Response to the Article
by Klocke et al. on
"Coronary Pressure-Flow Relationships:
Controversial Issues and Probable Implications"
which appeared in
Circ. Res. 56: 310-323, 1985

BOTH studies in the "Controversies" show that models play an important role in attempts to understand the physics of the coronary circulation. A model is a representation of and is supposed to be analogous to a different, more complex system. If the physics of the system is well understood and the boundary conditions are well defined, a model can be used as an analogous computer. Thus can the sailing characteristics of a mammoth tanker be designed by studies on a model no longer than a few meters. Unfortunately, in coronary physiology, there is as yet a dramatic lack in knowledge of anatomy and mechanical behavior of the microcirculation. Hence, models are used to test whether hypothesized mechanisms may indeed be operative at locations where observations are not yet possible. The chance that mechanisms are as hypothetized is greater, as more measured phenomena are being correctly described. Hence, an appraisal of these phenomena is important. In this respect, the two reviews are complementary.

To many researchers, but especially to clinicians, this discussion about models may seem very theoretical. However, the discussion has practical implications. This is clear from the different recommendations resulting from the two different papers in these "Controversies." According to the model based on intramyocardial compliance alone, the ratio between mean pressure and mean flow in the beating heart is an adequate index of vasomotor tone. If a waterfall element is thought to be essential, both the slope of the diastolic pressure-flow line and $P_{f=0}$ should be measured. In addition, a number of experimental requirements must be met.

Lumped Models

The models presented in both reviews are imperfect, in that they are discrete. Distributed quantities such as compliance are lumped into one or more capacitors. One has to be very careful with the physiological interpretation of model parameters estimated from fitting model equations to physiological data. In this context, I would like to point to a possible misinterpretation of the very valuable input impedance results of Klocke et al. The fit of the simple resistance-compliance model to the input impedance measured over a limited range of frequencies showed that vasodilation resulted in the increase of the compliance value. This could lead to the conclusion that the compliance per unit length decreases with increasing vascular tone. However, in the RC model, the distributed compliance is thought to be concentrated in one proximal compliance. Since the distributed resistance decreases with reduction of vascular tone, the vascular space represented by the lumped compliance may increase. Hence, even if compliance per unit length of all vessel types remain unaltered, the value of the lumped compliance would increase due to a reduction in resistance.

Nonlinearities and Time Constants

The study of the mechanics of the coronary circulation is hampered by nonlinearities. The nonlinear behavior of resistances and compliances of the large and small coronary vessels has been emphasized in both reviews. As a result of these nonlinearities, a simplified model may be useful only under limited circumstances. Probably the "controversies" have been created by unjustified extrapolation from one set of experimental conditions to the other. In this respect, it is worth noting that Klocke et al. emphasized studies on the fully dilated coronary bed, whereas my own attention was directed primarily to autoregulation.

In the autoregulated coronary bed, the time constants for venous outflow and peripheral coronary pressure decay are of the order of seconds (Fig. 4 of my review). Hence, the constant-pressure technique for obtaining pressure-flow lines may be free of epicardial compliance effects, but steady state in the microcirculation and venes was not established in most, if any, studies on diastolic pressure flow lines in the autoregulated bed. Klocke and co-workers (1981) showed a measurement on the fully dilated bed (their Fig. 3) in which coronary flow was stable in about 0.5 second after a pressure step. A similar response has been shown by Dole et al. (1984).
(Because of the low $P_{f_0}$ value and large perfusion pressure before the pressure step, one has to assume that the coronary bed was dilated in that particular experiment.) As has been discussed in my review, this difference may be explained by higher resistance and compliance values in the autoregulated bed. However, the study by Downey et al. (1983) showed the presence of a time constant of 0.055, and a possible one of 3 seconds in the autoregulated heart. The first one is in agreement with the fast initial fall in the coronary peripheral pressure decay curve and the second one is in agreement with the microvascular time constant estimated from coronary venous flow curves.

**Waterfall Pump Model**

One has to admit that, under certain circumstances, arterial and venous flow may cease at an arterial venous pressure difference. Bellamy et al. (1984) have shown this for drastic interventions such as barium contracture and acetylcholine infusion in the isolated pig heart. The question is, however, whether such a situation occurs in a normal heart. From the steady state measurements of Figure 1 of the opposing paper, Klocce et al. show an intercept of 12 mm Hg. One has to note, however, that $P_{f_0}$ was obtained by extrapolation of the measured pressure-flow relation. Increased curvature at lower pressures could indicate that true $P_{f_0}$ may have been overestimated (Klocce et al., 1981). Great cardiac venous pressure has not been reported in Figure 1 but amounted to 6 mm Hg in Figure 3. In other words, the arteriovenous pressure difference at stopped flow in the fully dilated bed has come to less than 6 mm Hg.

One may wonder whether stopped flow pressure is identical to back pressure when blood is flowing (Burton, 1951; Dole et al., 1984). This is the assumption in the waterfall-pump model. Should a waterfall exist, arterial pressure and/or anatomic location of the waterfall could be flow dependent. Especially the anatomic location deserves attention. Should back pressure to arterial flow equal $P_{f_0}$ then, judged by the value of $P_{f_0}$, the waterfall would be postcapillary in the fully dilated and precapillary in the autoregulated bed. At vasodilation, the anatomic location of the vascular collapse would move downstream from the arterioles to larger vessels or veins. However, should the location of the hypothetical waterfall be able to migrate gradually from the arteriolar site to the veins, all types of vessels would be disposed to show the waterfall behavior at low intraluminal pressures. The ultimate consequence would be a bloodless microcirculation in the excised heart. This is not the case.

In their review, Klocce et al. acknowledge the growing evidence for the existence of a significant intramyocardial compliance. However, they uncouple its influence on coronary arterial pressure and flow by a waterfall mechanism. Because of the necessary introduction of the intramyocardial compliance in the model, it becomes very hard to prove that the high $P_{f_0}$ values in the autoregulated heart are due to a waterfall mechanism. It is required not only that $P_{f_0}$ be higher than right atrial pressure, but it must also be higher than intramyocardial blood pressure, which, in the model, is the pressure proximal to $R_2$ (Fig. 2 of opposing review). In the case of zero venous outflow, one may assume that intramyocardial blood pressure equals venous pressure. However, the time constant for coronary venous outflow in the autoregulated bed is in the order of 3 seconds. Hence, real steady state measurements require stabilization times of 6 or more seconds. The requirement of such a long stabilization time at constant vasomotor tone can never be met.

It is not clear how backflow is explained in the waterfall-pump model. Is this backflow due to a discharge of $C_3$ before the waterfall becomes active, or has the hydrodynamics of the waterfall element still to be defined? This is an important point. Figure 3 of the opposing review depicts backflow at constant arterial pressure just after the pressure step. Hence, some intramyocardial compliance must influence arterial flow within 0.2–0.4 second after the pressure step. It seems rational, therefore, to include an intramyocardial compliance just prior to the waterfall element.

**Steady State Pressure Flow Lines**

The upper curve in Figure 3 of the opposing paper is important in two respects. First, the data on the curve have been measured at true steady states. Second, the curve is clearly nonlinear at lower pressure. This is in contrast to the typical pressure-flow line in the arrested heart presented by Downey and Kirk (1975). In their study, the pressure-flow line was only curvilinear in the beating heart. This curvature was thought to be caused by a systolic waterfall pressure varying across the ventricular wall. One has to conclude that the linearity of their diastolic pressure-flow line was due to compensating effects. Now that the steady state diastolic pressure flow line appears to be curvilinear, important evidence needed for the systolic waterfall hypothesis has been eliminated.

**Microvascular Studies and Lumped Models**

It seems realistic to assume a gradual pressure decrease from arteries to arterioles (Lipowsky et al., 1978). It is important to note that local vessel collapse, required for a waterfall mechanism, has not been reported in studies on the microcirculation. In a study from Burton's group (Nichol et al., 1951), a report is given on observations in the microcirculation of the mesentery of the frog at pressures around arterial stopped flow pressure. They found continuation of movement of blood. Diameters of vessels were changing with, in general, the smaller vessels becoming thinner and the larger vessels thicker. They also reported: "though we were seldom fortunate enough to have the vessels which closed com-
Further Dialogue in Controversies

D. SPAAN provides an explanation for the observed diastolic pressure-flow behavior of the coronary circulation based on his model of an intramyocardial pump. We agree that the intramyocardial pump provides the most plausible explanation for the phasic pattern of coronary venous outflow, but question whether the model also suffices to explain diastolic inflow behavior.

The limited amount of experimental data available for the coronary circulation makes it necessary to employ relatively simple lumped parameter models when attempting to characterize its complex behavior. The inherent limitations of any such model hamper the evaluation of alternate explanations for experimental observations. Dr. Spaan has concentrated his modeling on the autoregulating coronary bed. His model presents difficulties in interpretation, since the time constant for autoregulation (Spaan and Laird, 1981) is apparently similar to the time constant for charging or discharging the intramyocardial capacitance. In studies of our own and others in the vasodilated bed, a constant inflow pressure has been used to separate resistive and reactive components of impedance. This procedure cannot be extended in a straightforward way to the autoregulating bed, even if inflow pressure is constant, because of time variations in resistance, capacitance, and probably $P_{o,2}$ as well.

As we understand Dr. Spaan’s Appendix A, the “model” data in his Figure 7 are derived from an RCR simplification of the model shown in Figure 3, with $\sim 1/5$ of total coronary resistance being located upstream of the capacitive element. This characterization during effective autoregulation (Spaan and Laird, 1981) is apparently similar to the time constant for charging or discharging the intramyocardial capacitance. In studies of our own and others in the vasodilated bed, a constant inflow pressure has been used to separate resistive and reactive components of impedance. This procedure cannot be extended in a straightforward way to the autoregulating bed, even if inflow pressure is constant, because of time variations in resistance, capacitance, and probably $P_{o,2}$ as well.

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We are surprised by the suggestion that the compliance of vasoconstricted arterial segments can be greater than that of vasodilated segments at the same pressure level. Our own experiments, as well as those of Lewi and Schaper (1971) and Downey...
et al. (1983) cited in our Table 1, suggest that capacitance is lower with tone present. We understand that panels B and C in Dr. Spaan's Figure 2 were obtained by differentiating the relationships between cross-sectional areas and external pressure in panel A. These relationships were themselves derived from measurements of circumference and tension (e.g., Fig. 5, Mulvany and Halpern, 1977). We have reservations about the appropriateness of the differentiation procedure for the activated (i.e., contracted) artery. In the study by Mulvany and Halpern (1977), tension-circumference data for the activated artery were obtained by stretching the passive artery to a given initial length and then exposing it isometrically to an activating solution. This procedure was repeated at different initial lengths to obtain the active tension-circumference relationship. It is not clear that the slope of an isometric relationship derived in this fashion is related to the compliance of the activated muscle. If one first activates a muscle, and then stretches it, the resulting tension-length curve will differ from the isometric relationship. Indeed, using a square-wave length perturbation, Mulvany and Halpern (1977) determined the dynamic stiffness, dT/dL, to be 56 Δ T/L, where Δ T is the active tension at length L. At any given length, this stiffness is considerably greater than the slope of the maximum measured tension-circumference relationship indicated by the data of Mulvany and Halpern (1977, Fig. 5).

Because presently available data do not allow unequivocal definition of the mechanisms underlying coronary pressure-flow behavior, Dr. Spaan's and our own models, as well as those proposed by other investigators, need to be evaluated in a variety of additional experimental circumstances. Dr. Spaan's theoretical and experimental contributions have importantly advanced the thinking and understanding of all of us working in the area. We look forward to continuing dialogue with him.

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