Reactive hyperemia is the term used to describe the transient increase in flow rate above the control level which follows an interval of arterial occlusion. Bier (1) probably coined this term, and it appears to have been firmly established in the vernacular, if not in the literature, prior to the paper of Lewis and Grant in 1925 (2). Roy and Brown (3) attributed the first recorded observation of this phenomenon to Cohnheim (4), although it was probably well known to physiologists even before his monograph of 1872. Because an understanding of flow regulation during reactive hyperemia holds the promise of providing insights into regulation under more physiological conditions, this topic has been of abiding interest to cardiovascular physiologists. A reading of the early literature, however, forces one to realize just how elusive this goal has been; investigators today still grapple with the proof of hypotheses and interpret their results in terms of concepts put forward 50-100 years ago. For example, it has been 50 years since Lewis and Grant advanced their detailed and tightly reasoned hypothesis that reactive hyperemia in the human forearm is caused by the accumulation of normal products of tissue metabolism which are poorly diffusible and, therefore, slowly degraded during the course of reactive hyperemia. They argued that the long duration of the response excludes both a myogenic response and a direct effect of oxygen on the vessels themselves, although they carefully specified that the previous deprivation of oxygen may play an important indirect role (2). Work in the next 10 years led to the concept that the intensity of reactive hyperemia in skeletal muscle and in extremities is causally and quantitatively related to events during the interval of arterial occlusion and that the response can be described in terms of a flow "debt" and its "repayment" (5, 6). Katz and Lindner (7) extended these observations to the heart, perfusing fibrillating dog hearts with defibrinated blood at constant pressure and estimating coronary blood flow rate by measuring the rate at which the venous effluent dripped into a graduated cylinder. Their conclusions of 1939 are an appropriate introduction to the review which follows:

1. In this preparation, the coronary blood supply is greater than that necessary to meet myocardial needs.
2. The hyperemia due to the ischemia is more than adequate to make up for the myocardial deficit acquired.
3. The cause of the hyperemia seems to be an easily diffusible dilator substance which is eliminated in the presence of oxygen.
4. The degree of hyperemia not only varies with the duration of the ischemia and hence with the accumulation of the dilator substance, but also with the responsiveness of the coronary vessels to this substance.

**CHARACTERISTICS OF MYOCARDIAL REACTIVE HYPEREMIA**

Figure 1 is a record of electronically meaned aortic pressure and coronary blood flow in a conscious resting dog which illustrates myocardial reactive hyperemia following 11 seconds of coronary artery occlusion. Flow debt is the volume of flow which the heart is deprived of by the interval of coronary occlusion and is calculated as the product of the control flow rate and the duration of the occlusion. Reactive hyperemic flow is the volume of flow in excess of the control rate and is calculated as the difference between the total reactive hyperemic flow and the product of the control flow rate and the duration of reactive hyperemia. Repayment of flow debt is the ratio of reactive hyperemic flow to flow debt.

Myocardial reactive hyperemia in either open chest (8) or conscious (9) dogs is characteristically a predictable response, the volume of reactive hyperemic flow being determined by the duration
of coronary occlusion and the control flow rate. These two variables which determine flow debt do not exert equivalent effects on the volume of reactive hyperemic flow, however; it increases in proportion to the duration of coronary occlusion when control coronary flow is constant but in less than proportion to increases in control coronary flow when the length of occlusion is constant. The duration of reactive hyperemic flow is roughly proportional to the duration of occlusion, but because coronary flow returns to control levels so gradually at the end of this response, the inaccuracy of this measurement confounds a more detailed analysis. The percent increase in systolic stroke coronary flow exceeds that in diastolic stroke flow during reactive hyperemia, and this disparity appears to increase as a function of occlusion length. Furthermore, the increases are asynchronous, peak levels of systolic stroke flow being attained one to several beats earlier than peak diastolic stroke flow. An interesting feature of myocardial reactive hyperemia is that peak coronary flow rates are not achieved for several beats after the end of coronary vascular resistance which requires, in this example, 9–10 beats to reach its nadir. More recent work in our laboratory (Dr. R. F. Bellamy, unpublished observation) employing phasic pressure measurements from intracoronary catheters indicates that this inference is not entirely correct. Pressures in the epicardial coronary arteries are substantially lower than central aortic pressure during reactive hyperemia, and, when this fact is taken into account, it appears that at least 80% of whatever resistance change is generated by coronary occlusion will have occurred by the first beat. The additional small change over succeeding beats may reflect capacitance changes, perhaps modulated by time-dependent viscoelastic properties of the vessels themselves, such as creep. These tentative conclusions must be qualified by the uncertainty that even these improved pressure measurements probably still do not reflect the pressure and, therefore, the resistance at the arteriolar level. The peak flow rate during reactive hyperemia increases with increasing length of occlusion up to occlusions lasting 15–30 seconds. That longer occlusions do not increase peak flow further indicates that this degree of ischemia causes maximum dilation of this bed. Because there is no known stimulus to coronary vasodilation greater than that produced by ischemia, estimating peak reactive hyperemic flow following a 15–30-second coronary artery occlusion is a convenient way to estimate the maximum vasodilator capacity.
of this vascular system. Studies in conscious dogs have confirmed the observation of Katz and Lindner (7) that flow debt is overpaid, usually by several-fold.

The studies of flow in epicardial coronary arteries just reviewed have been extended in the past few years to an examination of how reactive hyperemic flow is distributed within the myocardium. The results are conflicting, in part because of differences in experimental design and, more importantly, the influence of the size of microspheres on their tissue distribution (10). Furthermore, these experiments are all subject to the potentially very serious errors that result from applying methods of flow estimation based on the Fick Principle to nonsteady flow states. This problem was circumvented in a study in conscious dogs by artificially restricting coronary flow rate to the control level for 20 seconds following the release of coronary artery occlusion and injecting the microspheres 5 seconds after release. Thus, coronary flow was stable for the 15 seconds following microsphere injection. Prior to the coronary occlusion, the endocardial-epicardial microsphere distribution ratio was slightly greater than unity. During restricted reactive hyperemia, the fraction distributed to the epicardium increased by 20% and the fraction going to the endocardium decreased by 26%. Phasic coronary flow curves showed that systolic stroke flow increased from a control value of 13% of total stroke flow to 26% of total stroke flow during restricted reactive hyperemia (11). These findings independently verify the observation that systolic coronary flow is distributed preponderantly to the epicardial half of the ventricular wall (12). Studies of microsphere distribution in unrestricted reactive hyperemia conducted in parallel with those during restricted hyperemia showed that the endocardial-epicardial microsphere distribution ratio was greatly increased relative to control (11). This change in distribution ratio cannot be reconciled with the increased fraction of systolic coronary flow occurring in unrestricted reactive hyperemia (9) and indeed may be an artifact resulting from nonsteady flow. Clearly, additional work is needed to verify the prediction based on the increased systolic-total stroke flow ratio that there is a redistribution of coronary flow to the epicardium during unrestricted reactive hyperemia.

METABOLIC RESPONSE TO MYOCARDIAL ISCHEMIA

Coronary artery occlusion very rapidly leads to myocardial anoxia. It has been estimated that cardiac oxygen stores are probably depleted in about 5 seconds in conscious resting dogs with heart rates in the range of 60 to 80 beats/min (13). Consistent with this estimate, coronary venous blood is almost completely desaturated immediately after release of the coronary occlusion, and, if the occlusion is longer than 5 seconds, there is also a release of lactic acid into the cardiac venous effluent (14). As coronary flow rises early in the hyperemic response, so does the coronary venous oxygen saturation, which may reach a level very near that of arterial blood. Venous oxygen saturation then gradually returns to control levels by the end of hyperemia. On the basis of current information, the most likely explanation for the decreased oxygen extraction is that erythrocytes traverse the exchange vessels too rapidly to permit the usual degree of hemoglobin deoxygenation. At the peak of the hyperemic response, coronary flow rates may be increased as much as 5-6 times control; although coronary blood volume may increase (15), the mean transit time of an erythrocyte, calculated as the quotient of vascular volume and flow rate, is nevertheless shortened severalfold. Despite this reduction in oxygen extraction throughout most of reactive hyperemia, the disproportionately greater increase in coronary flow rate results in a calculated oxygen consumption rate that is elevated, and "oxygen debt," like flow debt, is invariably overpaid, although only in rough proportion to the debt incurred (14, 16). A number of factors can contribute to the overpayment of oxygen debt (14): heart rate may increase, especially during longer occlusions; ventricular dimensions may change, affecting both preload and afterload; the elevation of coronary flow during reactive hyperemia may of itself stimulate the oxygen consumption rate (17), as may the release of catecholamines (18). These factors which promote myocardial oxygen usage can be opposed and modulated by factors tending to reduce it. For example, aortic pressure tends to fall during the period of coronary occlusion and may not return to control levels until well into the hyperemic response. Occlusions of sufficient length produce tissue acidosis, which tends to inhibit both anaerobic and oxidative metabolism (19). Such a complex interplay of chemical and hemodynamic events during both the interval of ischemia and the ensuing reactive hyperemia prevents an exact accounting for the overpayment of oxygen debt.

THE CAUSE(S) OF MYOCARDIAL REACTIVE HYPEREMIA

The tissue metabolite hypothesis proposed by Lewis and Grant (2) has dominated thinking about the cause of reactive hyperemia ever since it was
proposed. Four pieces of evidence are customarily cited in support of this mechanism for myocardial reactive hyperemia. (1) The volume of reactive hyperemic flow is proportional to the duration of coronary occlusion and, to the extent that elevations of control coronary flow imply elevated oxygen utilization, the response is augmented at higher coronary flow rates. (2) Stimulation of cardiac oxygen demand during the interval of coronary occlusion by pacing the ventricle at higher rates or by applying paired pacing increases the volume of reactive hyperemic flow (20, 21). (3) Lowering myocardial oxygen requirements by cooling the heart diminishes the hyperemic response (22). (4) The time course of the change in coronary blood flow rate is consistent with the existence of a vasodilator that is constantly produced by the heart; this substance accumulates during the interval of coronary occlusion, and its dissipation during reactive hyperemia follows exponential kinetics (13). As will be pointed out later in this review, this evidence is consistent with some sort of oxygen-dependent mechanism, but it does not explicitly establish the existence of a vasodilatory metabolite.

It is clear that the enhanced flow during reactive hyperemia is not absolutely required to restore the heart to its preocclusion state. The consistently greater repayment of flow debt compared with the repayment of oxygen debt (8, 9, 14, 16) suggests a vasodilator whose hemodynamic effects are out of proportion to the stimulus for its production. Two laboratories have recently shown that the heart is able to recover from an interval of coronary artery occlusion even when coronary flow is artificially restricted during reactive hyperemia (23, 24). In these experiments, flow debts were overpaid but by only a third as much as they were when coronary flow was unimpeded.

The list of vasodilatory metabolites which have been proposed to regulate coronary flow and therefore reactive hyperemia is long: adenosine, bradykinin, carbon dioxide, catecholamines, histamine, hydrogen ion, lactic acid, increased osmolarity, potassium, prostaglandins, and serotonin (25). The evidence favoring adenosine as a primary mediator, although far from complete, is the most detailed and, therefore, the most persuasive at this time. This statement should not be construed as excluding the participation of other substances, e.g., potassium ion or prostaglandins, which may also be released during the interval of coronary occlusion. Adenosine is produced constantly in oxygenated dog hearts, and it accumulates during even brief periods of anoxia (26, 27). Adenosine and its degradation products have been recovered from the coronary effluent of hearts during ischemic perfusion (28, 29), during reactive hyperemia (30), and during pacing-induced ischemia in man (31). The extensive degradation of adenosine during its transit into the vascular space (32) prevents using these data to predict adenosine concentrations in the vicinity of the coronary resistance vessels, an essential part of assessing a causative role for this nucleoside in this response. Indeed, this problem is a weakness in the support for any of the various substances which have been proposed as mediators of reactive hyperemia.

The role of adenosine has recently been challenged by studies employing methylxanthines, which antagonize the coronary vasodilatory effects of adenosine in oxygenated hearts (33) but have little or no effect on myocardial reactive hyperemia (34–36). This finding constitutes a serious though not necessarily fatal objection to a role for adenosine in the hyperemic response. Judgment must await more information about the mechanism of adenosine-induced coronary vasodilation and the mode of action of the methylxanthines in antagonizing this effect. There is no reason to believe a priori that the biological effects of an exogenously administered metabolite should be quantitatively similar to those of the metabolite produced in situ. It is also possible that the responsiveness of the coronary arteries to adenosine is altered by the ischemic interval. The coronary vascular smooth muscle cells are exposed to hypoxia just as the striated cardiac muscle cells are and could be expected to require some time to be restored to their preocclusion metabolic state. It is known that adenosine and hypoxia act synergistically to relax coronary arteries (37) and possibly such an effect prevails over methylxanthine antagonism.

Prostaglandins are the most recently proposed candidate mediator(s) of reactive hyperemia, and it is, therefore, appropriate to summarize the existing evidence regarding their role in this response: (1) in canine open-chest or heart-lung preparations, coronary occlusions lasting 10–20 seconds lead to the enhanced release of material reacting immunologically like prostaglandin E, and (2) the administration of either meclofenamate or indomethacin, drugs which block prostaglandin synthesis, results in significant reductions in both the volume of reactive hyperemic flow and the release of prostaglandin-like material during reactive hyperemia (38). It is difficult to evaluate the report on the involvement of prostaglandins

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(38) because the number of dogs tested was small, certain critical hemodynamic data, e.g., blood pressure, were not given, and it was not established that prostaglandin production was either dependent on the duration of coronary occlusion or related to the volume of reactive hyperemic flow. A study similar in experimental design failed to show an effect of these drugs on reactive hyperemia (39), and a study of the formation of prostaglandinlike materials in response to cardiac anoxia, although confirming that these compounds are released, was interpreted as indicating that the time course of release could not account for the changes in coronary flow which were observed. This study also failed to confirm an effect of prostaglandin synthetase inhibitors on the intensity of the coronary flow response to anoxia (40). It is difficult to see how prostaglandins, whose synthesis requires molecular oxygen (41), could be formed to any great extent during complete coronary occlusion. None of these findings completely excludes the possibility that vasoactive prostaglandin precursors rather than the prostaglandins themselves might be the physiologically active agents. Obviously, this is a relatively new field of research and much more work is necessary to define or exclude any role for the prostaglandins as mediators of coronary flow in general and in reactive hyperemia in particular.

Two alternative hypotheses challenge the orthodox view that reactive hyperemia is mediated by vasodilatory tissue metabolites. The first is based on the proposal of Hilton and Eichholdt (42) that coronary vascular tone is normally regulated by and is dependent on the availability of oxygen to the vascular smooth muscle cells. Although it is entirely possible that the vascular smooth muscle cells may undergo metabolic changes when they are exposed to anoxia, the experimental evidence supporting this possibility is controversial (43, 44). As indicated earlier, some time may elapse before these cells recover from hypoxia, and this fact could account for their relaxation during reactive hyperemia even though they are exposed to an abundant supply of oxygen. This hypothesis can also account for the effects of the duration of occlusion and prevailing coronary flow rate on the size of the hyperemic response. Since this hypothesis envisions the control of coronary vascular tone as residing in the coronary vessels themselves and as independent of the oxygen needs of the striated cardiac cells, it easily explains the manifold overpayment of flow debt. Indeed, all of the evidence favoring control by a locally produced vasodilatory metabolite can equally well be used to support the hypothesis that reactive hyperemia is due to the metabolic consequences of hypoxia within the coronary vessels themselves. The extraordinary sensitivity to oxygen lack which this hypothesis presupposes is not entirely consistent with the observation that isolated coronary arteries maintain their tone reasonably well under hypoxic conditions until extremely low levels of oxygen tension are reached in the range of 5–10 mm Hg (37). Although Honig (43) has cited evidence that the oxygen consumption rate of coronary smooth muscle may be higher than that of an equivalent mass of striated cardiac muscle, this difference has not been confirmed by other studies (45), nor is it compatible with the histologic observation (46) that mitochondria occupy a much smaller fraction of total cell volume in vascular smooth muscle cells than they do in cardiac muscle cells, wherein they may occupy up to one-third of the cell volume (47). Finally, neither this hypothesis nor the vasodilatory metabolite hypothesis can explain the reactive hyperemia which follows a coronary occlusion for only a single heart beat (24).

Reactive hyperemia has also been attributed to myogenic relaxation of the coronary myocytes during the interval of arterial occlusion. Myogenic tone is thought to be stimulated by the distending force exerted by intraluminal pressure, causing a counterbalancing contraction of the smooth muscle in the vessel wall. Thus, the caliber of a blood vessel is the resultant of these opposing forces (48). This hypothesis can account for autoregulation, the adjustment of vascular resistance which maintains flow very nearly constant in the face of changes in perfusion in the physiological range. These autoregulatory adjustments do not occur instantaneously, however; abrupt increases or decreases in perfusion pressure cause a directionally similar over- or undershoot of flow rate before the new steady-state level is reached (49, 50). These flow transients probably reflect the contractile state of the vascular smooth muscle prior to the change in pressure and also the characteristically slow contractile response of this type of muscle. Superficially at least, myocardial reactive hyperemia resembles such a response. The pressure distal to a coronary artery occlusion falls within a few seconds to levels on the order of 2–15 mm Hg (51) and rises rapidly when the occlusion is released, so that the ensuing reactive hyperemia could reflect myogenic relaxation during the preceding interval of coronary occlusion. Eikens and Wilcken (24) have observed reactive hyperemia following coronary occlusions as short as a single beat, and they point...
out that, because occlusions this brief are unlikely to cause significant myocardial ischemia, the hyperemic response may be myogenic. Although these authors did not prove that intraluminal coronary pressure fell in their experiments, an immediate and rapid fall in “peripheral coronary pressure” is so well documented (see Fig. 3 of ref. 51, for example), that there can be little doubt that this necessary precondition for a myogenic response also occurred in their experiments. It is this reviewer’s opinion that a myogenic mechanism is the only plausible explanation for reactive hyperemia in the special case of 1- and 2-beat coronary artery occlusions. In another series of experiments, these authors restricted coronary flow to levels roughly 15% above control during reactive hyperemia and found that on release there was a transient increase in flow. They observed aortocoronary pressure gradients of 5-42 mm Hg at the time of release and, because the flow debt had been more than repaid by this time, reasoned that the transient hyperemia represented a myogenic response. This evidence would be more persuasive had they shown that cardiac oxygen metabolism had also returned to normal at the time the coronary constriction was released, since Bache et al. (11) have recently shown that coronary constriction during reactive hyperemia leads to subendocardial ischemia in the presence of coronary flow levels which, if uniformly distributed across the ventricular wall, would have prevented regional ischemia. Thus, the possibility remains that the transient hyperemia actually was ischemia-induced reactive hyperemia of the deeper layers of the myocardium.

The myogenic hypothesis fails to explain the proportional relationship between occlusion length and the volume of reactive hyperemic flow. Available evidence on smooth muscle relaxation indicates that this process is exponential rather than linear (52), and, indeed, diastolic peripheral coronary pressure reaches a stable minimum value within 5–7 heart beats after coronary occlusion (51). Thus, the bulk of any vascular relaxation induced by a coronary occlusion occurs relatively early in the occlusion, and, if the degree of relaxation is the sole determinant of the following hyperemia, the volume of hyperemic flow following occlusions longer than, say, 5–7 beats should be independent of occlusion length.

Therefore, one must conclude from the evidence reviewed in this paper that reactive hyperemia in the heart is a complex response having both physical and chemical determinants. No single hypothesis for the control of coronary blood flow can account for all of the features of this response, and, indeed, there is persuasive experimental evidence to support the participation of locally produced vasodilatory metabolites, vascular smooth muscle oxygen deprivation, and loss of myogenic tone during the interval of coronary occlusion. Although there is a consensus favoring regulation of reactive hyperemic flow by a vasodilatory metabolite, the supporting evidence does not unequivocally exclude the direct effects of oxygen lack on the coronary resistance vessels. Myogenic relaxation appears to be the dominant determinant of reactive hyperemic flow for extremely brief coronary occlusions, but any contributions it might make to hyperemia following longer occlusions seems to be obscured by metabolic factors and certainly has not been quantified. The concept of a flow debt and its repayment, which is a central feature of the hypothesis that reactive hyperemia is a preponderantly metabolic response, must be viewed as a semiempirical and approximate index of the events which are its real cause. Precisely because these parameters are only approximations of metabolic events which are modulated by a number of nonmetabolic events, their use should be abandoned in future experiments in favor of direct measurements of metabolic changes. The complexity of the metabolism and the lability of some of the putative vasodilators speak strongly for analysis of their concentrations in tissue samples rather than in coronary venous effluent. Furthermore, these concentration data should be related to coronary flow rate in some meaningful way, i.e., one should recognize that reactive hyperemia is a time-dependent process. Experiments which provide data for point-by-point comparisons of flow and one or another aspect of cardiac metabolic status will probably yield more conclusive information than integrated sampling techniques. Advances in biomedical instrumentation will hopefully make it possible to take the same approach in quantifying the physical factors which modulate the hyperemic response.

Although our understanding of the determinants of the reactive hyperemic response remains imperfect, this review documents steady progress toward this goal and predicts that, as an experimental model, reactive hyperemia should continue to yield useful insights into the physiological regulation of coronary flow.

References
2. Lewis T, Grant R: Observations upon reactive hyperemia in man. Heart 12:73-120, 1925-1926
43. HONG CR: Control of smooth muscle actomyosin by phosphate and 5'AMP: Possible role in metabolic autoregulation. Microwave Res 1:133-146, 1968
44. HERLIHY JT, MURPHY RA: Absence of a direct effect of phosphate or 5'-AMP on the contractile proteins of hog carotid arteries. Circ Res 28:434-440, 1971
47. PAGE E, EARLEY J, POWER B: Normal growth of ultrastructures in rat left ventricular myocardial cells. Circ Res 35(suppl II):II-12-16, 1974
48. BAYLISS WM: On the local reactions of the arterial wall to changes of internal pressure. J Physiol (Lond) 28:220-231, 1902
Myocardial reactive hyperemia.

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