diastole.

This systolic-diastolic interaction could influence the magnitude and distribution of flow (Hoffman, 1983). The extravascular pressure \( P_e \) in Figure 2 probably varies transmurally with ventricular stresses, being highest at the endocardium. In addition, the diastolic time course of \( P_e \) has not been established. Although the original model suggested that \( P_e \) is proportional to left ventricular pressure (Spaan et al., 1981), Bellamy's "modified" waterfall concept (Bellamy et al., 1980) suggests that myocardial blood content may play a role in regulating \( P_e \) as expanding blood vessels compress surrounding tissue. If \( P_e \) does depend on blood volume, as well as \( P_{l,v} \), its diastolic time course may differ from \( P_{l,v} \), being lower during early diastole and then increasing more rapidly as vessels are refilled. In such a setting, the maximum driving pressure for coronary flow \( (P_a - P_e) \) would be higher than expected in early diastole, and would decrease during diastole as arterial pressure falls and extravascular pressure rises (Klocke et al., 1984). Measurements that do not include the initial stage of diastole might not detect this effect. It also seems likely that systolic compression causes some redistribution of blood flow across the myocardium, an effect which could not be appreciated in inflow and outflow measurements.

Further studies of systolic-diastolic interaction are of interest, although their interpretation will no doubt be complicated (particularly in the autoregulating bed) by the numerous transients involved and the current lack of techniques for measuring local phasic pressure and flow.

Limitations of Resistance Calculations

As the preceding discussion has indicated, coronary input impedance is a complex quantity, and attempts to represent impedance by a single measure are of limited value. Marcus points out that at least ten different approaches for calculating coronary resistance have been proposed (Marcus, 1983, pp.
107–109). Calculations of resistance have been employed by most investigators to provide a measure of coronary vascular smooth muscle tone, to assess vasodilator reserve, and/or to define changes in vascular tone as a result of various interventions. Both mean and instantaneous values of pressure and flow have been used in the calculations. The fundamental difficulty in all such approaches is, of course, that the relationship between coronary arterial pressure and flow depends not only on vascular tone but also on several additional independent variables.

Figure 4 schematically illustrates some of these confounding factors in diastolic measurements of pressure and flow. Flow in the microcirculation is higher than inflow, since capacitive elements in the circulation are discharging as aortic pressure drops. As noted earlier, the magnitude of the capacitive flow depends on the instantaneous rate of change of pressure and absolute value of capacitance. In the hope of minimizing reactive effects (including early diastolic refilling of vessels emptied during systole), calculations of diastolic resistance have sometimes employed values of end-diastolic pressure and flow, rather than mean diastolic pressure and flow. End-diastolic resistance derived from these values and coronary outflow pressure (R) differs from the actual resistance at end-diastole (R'), not only because measured inflow differs from microcirculatory flow, but also because the actual back pressure to flow—which is itself dependent on ventricular diastolic and coronary venous pressures—is higher than venous pressure. Finally, coronary resistance varies inversely with pressure, as reflected by the nonlinear pressure-flow relationship.

Whereas capacitive effects can be minimized by utilizing mean full-cycle values of pressure and flow rather than end-diastolic values (Vlahakes et al., 1982), the resistance derived from the full-cycle values is influenced by effects of back pressure and curvature of the pressure-flow relationship, as well as by heart rate and contractility and the possibility that back pressure and/or conductance differ in systole and diastole.

The most desirable approach for quantifying vascular conductance would seem to be to establish (at a normal level of arterial pressure) the slope of a diastolic pressure-flow curve which is free of reactive effects. This is not an easy task experimentally. Phasic recordings of coronary inflow and inflow pressure would be required. Pressure-flow data in early diastole, which include capacitive refilling of vessels emptied during the preceding systole, cannot presently be corrected for this effect in any quantitative sense. If systolic-diastolic interactions are assumed to be negligible in later diastole, there is the possibility of applying currently available estimates of coronary capacitance and directly measured central aortic dP/dt to calculate the amount of unmeasured capacitive flow which needs to be added to measured inflow. If capacitive flow is small in relation to measured inflow, and similar in magnitude before and during an intervention, the correction might be practical. Changes in outflow pressure and/or ventricular diastolic pressure sufficient to alter conductance would also need to be considered. Finally, a relatively slow heart rate would be required to allow data to be collected over a sufficient pressure range to allow a meaningful slope calculation.

Because of the limitations of all currently available approaches for determining resistance (or conductance), we agree with Marcus that modest changes in this parameter must continue to be interpreted with considerable caution (Marcus, 1983, pp. 107–109). In attempting to define mechanisms of flow adjustment, one must consider the back pressure to coronary flow as well as resistance. However, as pointed out by Vlahakes et al. (1982), shifts in pressure-flow relationships can sometimes be noteworthy, even when underlying mechanisms cannot be clarified.

Summary

On the basis of the material discussed, our current assessments of the controversial points mentioned at the beginning of this article may be summarized as follows:

1. \( P_{rd} \) is the minimum back pressure to coronary flow associated with a measurable conductance, is indeed greater than coronary outflow pressure (and usually left ventricular diastolic pressure, as well). \( P_{rd} \) needs to be taken into account in attempts to determine coronary driving pressure.

FIGURE 4. Complexities of attempts to quantify diastolic resistance from measurements of arterial pressure and coronary inflow. Diastolic coronary inflow measured during declining aortic pressure is shown by the solid line, and flow at the microcirculatory level by the dashed line. \( P_d \) represents end-diastolic pressure, \( P_v \) coronary venous pressure, and \( P_{rd} \) the capacitance-free zero-flow pressure. \( R \) is end-diastolic resistance derived from end-diastolic aortic pressure and coronary flow and coronary venous pressure, \( R' \) is actual resistance at end-diastole, derived from the slope of the microcirculatory pressure-flow relationship at end-diastolic aortic pressure. (Redrawn from Klocke et al., 1984, and reprinted with permission.)
2. In maximally vasodilated beds, \( P_{\text{m}} \) derived from diastolic pressure-flow relationships exceeds coronary outflow pressure by at least a few mm Hg. \( P_{\text{m}} \) varies with coronary outflow and/or diastolic ventricular cavity pressure. When left ventricular preload is elevated, \( P_{\text{m}} \) exceeds outflow pressure by increasing amounts.

3. \( P_{\text{m}} \) appears to be systematically higher and pressure-dependent in beds in which vasomotor tone is operative. An improved understanding of the nature of, and basis for, time-dependent changes in resistance and/or \( P_{\text{m}} \) during long diastoles in nonvasodilated beds is needed.

4. The contour of pressure-flow relationships which are free of reactive effects is curvilinear rather than linear. The degree of curvilinearity is substantial and can change with interventions. Curvilinearity is accentuated at lower pressures and may reflect changes in the number of perfused vascular channels as well as the caliber of individual channels.

5. Capacitive effects need to be dealt with quantitatively in studies of pressure-flow relationships. Values of the capacitance which is involved in these effects vary with both pressure and tone. Capacitive flow also depends upon the instantaneous rate of change of pressure, which has not usually been defined in published studies.

6. Although intramyocardial capacitance is large and plays an important role in systolic-diastolic flow interactions, a controlling role in diastolic coronary arterial pressure-flow relationships has not been established experimentally. In vasodilated beds, in-flow remains remarkably constant for several seconds after the brief transient associated with a step-change in the level of constant pressure perfusion during a long diastole.

7. Calculations of coronary vascular resistance (by whatever method) remain of limited value, particularly when changes in response to an intervention are modest. Because of the curvilinear diastolic pressure-flow relationship, resistance is pressure-dependent and, at any given pressure, is probably best defined by establishing the slope of a diastolic pressure-flow curve which is free of reactive effects.

8. A modified vascular waterfall seems a plausible explanation for experimental findings indicating a regulated pressure within the coronary bed which is higher than outflow pressure. Any model of the coronary circulation describing flow throughout the cardiac cycle needs to deal with systolic-diastolic interactions, as well as \( P_{\text{m}} \) and reactive effects. More definitive evaluation of waterfall or other models which appear compatible with existing data will require additional experimental studies which test the models' implications (and expose their inadequacies) more fully.

Supported by grants from the National Heart, Lung, and Blood Institute G-PHI-HEL-315194, 1-K08-HEL-01168, American Heart Association (83-717), and The Alexandrine and Alexander L. Sinaiheimer Fund.


Coronary pressure-flow relationships. Controversial issues and probable implications.
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Circ Res. 1985;56:310-323
doi: 10.1161/01.RES.56.3.310

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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