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REACTIVE HYPEREMIA IN CAT MESENTERY CAPILLARIES

by

George Paul Pollock

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PHYSIOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

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THE UNIVERSITY OF ARIZONA

1975

THE UNIVERSITY OF ARIZONA

GRADUATE COLLEGE

I hereby recommend that this dissertation prepared under my direction by George Paul Pollock

entitled Reactive Hyperemia in Cat Mesentery Capillaries

be accepted as fulfilling the dissertation requirement of the degree of Doctor of Philosophy

Paul C. Johnson — Dissertation Director

April 11, 1975 — Date

After inspection of the final copy of the dissertation, the following members of the Final Examination Committee concur in its approval and recommend its acceptance:*

Robert K. Gore	April 11, 1975
[illegible]	April 11, 1975

*This approval and acceptance is contingent on the candidate's adequate performance and defense of this dissertation at the final oral examination. The inclusion of this sheet bound into the library copy of the dissertation is evidence of satisfactory performance at the final examination.

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ABSTRACT

The hyperemia following release of an arterial occlusion has been most commonly attributed to metabolic factors such as oxygen depletion and accumulated metabolites. Some investigators, however, have suggested that the pressure reduction during the occlusion induces a myogenic relaxation of the resistance vessels. Since the mesentery has a low metabolic rate we felt that myogenic mechanisms during reactive hyperemia might be observed more clearly in this tissue. The dual slit method for red cell velocity measurement was used to measure flow in mesenteric capillaries of an isolated, autoperfused cat intestine preparation. Arterial occlusions of 15-60 sec duration were performed by clamping the arterial inflow circuit. Four types of reactive hyperemia responses were observed in mesenteric capillaries. Analysis of these responses were performed measuring several variables as functions of duration of occlusion. The data from these vessels indicated that metabolic regulation during reactive hyperemia was eminent in 43% of the Type III vessels and 38% of the Type IV vessels. When arterial pressure was pulsed (20-80 mm Hg) for 5 to 20 seconds, a brief initial hyperemia was followed by a marked decrease in flow. This decrease was a function of the

magnitude of the pressure pulse. However, a slow ramp increase in pressure of the same magnitude did not produce an initial hyperemia or a secondary fall in flow. It was concluded, therefore, that both metabolic and myogenic mechanisms contribute to reactive hyperemia in the cat mesenteric microvasculature. It was furthermore concluded that the myogenic mechanism was the dominant mechanism.

INTRODUCTION

This dissertation is concerned with the mechanisms responsible for reactive hyperemia. Reactive hyperemia is commonly recognized as the transient period of increased blood flow which occurs following a period of arterial occlusion. This response has been studied extensively for almost 100 years, but its mechanisms are still not understood. The controversy centers around two theories: the myogenic and the metabolic theories.

Bayliss (1902) proposed the myogenic theory. He maintained that vascular smooth muscle possesses an intrinsic ability to respond to changes in intravascular pressure. Decreased intravascular pressure, such as that developed during arterial occlusion, was thought to induce vasodilation and, therefore, caused the subsequent hyperemia immediately following release of the occlusion. The hyperemia was terminated by a vasoconstriction induced by the intraluminal pressure increase which followed flow restoration.

The metabolic theory evolved from the strong criticism of Bayliss' work posed by Anrep in 1912, and later by Lewis and Grant in 1925. This theory suggested that normally occurring vasoactive metabolites accumulated in excess concentration during arterial occlusion. The metabolites were thought to act on the smooth muscle of resistance vessels to cause relaxation. This

dilatation allowed a hyperemia, when flow was restored, which persisted until the normal concentration of vasodilator metabolites was reestablished.

Selkurt, Rothe, and Richardson (1964) studied gross flow reactive hyperemia in the isolated, autoperfused, canine intestine and evaluated the respective importance of these two mechanisms in that preparation. They concluded that the response was mediated by metabolic factors and that the myogenic contribution was negligible, if indeed it existed at all. In view of these conclusions, the observations of Johnson and Wayland (1967) indicate that the picture is not that clearly defined. They presented evidence that autoregulation in capillaries of the cat mesentery is mediated by a myogenic mechanism. Althouth it was not studied in detail, they noted a well-defined reactive hyperemia when arterial pressure was restored to normal levels after a period of hypotension. It is, therefore, provocative to consider the possibility that the reactive hyperemia response they observed might be mediated by the myogenic mechanism, especially in light of the observations of Selkurt et al. (1964) that intestinal reactive hyperemia is probably metabolic in nature. Since reactive hyperemia has not been studied in detail in the mesentery, the question of the underlying mechanism is unresolved.

Only two studies of reactive hyperemia in microvessels have been conducted. Burton and Johnson (1972) observed the response in cat sartorius muscle capillaries and found evidence of

both myogenic and metabolic regulation. They categorized four different groups of capillaries based on the duration of the post-occlusion hyperemia. In the other investigation, Gentry and Johnson (1972) studied reactive hyperemia in frog pectoralis muscle microvessels. They concluded that reactive hyperemia in that preparation was controlled by metabolic factors.

These findings emphasize the fact that the mechanism of reactive hyperemia is not well understood. Furthermore, they indicate that a controversy still exists about whether the myogenic and metabolic mechanisms act singly, or in combination, to regulate local flow phenomena. In the minds of some physiologists, there is considerable doubt that the myogenic mechanism exists. A brief search of the literature quickly reveals the paucity of direct supportive evidence of the myogenic mechanism.

The purpose of this study was to observe reactive hyperemia in cat mesentery capillaries. It was of primary consideration to determine if myogenic regulation was involved in this response. This tissue was selected for study because: 1) reactive hyperemia was known to occur in its microvessels, 2) evidence of myogenic regulation was previously found in this tissue, and 3) microvascular responses could be studied in this tissue with existing techniques.

HISTORY

Reactive hyperemia is the transient increase in blood flow which occurs following a period of arterial occlusion. The first descriptions of this phenomenon were provided by Cohnheim (1872) and Lister (1878) in their writings about battlefield surgery. They explained that this hyperemia developed because of vasomotor nerve paralysis incurred during tourniquet application. This theory met its demise with the observations of Roy and Brown (1879-80) and Bier (1897). Roy and Brown (1879-80) reported that reactive hyperemia occurred in the denervated frog leg, but not until 1897 did Bier clearly demonstrate, in the pig and in humans, that the response was independent of the nervous system. He did this by showing that reactive hyperemia occurred in limbs whose only connections to the body were an artery and vein. Bier explained that circulatory arrest stagnated the blood and caused vasoconstriction. He further contended that the hyperemia did not occur until entering arterial blood induced vasodilatation.

Support of this theory remained strong until the 1920's when August Krogh (1922) conducted experiments which proved that dilation occurred during the arterial occlusion. His most definitive experiment showed that the skin of hands rendered ischemic blanched when digital pressure was applied, but that the previously existing cyanotic appearance immediately returned upon removal of the pressure.

Other theories were proposed to explain the mechanism of reactive hyperemia during this time. The first of these involved an inverse relationship between intravascular pressure and vessel diameter. This theory was proposed by W. M. Bayliss (1902) and it is now known as the Bayliss or myogenic theory. Bayliss derived his theory from experiments performed on the denervated hindlimbs of dogs and cats, dog kidney, rabbit intestine, and isolated segments of dog carotid artery. He observed that temporary arterial occlusion in denervated preparations resulted in vasodilatation. To test the converse, vasoconstriction in response to elevated arterial pressure, he stimulated the central end of the sectioned sciatic nerve. This initially produced a passively induced increased limb volume, but eventually gave way to a decreased limb volume. This was said to result from an active constrictor response of myogenic origin. Similar results were reported from experiments in the dog kidney and rabbit intestine.

Bayliss also reported the results of experiments on isolated dog carotid artery segments as intraluminal pressures were altered. An artery segment was tied off at one end, fitted with a cannula at the other end, and filled with defibrinated blood. This system was then attached to a mercury filled reservoir, the height of which was adjustable to establish different intraluminal pressures in the vessel. As described by Bayliss (1902, p. 229), "When now the pressure was raised inside the artery it was seen at first to swell, but immediately, and while the mercury was still kept at its height, a powerful contraction took place, in which the artery appeared to

writhe like a worm." A "considerable relaxation" was observed when the pressure was lowered. Objective data on this point was not presented and Bayliss terminated this section of his report by indicating his regret that the kymographic tracing of this experiment had been "spoilt in varnishing."

A few years later, Anrep (1912) essentially duplicated Bayliss' experiments but placed a different interpretation upon the results obtained. For instance, while Bayliss considered metabolic factors inconsequential in his experiments because the occlusion durations (8 seconds) in his experiments were too short, Anrep contended that any circulatory deprivation, no matter how short, introduced metabolic factors which affected the vasculature. Secondly, he believed splanchnic nerve stimulation caused massive release of adrenalin, a substance unknown to Bayliss at the time of his experiments, which produced the constrictor response. This belief stemmed from his observation that the constrictor response only occurred in those animals in which the adrenals and both splanchnic nerves were intact. In those animals subjected to splanchnic nerve section and adrenalectomy no constrictor response was ever observed. When other tests were performed to observe vascular responses to elevated arterial pressure, the limb volume passively followed the pressure changes in all instances.

The experiments were also performed on excised artery segments and Anrep was unable to confirm the results of Bayliss' experiments. At no time did he observe an active response to a change in pressure in isolated vessel segments.

Anrep postulated that asphyxial metabolites were responsible for reactive hyperemia. To test this hypothesis, he perfused the rabbit ear with solutions of lactate, acetate, and hydrochloric acid. Blood flow increased through the preparation and demonstrated the vasodilator influence of each of these substances. Perfusion with Ringer's solution equilibrated with a 7 percent carbon dioxide mixture also caused a hyperemic response. An additional experiment in which the brachial artery and vein were clamped and released simultaneously produced such a prodigous hyperemia that Anrep considered it to be totally of metabolic origin. He concluded that vasodilator asphyxial products accumulated during circulatory restraint and caused vasodilatation. He did not accept the existence of a myogenic response to intravascular pressure. His work, therefore, fostered the metabolic theory of reactive hyperemia.

Reactive hyperemia was also explained by the tissue pressure theory for a period of time. This theory was particularly pleasing to many physiologists because it postulated a simple relationship of physical factors in the regulation of blood flow. Briefly, the tissue pressure theory (Rodbard, 1962) suggested that filtration of fluid across the capillary network contributed to the local extravascular fluid pressure which acted to control local blood flow. It was presumed that increased blood flow led to increased capillary filtration, which in turn caused tissue pressure to increase. Eventually a compressive force, sufficient to collapse the capacitance vessels, was said to develop and thus return blood flow to normal levels. Conversely, decreased blood flow, for instance the

ischemic period prior to reactive hyperemia, was explained to cause tissue fluid reabsorption. Because of their anatomical structure and low internal pressure the small veins were considered to be the site of regulation.

This theory is not a valid explanation for autoregulatory phenomena such as reactive hyperemia. In the first place, it is generally held that the precapillary vessels, not the capacitance vessels, house the mechanisms which control local blood flow (Stainsby 1973 and Zweifach 1973). Secondly, since the tissue pressure theory is based upon purely mechanical factors, vascular beds which have been treated with metabolic poisons or smooth muscle relaxants should exhibit unmodified autoregulatory responses. However, Johnson (1964) showed that autoregulation no longer occurred in intestinal preparations treated with cyanide or papaverine. Furthermore, the necessity of a sufficiently rigid capsule, capable of withstanding elevated tissue pressures, was implicit in the tissue pressure theory. Most tissues lack such a structure. Moreover, tissue pressures, as measured by various techniques and in various tissues, are much too low to have the function suggested by this theory. For instance, the needle puncture technique for tissue pressure measurement indicated that tissue pressures in dog muscle (Henderson et al., 1936) and human subcutaneous tissue (Burch and Socleman, 1937) were slightly higher than atmospheric pressure. Johnson (1964) used this same technique and found tissue pressure in the cat mesentery to be approximately 0.3 to 0.4 mm Hg. He also

determined tissue pressure remained unchanged even though venous pressure was elevated in small increments to 15 mm Hg.

Guyton (1963) measured interstitial pressure in another manner. He implanted plastic capsules in various tissues and organs. Pressure within the ingrown capsules were subsequently measured by needle puncture and found to be subatmospheric.

A wick method (Scholander, Hargens and Miller, 1968) produced tissue pressure values comparable to those of Guyton's capsule method. A comparison of the capsule and wick methods was made by Prather et al. (1971) and although the wick method indicated slightly higher tissue pressures, all values were determined to be subatmospheric.

With the elimination of the tissue pressure theory as a suitable explanation, two theories remain to be considered as possible explanations for reactive hyperemia. These are the myogenic theory of Bayliss (1902) and the metabolic theory of Anrep (1912). These theories will now be critically reviewed, separately and in detail, with particular emphasis placed upon that literature which pertains to intestinal and microvascular reactive hyperemia experiments.

THE MYOGENIC THEORY

The concept that vascular smooth muscle possesses an ability to actively respond to changes in intraluminal pressure was proposed by W. M. Bayliss in 1902. His studies of isolated carotid artery segments were repeated by Wachholder (1921) and Burgi (1944) who found transient periods of constriction and dilation occurred when intravascular pressure was raised and lowered, respectively. However, Bayliss' report (1902) of a sustained contraction with pressure elevation has not been confirmed.

A series of experiments conducted by Bjorne Folkow in 1949 served to revitalize the myogenic theory. These experiments were conducted because earlier investigations (Folkow, Haeger, and Kahlson, 1948) of the role of several humoral agents in the reactive hyperemia response yielded negative evidence of metabolic regulation. Folkow examined the possibility that physical factors were involved in local regulation of blood flow. To test this hypothesis, extensive experiments were done using the hindlimb or intestinal preparations of dogs, cats, and rabbits. Arterial pressure reductions and elevations were effected and the consequent variations in venous outflow were measured. Pressure reductions were created by partial or total occlusion of the abdominal aorta. A representative recording of the flow change caused by a partial arterial occlusion was shown. From this single figure, and the assurance that the other six intestinal preparations responded similarly, it can be determined that

3 to 5 second arterial occlusions produced 10 to 25 second periods of vasodilatation. Arterial pressure elevations were said to induce vasoconstriction, although no records were shown to substantiate this claim. Although more thorough documentation of the data might have provided more credibility to Folkow's conclusions, he nevertheless reported that both aspects of the myogenic response were seen in the intestinal circulation.

Critical evaluation of Folkow's experiments reveal that excellent controls were incorporated. These responses were observed in adrenalectomized, properly anesthetized animals. The possibilities that they were related to the type of anesthesia, or to metabolic agents, were thoroughly evaluated and were found to be negative.

Prior to Folkow's evidence of myogenic activity, a 40-year period existed where experimental emphasis was placed on the determination of "the regulatory metabolite" of local blood flow phenomena. It is a tribute to the excellence of Folkow's work that the myogenic theory became such a popular area for investigation in the following years.

One series of experiments employed the venous plethysmographic technique with human subjects (Patterson, 1954). The basic premise of these experiments was that transmural pressure was the stimulus for the myogenic response. Increased vascular transmural pressures were created by exposing the limbs of humans to subatmospheric pressures. Using this procedure, Patterson and Shepard

(1954) determined that resistance to blood flow increased in human forearms as a result of increased transmural pressure. Similar results were obtained from the forearm and calf of humans (Coles, Kidd, and Patterson, 1956; Blair et al. (1959).

Variations of this technique, where the limbs were prepacked with blood prior to arterial occlusions were performed by Wood, Litter, and Wilkins (1955). Since reactive hyperemia was significantly reduced by this procedure, they concluded that the myogenic mechanism was responsible. These observations were confirmed by Patterson (1954). Barcroft (1972) criticized those experiments on the grounds that prepacking with red cells increased oxygen supplied to the resistance vascular smooth muscle. This would theoretically provide for a higher vascular tone for a longer period of time. But it remains to be shown that local oxygen supply directly controls vascular smooth muscle tone. His criticism, furthermore, cannot be applied to other experiments which have shown myogenic activity in response to transmural pressure alterations.

Johnson (1959) showed that venous pressure elevation caused precapillary resistance to increase in the dog intestine. Since neural blockers did not alter the response, it was concluded that myogenic activity was responsible. Similar observations and conclusions were made in the limbs of anesthetized dogs by Haddy (1964). Elevated venous pressure also effectively decreased the capillary filtration coefficient during constant arterial perfusion pressure experiments (Mellander, Oberg, and Odelram, 1964).

These observations were confirmed by Baker (1970) and Imao (1971) in constant flow experiments with the limbs of dogs.

The above-mentioned experiments represent indirect proof that myogenic activity occurs as a result of transmural pressure change. The strongest evidence has come from those experiments in which direct examination of microvascular responses were made.

Spontaneous contractions of arterioles in the bat wing were described by Wiedeman (1966). The strength of the contractions were found to vary, but occasionally were strong enough to stop blood flow. Terminal arterioles arising from the same parent vessel were observed to have different contraction frequencies. Some arterioles were always found to be very active, while still others never exhibited contractions. Infusion of saline solutions into the major artery of the bat wing produced pressure elevations, but the actual magnitudes were not recorded. The duration of contraction increased with pressure elevation. Control contraction durations averaged 25 seconds. "Slight" pressure elevations increased the duration to 44 seconds (11-82 seconds) and pressure increases to levels approximately twice this "slight" elevation prolonged the contractions to 60 seconds (25-82 seconds). These experiments, while somewhat deficient in control and quantitation, generally support the mechanism of myogenic activity proposed by Folkow (1964). They are subject to criticism on the basis that saline infusions are known to inhibit myogenic activity in some preparations (Folkow 1952). However, no inhibition of vascular reactivity was reported by Wiedeman. It is possible that the

infusions were of such short duration that they did not affect myogenic activity. Alternatively, the responses may have been metabolically regulated and resulted from the transient reduced concentration of some local vasodilator metabolite which provided a momentary increased vascular tone.

The periodic fluctuations in the red cell velocity of some capillaries, observed by Johnson and Wayland (1967), was considered to be the result of myogenically regulated opening and closing of precapillary sphincters. Johnson (1968) also observed increased arteriolar diameters with arterial pressure reductions. Arteriolar constriction also occurred when arterial pressure was increased. A latent period of 5 to 15 seconds between the pressure reductions and the onset diameter change was noted.

These experiments represent the strongest support that exists for the myogenic theory because they demonstrated both the dilator and constrictor aspects of the myogenic mechanism in isolated, denervated, autoperfused preparations.

The relationship between internal pressure and vessel lumen diameter of artificially perfused rat mesoappendix vessels was studied by Baez (1968). Observations were made of precapillary arterioles, sphincters and capillaries under zero flow conditions. Sixty-seven percent of the vessels studied showed no change in lumen diameter as internal pressure was raised to 40 mm Hg. At this pressure, constrictor responses were initiated with a latency of 6 seconds after pressure reduction of 24 mm Hg, but subsequently gave

way to an apparently active dilatation. While pressure was maintained at 24 mm Hg, stepwise increases of lumen diameter from 13.6 to 16.1, 16.9 to 19.6 micro developed at 60, 80, 105, and 120 seconds, respectively.

Baez (1968) further determined that the Bayliss response was evident in precapillary sphincters and metarterioles. An arteriole was observed to dilate as pressure was decreased to 75 mm Hg. This vessel was determined to control the vasomotor activity of at least one precapillary sphincter. Vasomotion occurred via this sphincter at a frequency of 2/minute. The myogenic response was observed in metarterioles over a more limited range (40-50 mm Hg). Dilation and constriction occurred as pressure was lowered and raised respectively. The diameter change was not proportional to the magnitude of the pressure change and the vessel was completely closed during the contraction phase.

The cellular mechanism whereby myogenic activity originates still is not known. There is evidence, however, that it involves a response to passive stretch. Hill (1926) observed that visceral smooth muscle possessed the ability to actively contract when quickly stretched. Bozler (1947, 1948) also observed an increased rate of activation in response to passive stretch in other smooth muscles of single unit type. Passive stretch has also been demonstrated to stimulate vascular smooth muscle contractions in in vitro vascular preparations. Contractile responses to quick stretch were recorded in the human umbilical artery by Davignon,

Lorenz, and Shepard (1966), in isolated subcutaneous arteries by Johansson and Bohr (1966) and in helical strips of dog superior mesenteric artery by Sparks and Bohr (1962). In this latter study a latency of 8 to 20 seconds was observed between the stretch stimulus and the onset of tension development. In vivo observations of the bat wing by Nicoll and Webb (1955) and Wiedeman (1966) have also indicated that stretch stimuli are capable of modifying vasomotion contraction frequencies.

The relationship between passive stretch induced contractions and smooth muscle electrical activity was suggested by Bozler in 1941. Proof of this relationship was impossible to obtain at that time. However, with the advent of more refined microelectrodes, intracellular recordings became possible. By 1954, Bulbring was able to record the electrical activity of intestinal smooth muscle, but technical problems still prevented recording electrical events in vascular smooth muscle.

With the development of more sophisticated microelectrodes and other instrumentation, Funaki (1961) recorded intracellular electrical activity in situ in frog vascular smooth muscle. A stable resting potential of approximately -25 mV was observed. Spontaneously generated single spike potentials having a magnitude of 36 mV, an overshoot of 10 mV and a duration of 200 msec were described. The typical configuration of these action potential spikes was a slow rising pacemaker potential followed by a large, simple spike. Similar observations were made by Trail (1963) in situ

in rat mesenteric arterioles (100 - 200 μ). The recorded potentials varied from -30 to -50 mV and showed slow oscillations with a period of 5 to 7 seconds and an amplitude of 2 to 13 mV.

Vascular smooth muscle possesses, as do other smooth muscles, a lower resting potential than skeletal muscle. Frequently, this low resting potential is unstable and it is generally accepted that this instability gives rise to spontaneous pacemaker activity. Rhythmical activity such as this has been described in the rat portal vein in Axelsson et al. (1967) and Funaki (1966). Similar observations were made in mesentery vessels of the rabbit by Holman and McClean in 1967. These studies have shown that rhythmical contractions of vascular smooth muscle are directly related to action potentials which arise from slow waves. Furthermore, Cuthbert (1966) and Johansson and Bohr (1966) have reported the frequency of pacemaker activity is increased when vascular smooth muscle is stretched.

Folkow (1964) presented a model which incorporated the known electrical activity of visceral type vascular smooth muscle with the facilitatory influence of stretch. He considered stretch to preload the muscle and enhance its force of contraction. Secondly, he suggested that stretch increased the firing frequency of pacemaker cells. Under such circumstances, the ratio of contraction time to relaxation time would increase, implying that the vessel would be closed a greater part of the time. According to this model, it might be predicted that stretch induced by increased

perfusion pressure might become so extensive that tetanic fusion would result. The effect could be greatly enhanced if several pacemakers were simultaneously induced to increase their firing frequency, and closure of capillary ostia could theoretically result. Conversely, removal of stretch by decreased perfusion pressure would reduce the pacemaker firing frequency and cause vasodilatation. Therefore, both aspects of this model suffice to explain the flow changes seen in the typical reactive hyperemia response.

It can be argued that short duration pressure alterations would most effectively demonstrate myogenic activity. However, the experimental evidence which stems from this argument is less than conclusive. Bayliss (1902) observed no differences in the magnitude of reactive hyperemia with 8 to 20 second occlusions. Others have used occlusions of 3 to 5 seconds duration and observed pronounced vasodilatation (Hirose and Schilf 1931; Geber and Schwinghammer 1965; Kontos, Mauck and Patterson 1965; Konradi and Levtov 1970). Burton and Johnson (1972) most frequently used 60 second occlusion trials, but did observe prominent hyperemic responses in cat sartorius muscle capillaries with 5 second occlusions.

Other investigations have demonstrated that dilation occurs when either short term pressure reductions or elevations are induced (Jones and Berne 1962; Zsoter 1961; Smiesko 1971). Jones and Berne (1962) reported that an "active" vasodilatation, not to be confused with neurogenic mechanisms, occurred in dog skeletal muscle after either brief arterial occlusions or pressure increases. Zsoter (1961) injected a physiological saline solution over 1 to 5 seconds to create

rapid pressure elevations. Although pressure increases of 119 mm Hg were created by this procedure, no evidence of myogenic constriction was obtained. This, of course, contradicts the observations made by Wiedeman (1966), but is consistent with Folkow's contention that artificial perfusates destroy myogenic activity.

Smiesko (1971) observed that active vasodilatation occurred in the dog gracilis muscle in response to a one second square wave pulse of either increased or decreased perfusion pressure. The peak time was about 4 seconds and the duration was 25 seconds. The magnitude of the vasodilatation was proportional to the amplitude of the perfusion pressure change. It was also dependent on the initial perfusion pressure. Maximal responses only occurred over the ranges 77 to 112 and 79 to 114 for pressure increases and decreases, respectively. It was also determined that the duration of the vasodilatation was proportional to the amplitude of the pressure change.

Folkow (1949) generated pressure elevations by performing bilateral carotid occlusions in his preparations and observed vasoconstriction. He cautioned that the vasoconstriction only resulted when very rapid and very large pressure increases were used. Folkow did not emphasize the implication of this observation. That is, that the rate of pressure change is evidently a very important component of myogenic reactivity.

In summary, there is a substantial volume of literature which suggests that myogenic activity does exist, and that it is

associated with the electrical activity of vascular smooth muscle pacemaker cells. Some evidence exists which indicates that stretching vascular smooth muscle serves to augment its myogenic activity. There is also evidence that reactive hyperemia is initiated by a myogenic response to pressure reduction, or to lack of stretch. The converse reaction, vasoconstriction with elevated pressure is not as well substantiated generally, but has been observed more frequently in the more direct studies of the microvasculature. Two studies have demonstrated reactive hyperemia in microvascular beds, one of which produced evidence of a myogenic control mechanism. Neither study was of the mesentery microvasculature.

THE METABOLIC THEORY

According to this concept, the vasodilatation of reactive hyperemia is due to an accumulation of tissue metabolites during the period of flow stasis. This may be a consequence of reduced wash-out of metabolites which are normally produced by the tissues. Alternatively, it may be a metabolic change caused by ischemia. In this latter instance, the metabolic change is presumably due to oxygen deficiency as suggested by Barcroft (1972).

Certain prima facie evidence supports the metabolic theory. For instance, Lewis and Grant (1925) determined that the peak flow and the duration of reactive hyperemia in human forearms increased as a function of occlusion duration. These observations were confirmed by others in human studies (Freeman 1935; Jepson 1954; Catchpole and Jepson 1955). Lewis and Grant (1925) also observed these changes when forearm temperature was caused to increase. Their observations were later confirmed by Bache and Ederstrom (1965) in dog hindlimb studies. It can be argued that these changes reflect elevated levels of vasodilator metabolites.

The evidence for specific mediators as proposed by various workers will now be reviewed. The principal metabolites which have been considered are: histamine, oxygen deficiency, carbon dioxide, adenosine and adenine nucleotides, inorganic phosphate, hydrogen ion, potassium, and certain combinations of these substances.

Histamine

Lewis (1927) suggested that either histamine, or a histamine like substance, was released from tissues during arterial occlusion and caused hyperemia. Chemical analysis of dog venous blood collected during reactive hyperemia was later reported to show elevated histamine concentration (Barsoum and Gaddum 1935). Their work was confirmed by Anrep and Barsoum (1935) and Barsoum and Smirk (1936).

Similar experimental procedures were followed by Kwiatkowski (1941) in studies of human forearm reactive hyperemia. No evidence of histamine release was found. Anrep and Barsoum responded to this attack of their work by performing still more experiments using the same chemical analysis and again determined higher than normal histamine levels (Anrep et al. 1944). Others measured histamine levels of the venous effluent during reactive hyperemia in the ear and forelimb of dogs and the human forearm and confirmed Kwiatkowski's work (Emmelin, Kahlson, and Wicksell 1941).

This controversy was ended by a study of reactive hyperemia in the hindlimb of cats. Folkow, Haeger and Kahlson (1948) obtained control flow data during reactive hyperemia. Next they injected physiologic doses of histamine intra-arterially and comparable flow increases resulted. They found that this vasodilatation was blocked when the animals were treated with antihistamines such as benedryl and related compounds. However, the reactive hyperemia response was

not blocked by these agents. These observations have been confirmed in experiments with the human forearm (Duff, Patterson and Whelan 1955) and in the dog hindlimb (Geber and Schwinghammer 1965).

Kobold and Thal (1963) reported that histamine release from the canine intestine increased greatly over 4 hour ischemic periods. However, it would appear that such studies are more relevant to the pathophysiology of intestinal strangulation. No evidence has been found which indicates that histamine release occurs in the intestine during short term occlusions induced reactive hyperemia.

Hamster cheek pouch microvessels were shown to respond to iontophoretically applied histamine, and displayed vasodilation or vasoconstriction in a dose-dependent manner (Duling, Berne and Born, 1968). Others have demonstrated that topically applied antihistaminics induce vasoconstriction in several tissues (Altura and Zweifach, 1965; Altura, 1968, 1970; Bentley and Jackson, 1970). Schayer (1970) interpreted these observations to mean that endogenous histamine normally opposes some constrictor mechanism to regulate local blood flow. The above findings do not necessarily indicate that histamine has a regulatory role. An alternative explanation to Schayer's conclusions is that the antihistaminics are in themselves vasoconstrictive agents. So far as Duling's et al. (1968) observations, they seem to argue against histamine's involvement in reactive hyperemia. For instance, longer occlusion

durations should progressively increase the vasodilatation to a point, at which time only vasoconstriction would be effected. This type of response has not been reported.

Summary of Histamine and Reactive Hyperemia

Histamine is capable of inducing resistance vessel dilatation when injected intraarterially or when topically applied to the mesentery (Baez 1969). But the experimental evidence obtained from microchemical analysis, and also from pharmacological blockade, does not support histamine as a mediator of short term post-ischemic hyperemia. Although the evidence from microvascular studies indicate that histamine is a complex vasoactive agent of uncertain function, at the present time, histamine is not strongly implicated as the metabolic agent responsible for eactive hyperemia.

The Role of Carbon Dioxide in Reactive Hyperemia

Carbon dioxide has been shown to have vasodilator effects in many vascular beds. Because of this ability, it has been thoroughly examined for its role in reactive hyperemia. Folkow (1949) raised the CO_2 levels in the air inspired by dogs, from 0 to 5 percent, and did not observe dilatations comparable to those caused by partial arterial occlusions. Basal flow and experimental controls were not well defined in these experiments. Therefore, in the absence of any hyperemia it must be asked if the animals were already dilated when CO_2 was administered.

The experiments of Kontos, Mauck, and Patterson (1965) cannot be criticized in this way. They administered phentolamine to dogs prior to manipulating tissue CO_2. When an adequate blockade was determined, blood and tissue P_{CO_2} were lowered by hyperventilating the animals. This hypocapnia effectively reduced reactive hyperemia responses in their skeletal muscle preparations. They also determined that local hypercapnia, induced by the carbonic anhydrase inhibitor acetazolamide, augmented hyperemia. These observations contradict the conclusions of Folkow (1949) and Crawford, Fairchild and Guyton (1959), that CO_2 has no role in skeletal muscle reactive hyperemia.

It has been shown that hypercapnia induces vasodilatation in the intestinal circulation (Sidky and Bean 1951; Grim 1963). Sidky and Bean used different gas mixtures to vary the CO_2 content of blood used to perfuse isolated canine intestine. Hypercapnic blood (6.7% CO_2) caused increased venous outflow, and perfusion with control blood returned flow to normal. Blood equilibrated with 10% CO_2 caused a 300% increase in flow. Hypocapnic blood caused a 50% reduction in blood flow.

Although these experiments demonstrated that CO_2 induced vascular resistance changes in the intestine, they did not establish that tissue or blood P_{CO_2} increased during arterial occlusion. It is unlikely that P_{CO_2} increases to 76 mm Hg (10% CO_2 equilibrated blood) during arterial occlusions of less than one minute. Since

Selkurt et al. (1964) found that intestinal flow doubled following occlusions of this length, the possibility that CO_2 caused the response does not seem likely.

It is evident that carbon dioxide possesses vasodilator ability in most tissues. But the evidence only indicates a regulatory capacity for CO_2 in the cerebral (Rapela and Green, 1964) and, with reservation, the skeletal muscle vasculature (Kontos, Mauck, and Patterson, 1965). Furthermore, the accumulated evidence is less than conclusive that CO_2 mediates reactive hyperemia, even in skeletal muscle, and no evidence exists which indicates that CO_2 regulates reactive hyperemia in the intestine.

The Role of Oxygen Deficiency in Reactive Hyperemia

Oxygen deficiency was first suggested to be the cause of reactive hyperemia by Roy and Brown in 1879-80. They recognized that ischemia impaired nutrient supply and waste product removal. But they considered the distribution of oxygen to the tissues to be the critical issue, and associated oxygen depletion during ischemic periods with the vasodilatation of reactive hyperemia. According to this hypothesis, oxygen deficiency would directly affect the ability of vascular smooth muscle to contract.

Lewis and Grant (1925) found evidence of extensive vasodilatation during reactive hyperemia but rejected oxygen deficiency as the cause. They reasoned that the brilliant red coloration of the limb following an ischemic period was due to fully oxygenated

blood entering the tissues. Thus, they concluded that oxygen was actually in abundant supply and that oxygen deficiency was not a factor in reactive hyperemia. But it should be mentioned that resistance vessels dilate during the occlusive period and not after its release. Furthermore, the ischemic periods they used were of sufficient length that the ensuing hyperemia could be explained by oxygen deficiency (Barcroft, 1972).

Earlier Krogh (1922) showed that hypoxic blood caused dilatation in most tissues. However, he maintained that if oxygen were a key factor in reactive hyperemia, then it was necessary to demonstrate three things: (1) that oxygen would exert its effect on the vasculature over the same concentration ranges extant in the blood during the hyperemic response, (2) that it was also necessary to demonstrate that the magnitude of the hyperemia response normally seen could be approximated by artifically altered oxygen tensions through this same range, and (3) that the time course of reactive hyperemia and the corresponding variations in blood oxygen were comparable. Krogh was not able to prove that these relationships existed. Exact proof of these relationships still has not been established. However, a considerable body of evidence which relates to the role of oxygen deficiency in reactive hyperemia has accumulated.

A decrease in oxygen content, saturation and tension of deep venous blood was demonstrated during ischemia in cardiac muscle (Olsson and Gregg 1965), skeletal muscle (Fales, Heisey and Zierler 1962; Kontos and Patterson 1964; McNeill 1956) and kidney (Scott

et al. 1965; Selkurt 1965). Other studies have shown that as oxygen tension in the perfusing blood decreases, resistance to blood flow decreases in the coronary circulation (Berne 1963; Daugherty et al. 1967) hindlimb, (Attinger et al. 1967; Fairchild, Ross and Guyton 1966; Ross et al. 1962), intestinal circulation (Fleisch, Sibul, and Ponomaren 1932), and gracilis muscle of the dog (Skinner and Powell 1967).

Ross et al. (1962) observed a three-fold increase in blood flow through the dog hind leg when arterial hemoglobin saturation was decreased from 100 to 10%. When hemoglobin saturation was decreased from 100 to 90 percent, flow increased by only 25 percent. They, therefore, suggested that oxygen deficiency directly caused reactive hyperemia. It should be emphasized, however, that no experiments were performed where changes in arterial hemoglobin saturation in the occlused limb were correlated to any parameter of post-occlusion hyperemia. Furthermore, these experiments did not eliminate the possibility of altered tissue metabolism as a cause for the dilatation.

Fairchild et al. (1966) pursued the investigation of oxygen deficiency and its import to reactive hyperemia. Following a ten minute ischemic period, they perfused the hindlimbs of anesthetized dogs with blood having "zero" oxygen content. This procedure resulted in a sustained hyperemia which persisted until 100 percent oxygenated blood was supplied to the tissue. They interpreted, in classical fashion, that a reactive hyperemia response which was dependent on

washout of metabolites would characteristically display an overshoot and an exponential decline to control level flow. Since neither of these was seen in their responses, they strongly suggested that reactive hyperemia was a direct response of resistance vessels to oxygen deficiency per se. However, by their own admission, this experimental procedure does not eliminate the involvement of a vasodilator metabolite whose appearance, or removal, is oxygen dependent.

The impact of oxygen deficiency was further championed by Barcroft (1972). He calculated that anoxic conditions would be realized in skeletal muscle if the arterial supply was arrested for 3 minutes. He approximated oxygen consumption as 0.3 ml/min (Mottram 1955) and assumed that 0.6 ml O_2/100 ml muscle was stored in human muscle myoglobin (Farhi and Rahn 1955).

Evidence which contradicts a regulatory role for oxygen deficiency in autoregulation and reactive hyperemia also has been reported. For instance, Daugherty et al. (1967) observed no changes in vascular resistance in the perfused hindlimb anesthetized dogs until arterial P_{O_2} was decreased below 30 mm Hg. Kontos et al. (1970) varied the arterial blood P_{O_2} in the forearms of humans by having the subjects breathe gas mixtures of 9 and 12% O_2. Significant increases in forearm blood flow and decreased vascular resistance were observed when arterial blood oxygen tension decreased below 45 mm Hg. Comparison of the increased blood flow due to hypoxia, with

that in response to ischemia, revealed that the dilation due to hypoxia was only 26% of that caused by ischemia.

While these experiments show cause to suspect the role of oxygen in local blood flow regulation, they do not eliminate this role completely. They did not provide the crucial information about what tissue P_{O_2} is normally, how it changed during the course of their experiments, and whether local P_{O_2} alteration does affect vascular smooth muscle directly. Toward this end, Carrier, Walker, and Guyton (1964) observed that conductance increased in isolated small artery segments (0.5 to 1.0 mm o.d.) which were perfused and bathed with blood of low P_{O_2}. They also found that small arterioles increased their conductance by 15% following a 10 mm Hg (100 to 90 mm Hg) reduction in P_{O_2}, whereas a 50 mm Hg reduction was required to cause a similar change in larger vessels. This was interpreted to indicate that the contractile response of vascular smooth muscle from different regions of the vasculature is dependent on tissue P_{O_2}. Furthermore, it was concluded that the tension developed by the vascular smooth muscle from any region was dependent on local P_{O_2}. Detar and Bohr (1968) also demonstrated that the tension developed by hog carotid artery smooth muscle diminished with decreased P_{O_2}. Pittman and Duling (1973) also made this observation, but proved that the response was caused by limited diffusion of oxygen with thicker muscle strips, and was not related to a direct effect of P_{O_2}.

Pittman and Duling (1973) also estimated a value for the critical P_{O_2} in the vicinity of the vascular smooth muscle cells. For arterioles with wall thicknesses of 10 μm, this value was found to be 2 $\pm$ 6 mm Hg. According to this estimation, oxygen could only act as a regulator of blood flow in those vessels where P_{O_2} is 15 mm Hg or less. Regarding this point, Honig (1968) had earlier suggested that P_{O_2} was low enough in the vicinity of precapillary sphincters to regulate their activity. But Duling and Berne (1970) and Duling (1972) found that the P_{O_2} was not <15 mm Hg in the vicinity of the arterioles or the precapillary sphincter regions, but only reached such levels in the non-contractile capillaries.

The studies of Duling and Berne (1970) and Duling (1972) require more elaboration because they involved simultaneous measurements of tissue, perivascular, and vascular P_{O_2}, while vessel dimension changes occurred. They found that P_{O_2} values in the tissue surrounding hamster cheek pouch arterioles are essentially the same as inside the arteriole, which indicates that oxygen diffuses readily through the vessel wall. They also observed that an oxygen gradient exists along the length of arterioles. Thus, if tissue P_{O_2} was reduced, more oxygen would diffuse into the tissue and increase the longitudinal gradient along the arteriole. This could theoretically create a hypoxic environment in the vicinity of the precapillary sphincter and cause its relaxation. More recently,

Duling (1972) observed, in the same preparation, that a change in the P_{O_2} of the solution suffusing this tissue (84 to 11 mm Hg) caused the most distal arterioles to dilate by as much as 50%. Local P_{O_2}, however, remained almost constant because of increased blood flow. It, therefore, seems improbable that the P_{O_2} immediately surrounding the vascular smooth muscle is capable of regulating blood flow. However, Duling (1972) postulated that local P_{O_2} might indirectly stimulate the release of some regulatory metabolite. This possibility has not been eliminated experimentally, but neither has such a regulatory metabolite been elucidated as yet.

More recently, Duling (1974) examined the question of the direct effect of oxygen on vascular smooth muscle. He suffused the entire hamster cheek pouch vasculature with solutions of different O_2 content. Air equilibrated solutions caused arteriolar constriction (7 ± 1 μm) and flow cessation in numerous capillaries. However, when an even higher local P_{O_2} was established (186 ± 34 mm Hg) by application of O_2 rich solutions from micropipettes, the vasoconstriction of single arterioles was 5 times less. Furthermore, a similar constriction resulted when O_2 deficient solutions were applied. It was, therefore, clearly demonstrated that local P_{O_2} does not act directly to regulate vascular smooth muscle activity. Duling stressed the hypothesis that O_2 acts indirectly, via alteration of the concentration of some O_2 dependent metabolite, to regulate vascular reactivity.

In summary, several points should be emphasized on the role of oxygen deficiency as the regulator of local blood flow. In gross flow studies, oxygen deficient blood has been demonstrated to induce generalized vascular relaxation. Conversely, vasoconstriction occurs when oxygen is in excess. There is a body of evidence which suggests that oxygen deficiency is linked to reactive hyperemia. But those studies which have evaluated oxygen tension variations at the regulatory site, i.e., arterioles and precapillary sphincters indicate that local oxygen supply does not change significantly in these regions. This latter evidence appears more convincing than the gross flow studies and suggests either an indirect effect of oxygen on some metabolite, or possibly some other mechanism is instrumental in reactive hyperemia.

The Role of Adenosine and Adenine Nucleotides in Reactive Hyperemia

The vasodilator ability of adenosine and related compounds is well established (Haddy and Scott 1968). Even so, their regulatory role in local blood flow in various tissues is a controversial issue. Circumstantial evidence of their regulatory capacity originated from studies which employed intra-arterially injected adenosine, ATP, ADP, and AMP. This procedure caused vasodilator responses in dog skeletal muscle (Frolich 1963; Scott et al. 1965), human hands and forearms (Duff, Patterson, and Shepherd 1954) and the intestinal circulation

(Folkow 1949). Although these experiments clearly demonstrated the vasodilator quality of these compounds, they did not show regulatory function. If these substances do act to regulate blood flow, the regulatory site is probably on the extravascular side of the resistance vessels. Therefore, arterial infusion of these substances is an inadequate method for accurately reproducing the interstitial concentrations which develop during times of regulation, i.e., reactive hyperemia, and is, therefore, an unsatisfactory procedure to establish proof of their regulatory function.

Nevertheless, Berne (1963) postulated that adenosine, specifically, was the regulatory metabolite of myocardial reactive hyperemia, but did not negate a similar role in other tissues. Evidence supporting this hypothesis has since evolved from Berne's laboratory (Imai, Riley, and Berne 1964; Katori and Berne 1966; Rubio, Berne, and Katori 1969; Rubio, Berne, and Dobson 1973). The salient features of this evidence will now be presented.

In the initial investigations only inosine and hypoxanthine, the degradative products of adenosine, were found in the venous effluent of either isolated perfused or intact hearts (Berne 1963). Later, the adenosine deaminase inhibitor, 8-azaguanine, was found to effectively elevate the adenosine concentration in isolated rabbit hearts (Richman and Wyborny 1964) and also in guinea pig

hearts (Katori and Berne, 1966). Katori and Berne (1966) found that the adenosine concentration in myocardial venous blood was related to the extent of myocardial hypoxia. At this time, improved techniques for assaying adenosine made it possible to quantitate adenosine release under physiological conditions. Under control conditions hypoxanthine, inosine and adenosine were in either low or immeasurable concentrations (Rubio, Berne and Katori, 1969). During reactive hyperemia all of these substances were found to be in excess (adenosine at 12.5 nmoles per 100 ml of blood). More extensive incubation experiments were done to determine the degradative rates of adenosine, and to extrapolate what concentrations of adenosine existed in the interstitium to produce venous effluent concentrations of 12.5 nmole/100 ml of blood. It was determined that 75 nmole of adenosine/ml of interstitial fluid existed following a 40 second arterial occlusion. This concentration could effectively induce maximum dilation in this tissue.

A model of how adenosine might regulate coronary blood flow (reactive hyperemia) was proposed by Rubio and Berne (1969). Since 5'-nucleotidase is known to exist in the sarcolemma, transverse tubules and intercalated discs of the myocardium, it serves to dephosphorylate AMP to adenosine. Hypoxia augments AMP formation to promote this reaction and thus, effectively increase adenosine production. As the ATP concentration diminishes during hypoxia, 5'-nucleotidase becomes less inhibited and produces adenosine more

rapidly. With this model, Berne et al. (1971) postulated that adenosine acted directly to dilate the coronary resistance vessels and thereby increase the myocardial oxygen supply. Removal of the initial cause of the hypoxia would serve to activate AMP synthesis by adenosine kinase, and lead to restoration of the normal myocardial ATP concentration.

This hypothesis has been extended to include skeletal muscle blood flow regulation (Dobson, Rubio, and Berne 1971). The fundamental reasons for this are that adenosine is known to decrease skeletal muscle vascular resistance when injected intra-arterially (Scott et al. 1965; Hashimoto and Kumakura 1965) and accumulates in isolated ischemic or contracting rat muscle (Berne et al. 1971). Dobson et al. (1971) essentially eliminated ATP, ADP, and AMP as mediators of blood flow and restricted the regulatory function to adenosine or inorganic phosphate (Pi). Only the concentrations of these two agents were observed to be increased following periods of ischemic contraction. Adenosine concentrations in the venous effluent from dog muscle increased from 0.4×10^{-7} moles/l to 2.2×10^{-7} moles/l. This suggests that the interstitial concentration of adenosine was much greater (approximately 2 times) than that required to produce maximal dilation.

There is no evidence which indicates that adenosine regulates blood flow in the mesenteric circulation. Hashimoto and Kumakura (1965) have demonstrated that adenosine, ATP, ADP, and AMP

are effective vasodilator agents when injected intra-arterially, but these substances have not been found in the venous effluent following periods of intestinal ischemia. Based on the evidence found in skeletal muscle studies (Berne et al., 1971) adenosine does not appear to cause reactive hyperemia by itself but may act in contributory fashion with other agents, i.e., P_{O_2}, P_{CO_2}, lactate, pyruvate, inorganic phosphate, pH, particularly in long term occlusion responses (>3 minutes). A similar role can be proposed for intestinal post-ischemia responses, but at present there is no evidence which supports that role.

The Role of Inorganic Phosphate in Reactive Hyperemia

Hilton and Vrbova (1970) suggested that functional hyperemia in skeletal muscles was mediated by inorganic phosphate (Pi) released from the contracting muscle. They found that more Pi was released from fast skeletal muscles (gastrocnemius, tibialis anterior, and extensor digitorum longus) than from slow muscle (soleus). This is consistent with the fact that slow muscle ATPase is slower than that of fast muscle. Therefore, it follows that oxidative rephosphorylation is less efficient in fast muscles and leads to a greater release of inorganic phosphate from these muscles. Hilton and Vrbova (1970) also found that intra-arterial injections of isotonic NaH_2PO_4 and N_2HPO_4 caused a hyperemia of similar magnitude to that caused by 5 to 15 sec tetanic contractions of fast muscle.

Honig (1968) reported that Pi inhibited smooth muscle ATPase activity, but that 5' AMP augmented this inhibition in a greater than additive manner. These in vitro observations of turkey gizzard smooth muscle were extended to explain how Pi and 5' AMP serve as oxygen linked regulators of vascular smooth muscle. It was reasoned that exercise increased the extravascular concentrations of Pi and 5' AMP, which in turn caused vascular relaxation.

Barcroft and his associates (Barcroft, Foley, and McSwiney, 1970) infused sodium phosphate solutions (0.4 M-NaH_2PO_4 and Na_2HPO_4 at pH 7.4) into the brachial artery of human forearms to compare the hyperemia induced with that observed by Hilton and Vrbova (1970). These infusions increased plasma Pi in the forearm venous effluent by 400% and did not increase forearm blood flow. However, sustained or rhythmic exercise of the forearm muscles significantly increased venous plasma Pi levels by 20%, and forearm blood flow increased 10 fold. Barcroft concluded, therefore, that functional hyperemia is not regulated by Pi. It seems that this conclusion is not completely valid based on these experiments alone. The arterial infusions of Pi were probably ineffective in recreating the extravascular Pi environment present during exercise. While the venous effluent Pi during exercise increased by only 20%, it is suspected that the interstitial Pi increase was much greater. Conversely, the interstitial Pi created by the infusions was probably much lower than that following exercise, and the interstitium is presumably where Pi would act to

cause resistance vessel relaxation. To emphasize this point, it is known that the venous effluent from exercising fast muscles does not effectively induce vasodilation in a bioassay system (Hilton and Chir 1971). This may indicate that the Pi levels in the venous effluent have decreased by the time it is introduced to the second animal. Alternatively, the capillary network may not be very permeable to Pi. This would suggest that interstitial Pi would have to be very high to allow a 20% increase in venous effluent Pi.

No study has implicated Pi as the mediator of intestinal reactive hyperemia. If Pi serves any vascular regulatory function, it is most likely in the functional hyperemia of skeletal muscle.

The Role of Potassium Ion in Reactive Hyperemia

The first indication that potassium was a vasoactive substance came from Mathison's work in 1911. He injected isotonic KCl arterially in cats and observed pressor responses indicating vasoconstriction. Mathison's solutions contained 140 mEq K^+/l, and plasma [K^+] was undoubtedly much greater than normal. Subsequent attempts to confirm this observation resulted in conflicting evidence. Either vasodilatation or vasoconstriction was observed depending on the quantity of potassium injected (Dawes 1941). More recently, it has been shown that constriction can be induced by either hypokalemia, i.e., 3 mEq/l or hyperkalemia, i.e., 12 mEq/l (Chen et al. 1972), but that over this range the constriction can be blocked with oubain. At

higher concentrations constriction still occurs, but is not subject to oubain blockade. Exercise hyperemia is not diminished by oubain.

The contractions seen by Chen et al. (1972) with higher $[K^+]$ i.e., 12 mEq/l were probably caused indirectly from an adrenal discharge in response to the $[K^+]$. Emanuel, Scott and Haddy (1959) demonstrated that constrictor responses caused by K^+ infusions (10% K_3PO_4) were blocked by phentolamine. When plasma K^+ levels were raised by 3 to 8 mEq/l, the smooth muscle contracture was not affected by phentolamine. This suggests that K^+ has both a direct effect on vascular smooth muscle and an indirect effect via circulating catecholamines.

There is some basis for considering K^+ as mediator of exercise hyperemia. For instance, Kilburn (1966) showed that plasma K^+ levels increased following periods of exercise. Furthermore, it was determined that the potassium ions were released from the exercising muscle cells, and not from red cells. Others have found that venous $[K^+]$ increases after heavy exercise (Kjellmer 1965; Scott et al. 1970). Kjellmer (1965) reported that $[K^+]$ increased two fold in the venous effluent of human skeletal muscle following heavy work. Scott et al. (1970) found that a 50% increase in venous $[K^+]$ occurred during exercise, and caused a two fold reduction in arterial resistance.

Although K^+ apparently is released from exercising skeletal muscle and thus contributes to functional hyperemia, there is no

support for its action in reactive hyperemia. In fact, Rudko and Haddy (1965) and Scott et al. (1970) found that K^+ concentration was not elevated and, therefore, was not involved in the post-ischemic hyperemia of dog skeletal muscle. Scott et al. (1965) reached this same conclusion in kidney and heart experiments.

The Role of Combinations of Electrolytes in Reactive Hyperemia

Several other ions, i.e., Ca++, Mg++, HCO_3^-, H+, singly or in various combinations with each other, or with K+, have been demonstrated to be ineffective regulatory agents of reactive hyperemia (Haddy and Scott, 1968). These substances may be involved in other local flow phenomena, but even that possibility is not clear. The best evidence in this regard is Mellander's hypothesis that tissue hyperosmolarity induces the vasodilatation found in exercise hyperemia (Mellander and Lundvall, 1971). It is implicit in this hypothesis that several substances, i.e., lactate, pyruvate, adenosine and related compounds, H+ and others, act in concert from the extravascular compartment and cause vascular relaxation. Infusion of hyperosmolar solutions, to create a hyperosmolar venous blood similar to that found in exercise, i.e., 25 to 35 Osm/Kg H_2O above control, did not produce blood flows equivalent to those found during exercise hyperemia. Higher osmolarities, i.e., up to 75 nOsm/Kg of H_2O, caused blood flow to approach that seen in exercise.

Efforts were made to elucidate the mechanism of hyperosmolar induced inhibition of vascular smooth muscle activity (Mellander et al. 1967). They recorded the electrical and mechanical activity of the isolated, spontaneously active, rat portal vein, and found that hyperosmolarity inhibited pacemaker activity and initiated a pronounced and sustained relaxation. These changes can be explained on the basis of altered transmembrane ionic gradients and permeability changes.

Although the concept that non-specific substances act collectively to help regulate local blood flow has favorable aspects, it has received some criticism (Emerson, Scott, and Haddy, 1970; Frolich, 1966). These investigators argued that hyperosmolar solutions induced rheological changes in the blood and vessel walls. In the latter instance, it was suggested that smooth muscle cells became dehydrated. Mellander et al. (1967) and Lundvall, Mellander, and White (1969) countered these arguments effectively by infusing hyperosmolar solutions into papaverine treated vascular beds. No flow elevations occurred in these preparations when hyperosmolar solutions were infused. Therefore, it can be concluded that the hyperemic effects of osmolarity are not associated with vessel wall dehydration or reduced red cell volume.

Scott and his associates (Scott et al. 1970) did not find that venous osmolarity changed sufficiently to explain the increased

blood flow found in exercised dog skeletal muscle. There are no glaring faults in the procedures of either the Scott or Mellander investigations which explain their diametrically opposite observations. While the possibility of species difference, or of muscle fiber type, must be considered, these arguments appear weak, and suggest the need for further evaluation.

Skinner and his coworkers (Skinner and Powell, 1967; Skinner and Costin, 1971) investigated the response of the dog gracilis vasculature to combined alterations of potassium and oxygen. Using constant flow and interchangeable reservoirs, blood concentrations of one or both agents were manipulated. They perfused blood (13.7 vol % O_2) whose $[K^+]$ was varied from 3 to 8 mEq/l, and observed that vascular resistance varied inversely with $[K^+]$. When deoxygenated blood was used in combination with these $[K^+]$ alterations, an even more pronounced effect of resistance decrease was observed. The only instance where maximal dilation was achieved was when hypokalemic - hypoxic blood was used to perfuse the preparation. It was evident that oxygen and potassium acted in an augmentory manner to facilitate greater reductions in vascular resistance. Skinner and Costin (1971) observed that the addition of hyperosmolarity potentiated the effects of combined hyperkalemic - hypoxic blood perfusion.

All of the agents mentioned in this section show cause to consider that they contribute to exercise hyperemia. None of them have been found in excess concentration during reactive hyperemia. Therefore, it is possible that different mechanisms mediate these two responses.

The Role of Hydrogen Ion in Reactive Hyperemia

Increased local H+ concentration causes vascular smooth muscle to relax (Gaskell, 1880; Bayliss, 1901; Anrep, 1912; Haddy and Scott, 1968). The effect is not indigenous to any single tissue, but is well documented in the body, i.e., in the cerebral (Geiger and Magnes, 1947), the coronary and skeletal muscle (Daugherty et al. 1967), and intestinal circulations (McGinn, Mendel and Perry, 1967).

It is generally accepted that H+ accumulates in the interstitium and acts on the extravascular side of vessel smooth muscle (Haddy and Scott, 1968). However, most of the attempts to establish H+ as a regulator of reactive hyperemia have involved intra-arterial infusions of acidic substances. The vasodilator quality of excessive H+ was shown by this procedure, but no information was obtained about H+ accumulation and its effect on local resistance vessels during ischemia. Quite large pH changes (0.5 pH units) are required before blood flow increases to equal to that seen during post-ischemic

flow (Molnar et al. 1963; Haddy and Scott, 1965). Since the pH of venous blood was determined to decrease only 0.03 units during reactive hyperemia, (Rudko and Haddy, 1965), a change in H+ does not appear to be the cause for this response. It is probable that tissue pH is much lower than that of venous blood, but this evidence still suggests that pH changes alone do not explain the reactive hyperemia response.

Reactive Hyperemia in Intestinal Preparations

Gross blood flow reactive hyperemia responses were observed in the canine intestine by Green et al. (1954) and Selkurt et al. (1964). Green et al. (1954) found control blood flow averaged 19.4 ml/min/100 g of tissue (11.4 to 34.2) with an average arterial pressure of 87.2 mm Hg (37 to 155). Control resistance ranged from 1.92 to 21.5 PRU (peripheral resistance units) and averaged 16.16 units. Reactive hyperemia following one minute arterial occlusions was such that flow rose to 125 percent of the preceding control flow. Resistance was 80 percent of the control resistance. Sixty-three percent of the preparations exhibited a biphasic response where the initial vasodilatation gave way at 30 seconds post-ischemia to a vasoconstriction which raised resistance to 110 percent of control for a duration of approximately one minute. Strangely enough, the remaining 37 percent of the preparations did not show reactive hyperemia, but developed a

pronounced vasoconstriction upon occlusion release. This is the only report in the literature of vasoconstriction induced by arterial occlusion.

Selkurt et al. (1964) used the denervated, isolated, autoperfused dog intestinal preparation to study reactive hyperemia following 15 second to 5 minute arterial occlusions. After the longer occlusions, the typical response was a rapid increase to peak flow followed by a decline, a secondary peak, and finally return to control flow. The magnitude and duration of reactive hyperemia increased as functions of duration of occlusion. The arterial inflow in excess of average control flow, decreased with increased occlusion length. Repayment of flow debt was seen to decrease, with greatest (58%) repayment at 15 seconds and least (13%) at 5 minutes. In an attempt to discern the mechanism of intestinal reactive hyperemia, they compared the hyperemia following arterial occlusions alone with that produced by simultaneous arterial and venous occlusions. The combination occlusions produced a smaller hyperemia than arterial occlusion alone. This was observed by others (Wood et al. 1955; Geber and Schwinghammer 1965) Schwinghammer 1965) and explained to be due to a less extensive myogenic relaxation caused by the distending force of blood trapped in the blood vessels. But Selkurt et al. (1964) contended that this was caused by the trapped, but oxygen ladened, red cells allowing maintained vascular smooth muscle tone. They examined this hypothesis by infusing oxygenated dextran solution (6% in 154 mEq/l saline) intra-arterially to restored

and maintain intra-luminal pressure. Even though control pressure was exceeded in some experiments, hyperemia was found to equal, if not exceed, the control hyperemia response. The absence of a vasoconstriction under these circumstances is not totally surprising, however, since the dextran solutions could have directly inhibited any pre-existing myogenic activity. However, Selkurt and his coworkers concluded that the contribution of myogenic activity to intestinal reactive hyperemia was minor, if indeed it existed at all. Furthermore, they considered that the intestinal reactive hyperemia response originated from unknown metabolic factors.

Microvascular Studies of Reactive Hyperemia

Two studies of reactive hyperemia in skeletal muscle microvessels have been conducted (Gentry and Johnson 1972; Burton and Johnson 1972).. Both of these studies employed the dual slit method for red cell velocity measurement (Wayland and Johnson 1967). In one of these, short term micro-occlusions, 30 to 60 seconds duration, were used to study the post-occlusion response in amphibian skeletal muscle (Gentry and Johnson 1972). These micro-occlusions were performed by pressing a glass microprobe on a vessel. When individual capillaries were occluded in this manner, there was little evidence of reactive hyperemia when flow was restored. But when the parent arteriole of a capillary was occluded and then released, reactive hyperemia was observed. Moreover, a response similar to this

was also seen when all of the capillaries arising from the same arteriole were occluded simultaneously. It was, therefore, suggested that the metabolic environment of the arterioles was involved in the regulatory mechanism of reactive hyperemia in this tissue.

In a mammalian study, Burton and Johnson (1972) observed reactive hyperemia response at both the gross and capillary level. Only 60 second occlusions of the artery supplying the isolated, autoperfused, cat sartorius muscle were used to induce hyperemia in this study. Four categories of hyperemia responses were observed in the capillaries, but only one type of response was seen to be associated with a given capillary. Each of these responses was evaluated by the change which occurred in the velocity of erythrocytes moving through the capillaries. One group did not show reactive hyperemia. Another group of vessels had a long period of increased flow [60 $\pm$ 8 (S.D.) sec] and reached the peak flow in [35 $\pm$ 16 (S.D.) sec]. A third group of vessels mimicked the duration of gross flow hyperemia [22 $\pm$ 3 (S.D.) sec] and reached peak flow in 10 seconds. Flow in the last group of vessels rose quickly [5 $\pm$ 3 (S.D.) sec] and later showed a zero flow period before flow returned to control. They concluded that both the myogenic and metabolic mechanisms contributed to these cat skeletal muscle reactive hyperemia responses. They also suggested that different metabolic environments, due to the metabolism of red and white muscle fiber types, contributed to the response differences of their Type I and Types III and IV capillaries.

Type I vessels were found to have high basal flow rates, showed no hyperemia, and were suggested to be close to red muscle fibers. The other vessel types displayed pronounced hyperemia responses which were considered consistent with a variable metabolic environment of white muscle fibers.

Vasomotion and Capillary Flow Patterns

The phenomenon of vasomotion requires some discussion. Vasomotion is properly defined as the spontaneous constriction and dilation of blood vessels. Chambers and Zweifach (1944) considered that alternating contractions and relaxations of metarterioles and precapillary sphincters caused flow to vary in capillaries. Krogh (1922) believed that capillaries were capable of contracting and could, therefore, alter their own blood flow. This concept was proven incorrect by Sandison (1932) and Clark and Clark (1943). It is now generally believed that vascular smooth muscle is responsible for contractile activity in the microvasculature. According to Fulton (1957), capillaries are devoid of smooth muscle and, therefore, are incapable of contraction. Furthermore, Baez (1968) demonstrated that capillary diameters are invariant over a wide pressure range. Therefore, if one accepts these findings, it is conceivable that pre- or post-capillary resistance elements act to regulate blood flow in capillaries. Chambers and Zweifach (1944) considered that metarterioles and precapillary sphincters served this function. However, Johnson (1968) showed that arterioles also undergo diameter

variations too, which suggests that all resistance elements contribute to blood flow regulation.

Vasomotion was observed to occur in the small arteries, arterioles, terminal arterioles, precapillary sphincters and venules of the bat patagium (Nicoll and Webb 1955; Webb and Nicoll 1952). Recall that Folkow (1952) indicated that vascular smooth muscle activity, including myogenic behavior, was highly susceptible to anesthesia. Since the bats used by Nicoll and Webb (1955) were unanesthetized, perhaps this explains why they observed vasomotor activity, so apparently widespread, in bat wing microvessels. In their experiments, they applied physical stress to individual resistance vessels by repeatedly stroking them with a probe. This caused a transient dilation followed by a constrictor response which they concluded was of myogenic origin. An alternative explanation is that the stress they applied caused, sequentially, release of a dilator substance such as histamine, and then stimulated local release of norepinephrine which caused vasoconstriction.

Vasomotor activity, however, is thought to arise from the electrical activity of pacemakers located in vascular smooth muscle (Holman et al. 1968). The firing frequency of these pacemakers is subject to the degree of vascular smooth muscle stretch (Somlyo and Somlyo 1968).

Although the vascular behavior described above can explain the periodic and other flow patterns described by Johnson and Wayland

(1967), it should be mentioned that pressure redistribution in the mesentery can also act to alter flow in capillaries. This phenomenon, pressure redistribution, was suggested to exist in the mesentery by Gore (1974). He suggested that the arcade structure of the mesentery microvascular unit, described by Frasher and Wayland (1972), permits a given capillary to be influenced by more than one arteriole. This may account for the flow reversal, or the passive changes in flow which are often seen in failing preparations. But in autoregulating preparation, it is difficult to conceive of pressure changes occurring at both ends of a capillary, which are so synchronized in magnitude and frequency, that pressure redistribution is singly responsible for periodic blood flow in that vessel. Furthermore, the experiments of Johnson and Wayland (1967), which clearly showed autoregulation, seem to argue against pressure redistribution as a cause of capillary flow regulation. They lowered arterial perfusion pressure by 45 mm Hg and caused cessation of flow periodicity in capillaries. But when venous pressure was elevated by 6.5 mm Hg, while arterial pressure remained lowered, the periodic flow pattern returned.

In summary, experimental evidence indicates that flow in mesentery capillaries is controlled by a pressure sensitive mechanism which is more sophisticated than pressure redistribution alone. Johnson and Wayland (1967) proposed that a myogenic mechanism, possibly located in the precapillary sphincter, was involved in the

development of periodic capillary flow. Other flow patterns observed might also result from myogenic behavior, but suggest that other factors are involved.

METHODS

Surgical Procedure

Cats of either sex, weighing 2.0 to 4.5 kg, were preanesthetized with either propiopromazine hydrochloride (Tranvet-5, Diamond Laboratories, Inc.) or ketamine hydrochloride (Ketaset, Parke-Davis, Co.). These drugs were administered im at a dosage of 0.11 mg/kg body weight and 10 mg/kg body weight, respectively. When propiopromazine was used, α-chloralose (10% solution in carbowax) was given via the cephalic vein (75 mg/kg body weight). When ketamine hydrochloride was used, the left jugular vein of the animal was exposed and cannulated and α-chloralose (60 mg/kg body wieght) was given intravenously. This latter combination of drugs was used in all pressure pulse experiments. In no instance was additional anesthetic given during the experiment.

The procedure described by Gore (1973) was followed to prepare the isolated, autoperfused, cat mesentery. Gore stated that the major disadvantage of studying the isolated cat mesentery is the 4-5 hours of surgery required. The initial preparations of these experiments took that long, but generally, the surgery was completed, and the preparation was ready for viewing in less than two hours. A detailed description of this surgical procedure follows.

The neck, abdomen and inguinal regions were shaved. The left jugular vein was exposed and cannulated. All drugs administered during the course of the experiment were given via this cannula. Next the right femoral artery and vein were cleared for cannulation. In preparation for exposure of the intestine a surgical bath was placed on the abdomen. This bath consisted of an 8" Plexiglas ring to which plastic surgical drape (VI-Drape, Parke-Davis, Co.) was cemented with silicon rubber (Dow Corning, 732 RTV sealant). The surgical drape adhered tightly to the abdomen to form a water tight seal. The ring was supported by two lucite blocks which rested on the surgical table. A 4-inch longitudinal incision, centered on the umbilicus, was then made through the bottom of the surgical bath and the integument. After clearing away the adipose and connective tissue, the incision was continued through the linea alba and the peritoneum. A Tris buffered (pH 7.4) physiological saline solution was then poured into the bath. The terminal portion of the small intestine was then lifted into the bath. The free end of the omentum was removed from the intestine, wrapped with a gauze sponge and returned to the abdominal cavity. Extreme care was exercised in handling the mesentery tissue to avoid stretching and possible trauma. Moistened gauze pads were spread over the tissue to prevent direct exposure to the atmosphere.

A segment of the ileum approximately 5 inches in length was selected for surgical isolation. Two incisions were then made in the mesentery to establish the boundaries of the segment. The edges of these incisions were cauterized to prevent bleeding. Dissecting

foreceps were used to tease the connective and adipose tissue away from the superior mesenteric artery and vein. Small vessels were ligated to prevent bleeding. This clearance procedure was continued until a sufficient length of artery and vein (1 to 1.5 cm) was free for cannulation.

An incision was made in the anticaecal end of the preparation. A lumen tube consisting of a piece of Tygon tubing and a rubber stopper was inserted. It was tied in place with heavy ligature to prevent bleeding from the free end of the preparation. The animal was heparinized (5 mg/kg body weight) prior to cannulation of the artery and vein, and a booster dose of 2.5 mg/kg body weight was given every 30 minutes during the experiment. Propantheline bromide (3 mg Probanthine, Searle) was given to decrease gut motility and secretion.

The arterial perfusion circuit consisted of a series of polyethylene (PE) tubing (PE 280, 205, and 160) whose total length was approximately 20 inches. The cannulae for both the femoral and mesenteric arteries were PE 160. This size tubing, PE 160, was also used to cannulate the femoral and mesenteric veins. The remainder of the venous circuit, whose length was also 20" consisted of PE 205, and PE 280 fitted to 1/8" silicon tubing (Silastic, Dow Corning). Both the arterial and venous circuits were equipped with side branches which were connected to appropriate pressure transducers.

The cannulation procedure was as follows. The femoral vein and femoral artery were cannulated and the arterial circuit was allowed to fill to the cannula tip with blood. Then the superior

mesenteric artery was cannulated and arterial blood was allowed to perfuse the preparation. Arterial perfusion was halted prior to cannulating the superior mesenteric vein and was restored as quickly as possible following completion of this procedure. A lumen tube was then placed in the caecal end of the preparation.

The autoperfused ileum preparation was then carefully mounted on a constant temperature (37°C), water heated, microscope stage. The intestinal wall was covered completely by gauze sponges which were soaked with physiological saline solution. A transparent plastic membrane (Saran Wrap) was used to cover the preparation. This maintained the preparation in a moist condition for the duration of the experiment.

The mesentery preparation, mounted on the stage, was moved to the microscope and placed appropriately for observation of the mesenteric vasculature. This is represented diagrammatically in Figure 1. Velocity measurements of red blood cells moving through the capillaries were made according to the technique of Johnson and Wayland (1967).

Capillaries selected for observation were those which branched from an arteriole in a region relatively free of fat cells. A 60 second period of control velocity was recorded prior to each experimental trial. Each experimental trial consisted of a period of ischemia. This was achieved by clamping a guarded hemostat on the arterial circuit. Occlusion durations of 15, 30, 45 and 60 seconds

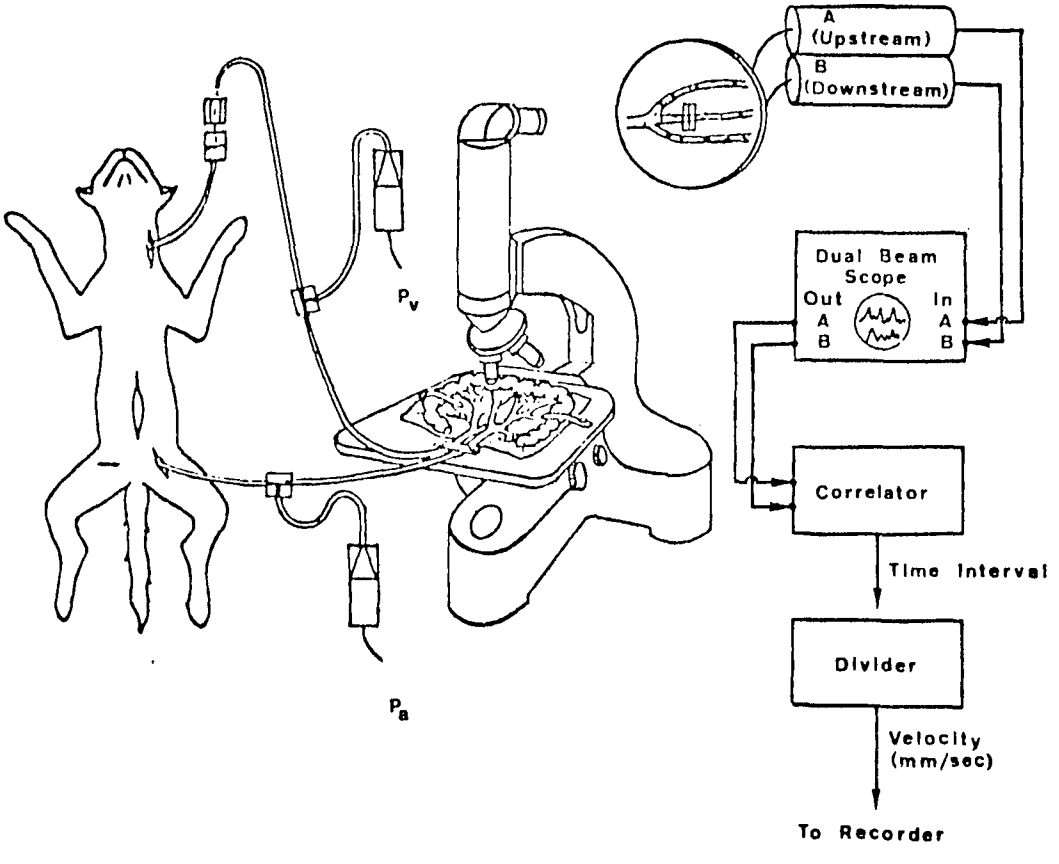

Fig. 1. Diagram showing the isolated, autoperfused, cat mesentery preparation -- The transilluminated microvascular bed's image is shown projected onto a viewing screen where photodetector slits were located. The red cell velocity was then quantitated by the electronic equipment represented in the block diagram at the right.

were used. At least three minutes were allowed for recovery between occlusions. Red blood cell velocity was recorded following flow restoration. Several trials (2 to 3) of the same occlusion duration were used to determine the reproducibility of the response for each vessel.

Pressure Pulse Experiments

Pressure pulse experiments were conducted on 20 animals. Each of these animals was given an anesthesia regime of ketamine hydrochloride and α-chloralose as described previously. All capillaries studied in these experiments exhibited either the Type III or Type IV reactive hyperemia response. Type III capillaries showed a quick rise to peak flow following occlusion and a return to control. Type IV capillaries also had a quick rise to peak flow, but subsequently had a period of flow stasis before control flow was reestablished. These vessels also showed autoregulation of blood flow; autoregulation was defined as maintenance of control red cell velocity at control level when the arterial perfusion pressure of the preparation was reduced. Arterial pressure was reduced by constricting the arterial circuit with a Gaskell heart clamp. Perfusion pressure was then adjusted to the lowest level at which red cell velocity could be maintained at control velocity. This pressure was maintained for at least three minutes prior to each pressure elevation trial. Pressure pulses of 1 to 20 seconds duration were produced by quickly loosening

and then retightening the clamp on the arterial circuit. In some instances the amplitude of pressure elevation was varied.

A separate set of experiments was conducted in which the rate of rise of the pressure elevation (dP/dt) was varied. The rate of pressure increase was varied by manual adjustment of the Gaskell clamps. This procedure produced dP/dt changes which ranged from less than 1 mm Hg/sec to 40 mm Hg/sec.

Red cell velocities during control and response periods were measured from the strip chart recording. Average values were determined by planimetry. Control velocity was taken as the mean value for the 60 second period of flow which preceded an arterial occlusion. Reactive hyperemia was considered to be terminated when the velocity reached the mean value of the control period.

Data Recorded

Red blood cell velocity, arterial pressure, and venous pressure were measured in all experiments. The record from a single trial is shown in Figure 2. Arterial and venous pressures were monitored using Statham P23Gb and P23Bb pressure transducers, respectively. Gross blood flow was measured during 10 experiments while red cell velocity was recorded in capillaries. The data were recorded on a Beckman Type R strip chart recorder at a paper speed of 60 mm/min.

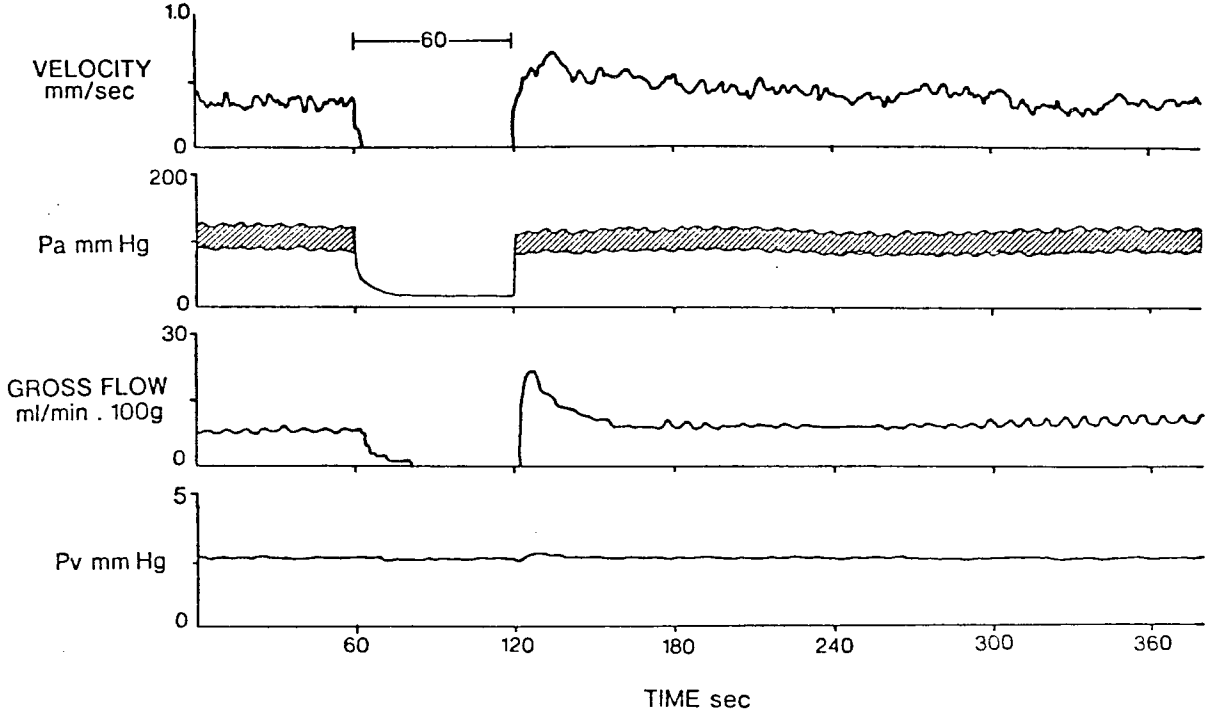

Fig. 2. The record from a single 60 second arterial occlusion is shown -- Red cell velocity, arterial pressure, gross blood flow, and venous pressure recordings are presented in panels 1 through 4, respectively.

Measurement of Gross Blood Flow

Total venous outflow from some preparations was measured with a drop counter coupled to an integrating system. The drop counter consisted of a light source whose beam impinged on a Clairex photocell type CL 604L. Drops of blood broke this light beam as they fell into a reservoir. A decrease in the voltage output of the photocell was recorded for each drop of blood. The venous outflow orifice was specially prepared so that 20 drops equaled 1.0 ml of blood.

The integrating circuit consisted of an operational amplifier (Philbrick PP85 AU) driven by a power source separate from the counter. The voltage output at the integrator accumulated at a rate of one volt/sec and was read out on the strip chart recorder. The integrator circuit was coupled to the counter by having the voltage drop from the counter trigger a relay circuit which reset the integrator. The gross blood flow readout was, therefore, proportional to the time interval between drops of blood.

The gross flow was also measured during some experiments with a digital electronic device which gave a direct readout of drops/sec on the polygraph. All gross flow data were normalized for 100 g of tissue. Flow values were thereby expressed in units of ml/min/100 g of tissue.

RESULTS

Reactive hyperemia was observed by measurement of gross blood flow in 10 intestinal preparations. The data from these studies are presented in detail in Table 1. Control blood flow was found to average 24.4 ml/min/100 g of tissue. Peak blood flow and, therefore, the peak flow to control flow ratio, and the duration of reactive hyperemia were all found to increase with longer periods of ischemia as reported by Selkurt et al. (1964). The peak flow was reached in approximately 8 seconds, regardless of occlusion duration.

These data support the conclusions of Selkurt et al. (1964) that metabolic factors may produce post-occlusion hyperemia in the total intestinal preparation. However, the intestine has a higher metabolic rate and a much greater blood flow than does the mesenteric circulation per se. Therefore, not much information about the control of this response in the mesenteric microvasculature can be extracted from gross flow data.

Control Flow Patterns

Reactive hyperemia was recorded from 53 capillaries in 22 preparations in this study. Four distinct patterns of red cell velocity were observed during the control period in these vessels. Examples of these patterns are shown in Figure 3. During the course of these

Table 1. Gross flow data from ten experiments -- All values represent the standard errors of the mean. Significance (*) was tested at the .01 level.

	Occlusion Duration (sec)			
	15	30	45	60
Control flow (mm/sec)	24.2 ± 1.4	24.2 ± 1.5	24.6 ± 1.8	24.4 ± 1.5
Peak flow (mm/sec)	52.7 ± 4.4	56.9 ± 4.9	61.6 ± 5.3	66.1 ± 5.7*
Peak flow/Control flow (P/C)	2.2 ± .2	2.35 ± .2	2.5 ± .2	2.7 ± .2*
Duration (sec)	14.3 ± .7	31.4 ± .9	48.8 ± 1.1	69.5 ± 1.5*

Values are means ± SE

Significance is indicated by (*).

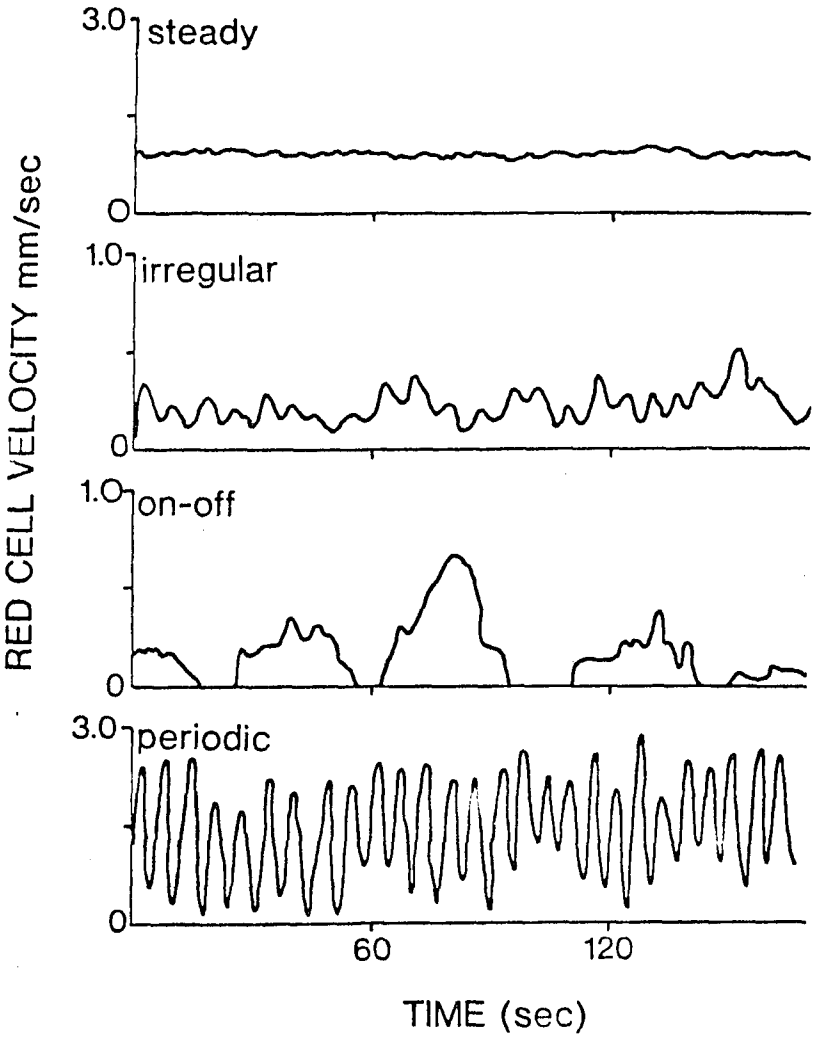

Fig. 3. Four patterns of red cell velocity observed in cat mesentery capillaries.

experiments, it was determined that each capillary was very consistent in its control pattern of flow. The top panel shows the record from a steady flow vessel in which the velocity did not vary more than 15 percent during control measurements. Fifty-one percent of the vessels studied showed this type of velocity pattern. Irregular variations in velocity were seen in 30 percent of the vessels (panel 2, Figure 3). A variation of as much as 100 percent within a 15 second period was common in these vessels. No established frequency of the flow irregularities was determined. An on-off flow pattern was observed in 11 percent of the capillaries (panel 3, Figure 3). A stream of red cells would rush through the vessel and suddenly flow would stop. These periods of zero flow ranged from 3 to 21 seconds, and the on periods ranged from 5 seconds to over 1 minute in length. No definite length of either the on or off period was found to be characteristic. A few of the vessels exhibited a periodic variation in the velocity, (panel 4, Figure 3). Less than 9 percent of the vessels observed showed this flow pattern. This flow pattern had a period of 6 seconds. A range of 5-11 seconds was found for the other vessels which showed periodicity.

The distribution of the average control velocities observed in all is shown in Figure 4. The mean red cell velocity in most of these vessels was between .1 and .3 mm/sec. Although no vessel had a mean velocity in the .7 and .9 mm/sec ranges, velocities were found, at least momentarily in these ranges. Reactive hyperemia was observed in vessels of all four flow pattern categories.

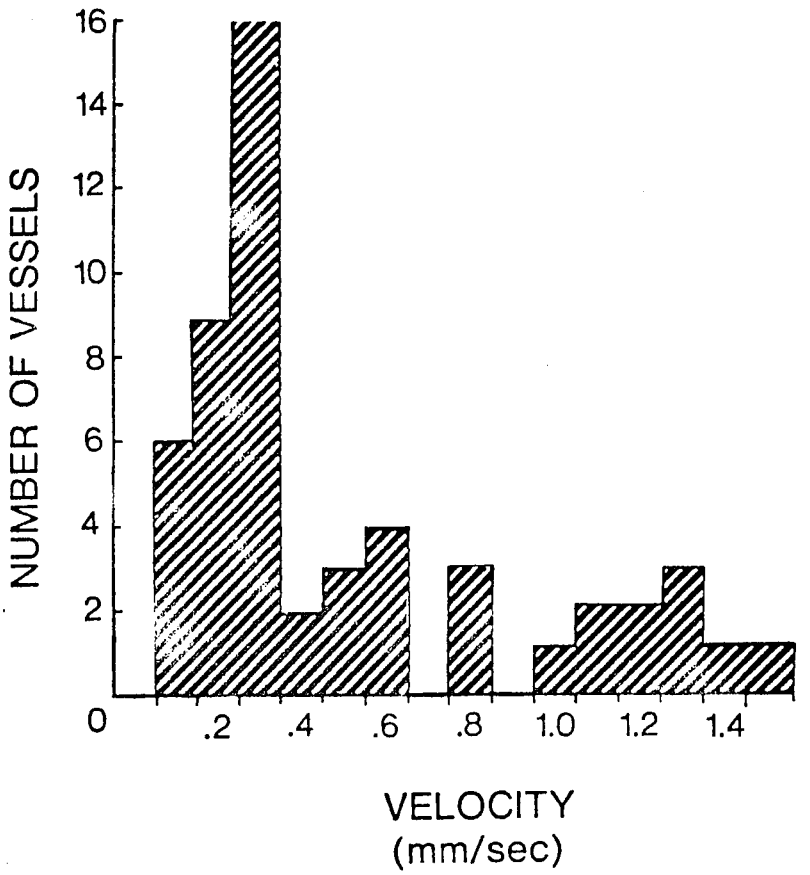

Fig. 4. The distribution of the average control red cell velocities of 53 capillaries.

The post-occlusion behavior of these capillaries was also categorized, using the classification that Burton and Johnson (1972) described in the cat sartorius muscle capillaries. The number and type of reactive hyperemia responses observed in each preparation are shown in Table 2. The characteristic features of these response types are shown in Figure 5. The Type I response (top panel) is an absence of reactive hyperemia. The red cell velocity returned to control when arterial pressure was restored. The Type II response was an extended period of hyperemia which averaged 143 sec and lasted as long as three minutes in some vessels. Considerable differences were often observed in the response profile of a given Type II vessel (second panel, Figure 5). The third panel (Figure 5) illustrates the Type III hyperemia response. Following release of the occlusion, the red cell velocity rose quickly to peak velocity and then quickly returned to control. The bottom panel of Figure 5 is representative of the Type IV hyperemia response. A quick rise in the velocity followed by a rapid drop to zero flow period ranged from 5 to 90 seconds and averaged 20 seconds.

Type I Response

The data from Type I vessels are summarized in Table 3. It is perhaps significant that the mean control velocity of the Type I vessels (0.81 mm/sec) was higher than that observed in Type II, III, and

Table 2. Distribution of the number of capillary types found in each experiment.

Exp. no.	Individual Capillaries Type I	Type II	Type III	Type IV
1		2		1
2			1	
3	1	2	2	2
4			1	1
5		1	1	2
6	1			2
7			1	1
8		1	2	
9		1	2	1
10			1	
11	1		2	2
12		1		
13	1		1	
14			1	2
15		1		1
16			2	
17			1	1
18	1		1	
19			1	
20				1
21			1	
22		1		
	5	10	21	17
	n=5	n=8	n=16	n=12

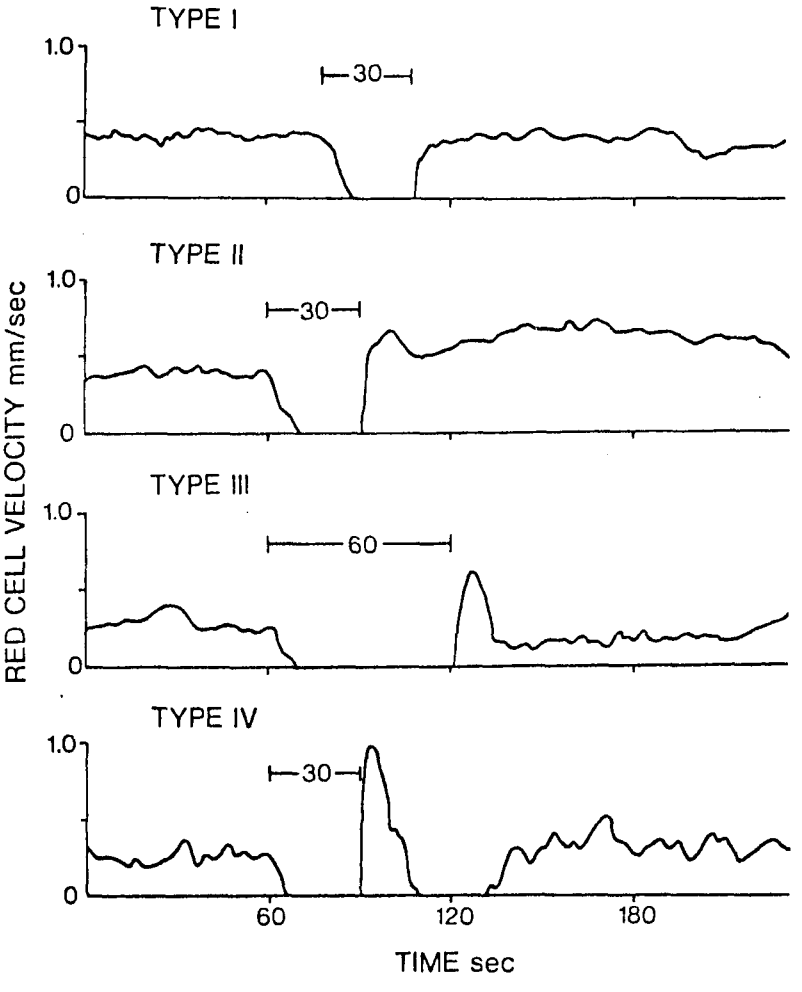

Fig. 5. Four capillary response types observed following periods of arterial occlusion.

Table 3. Type I vessel control and 60 sec post-occlusion velocities --

N value is 3, except for those trials marked (†) in which case N=2.

Vessel	15 sec response Control (mm/sec)	15 sec response 60 sec post-occlusion (mm/sec)	30 sec response Control (mm/sec)	30 sec response 60 sec post-occlusion (mm/sec)
1	.33 ± .01 (†)	.32 ± .01 (†)	.33 ± .01	.32 ± .01
2	.81 ± .01	.82 ± .01	.80 ± .01	.81 ± .01
3	1.58 ± .07	1.56 ± .04	1.53 ± .06	1.50 ± .05
4	1.13 ± .03	1.12 ± .03	1.13 ± .01	1.13 ± .03
5	.33 ± .01	.32 ± .01	.33 ± .01	.32 ± .02
N=5	.84 ± .54	.83 ± .53	.82 ± .52	.82 ± .51

Vessel	45 sec response Control (mm/sec)	45 sec response 60 sec post-occlusion (mm/sec)	60 sec response Control (mm/sec)	60 sec response 60 sec post-occlusion (mm/sec)
1	.34 ± .01	.33 ± .01	.33 ± .01 (†)	.32 ± .01 (†)
2	.83 ± .02 (†)	.81 ± .01 (†)	.79 ± .03	.80 ± .02
3	1.59 ± .04	1.58 ± .07	1.56 ± .08	1.57 ± .05
4	1.13 ± .03	1.13 ± .03	1.13 ± .02	1.13 ± .01
5	.33 ± .01 (†)	.33 ± .02 (†)	.34 ± .02	.34 ± .02
N=5	.84 ± .54	.84 ± .54	.83 ± .53	.83 ± .53

IV vessels. Flow in the Type I vessels consistently returned to control level, but the vessels with slower flow surpassed their own control level by more than 2.5 times. The effect of four different occlusion durations, 15, 30, 45, and 60 seconds (Figure 6) was tested on these, as well as the vessels which showed other response types. It is apparent that the Type I vessels showed the same response to a 15 second occlusion as they did to any other test occlusion

Type II Response

Examples of this Type II response are seen in Figure 7. The average control velocity of the Type II vessels was .42 mm/sec. This was not significantly different from the Type III vessels. Extremely variable profiles followed repeated occlusion in Type II vessels. This is clearly shown in the responses of the same vessel to two different 30 second occlusions (bottom two panels, Figure 7). During the first minute of hyperemia, the velocity averaged .669 mm/sec (third panel, Figure 7), as compared with .592 mm/sec for another trial response (bottom panel, Figure 7). However, when the post-occlusion velocity was averaged over two minutes, the mean velocities were then found to be .615 and .610 mm/sec, respectively. It is important to recognize that this vessel's control flow pattern was steady flow and, therefore, the response differences cannot be attributed to the basic flow characteristics of this vessel. Considerable variability was typical for Type II vessels and greatly hindered overall evaluation of this reactive hyperemia response. Data from

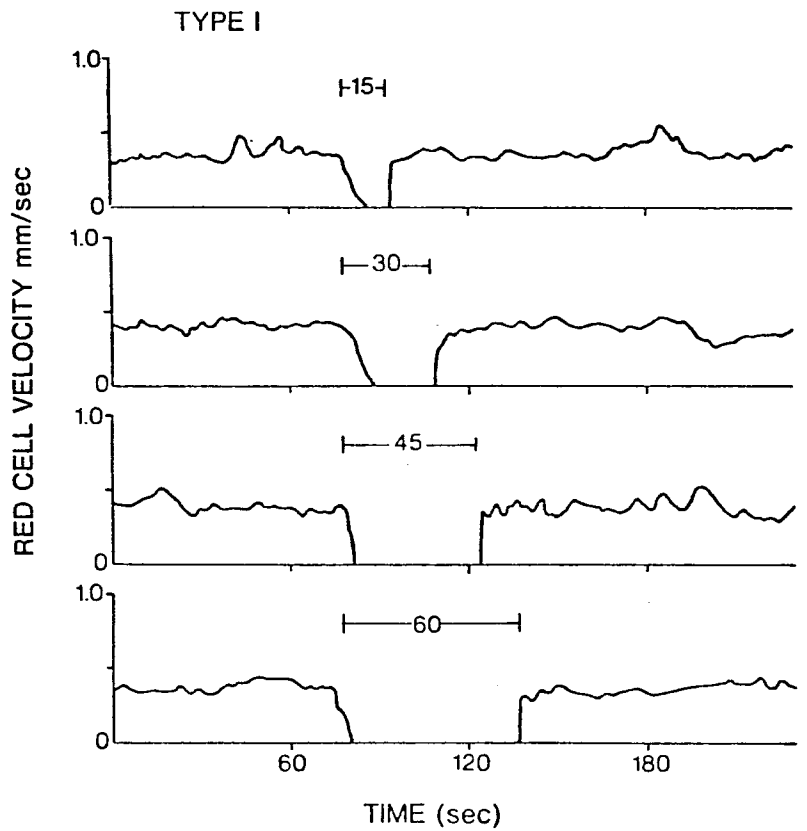

Fig. 6. The responses of a Type I capillary to 15, 30, 45, and 60 second periods of arterial occlusion.

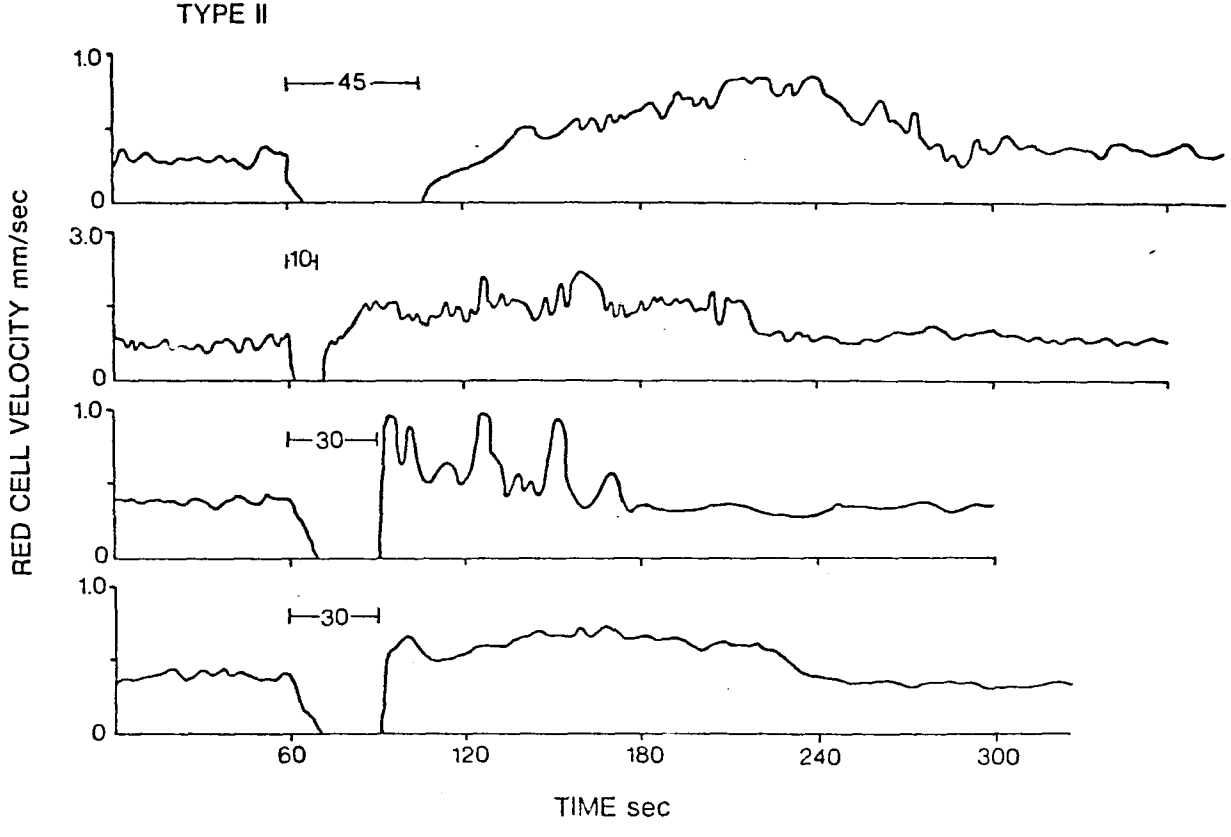

Fig. 7. Representative Type II reactive hyperemia responses -- The bottom two panels are responses from the same vessel. See text for explanation.

the Type II vessels are summarized in Table 4. Data for individual Type II vessels are presented in Appendix A.

Type III Response

The Type III vessels had a mean control velocity of .35 mm/sec and exhibited a consistent hyperemia response. This response was repeatable when consecutive, or intermittent, occlusions of the same duration were imposed. Most of these vessels (12 of 21) showed similar response profiles regardless of the occlusion durations used in these experiments. The responses of a single Type III capillary to three 60 second ischemia periods are seen in Figure 8. There is a noticeable similarity in the response profiles, but there are differences in the peak velocity, area under the hyperemia curve, and the duration of the response. Such differences were observed in all Type III vessels studied, but trends in any one of the parameters investigated were in the minority. Figure 9 shows a single vessel's response to 15, 30, 45, and 60 second occlusions. In this instance, there is a significant increase in the peak flow and, therefore, the peak flow to control flow ratio. The time to peak flow also increased with longer occlusions. Since the duration of the response lengthened, the area under the hyperemia curve also increased. Nine of 21 vessels studied showed increases in at least one of these parameters. Only 5 of these 9 showed significant increases in all of the parameters examined. The peak flow (velocity), time to peak flow, peak flow to control flow ratio, duration of hyperemia, and excess flow data of these vessels is presented in Tables 5, 6, 7, 8, and 9 respectively.

Table 4. Type II vessel reactive hyperemia response duration (sec) *

Vessel				
1	62 ± 7	112 ± 11†	83 ± 24†	45 ± 7† †
2	177 ± 5†	150 ± 9	162 ± 8	145 ± 9†
3	132 ± 15	145 ± 22	153 ± 9	147 ± 12
4	192 ± 17	212 ± 17	194 ± 10	205 ± 4
5	62 ± 1	50 ± 10	74 ± 9†	45 ± 9†
6	92 ± 10	135 ± 17	122 ± 20	142 ± 25
7	205 ± 7	192 ± 10	223 ± 30	240 ± 2†
8	179 ± 13	86 ± 51	127 ± 10	140 ± 24
9	105 ± 11	160 ± 16†	142 ± 14†	137 ± 10
N=9	134 ± 56	138 ± 50	142 ± 48	138 ± 64

* N value is 3, except for those trials marked (†) in which case N=2. Additional data for the Type II vessels are in Appendix A.

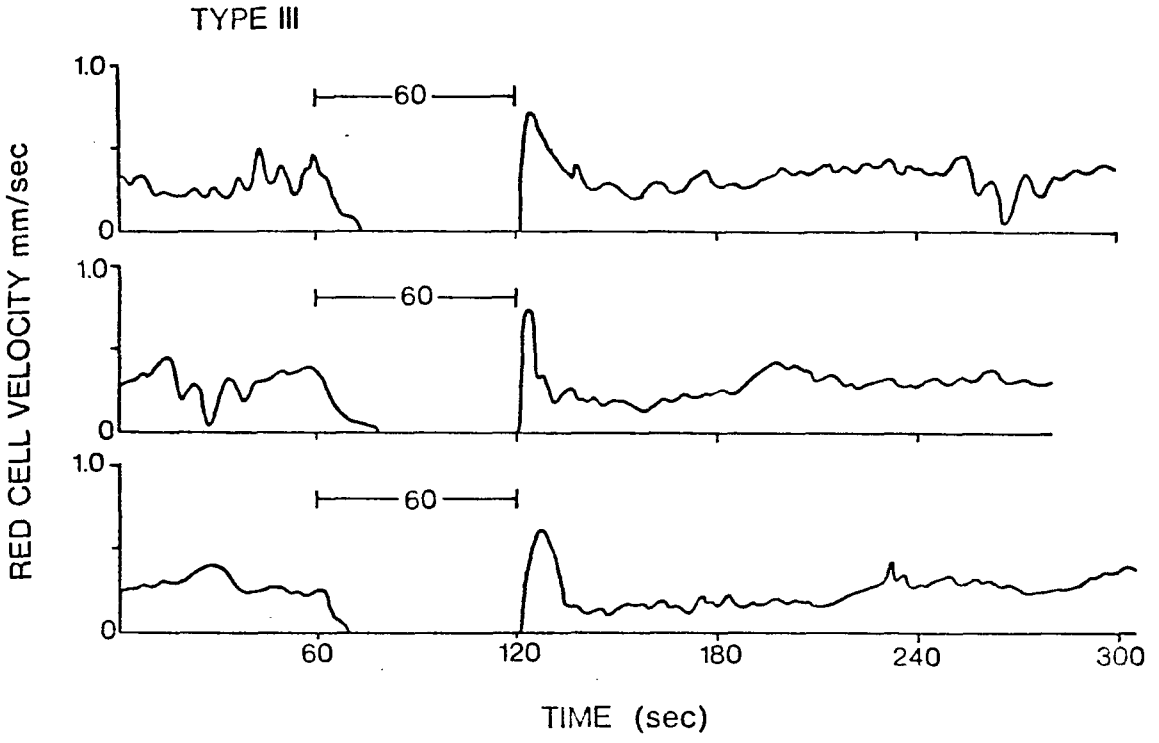

Fig. 8. Three responses of one Type III capillary to a 60 second arterial occlusion.

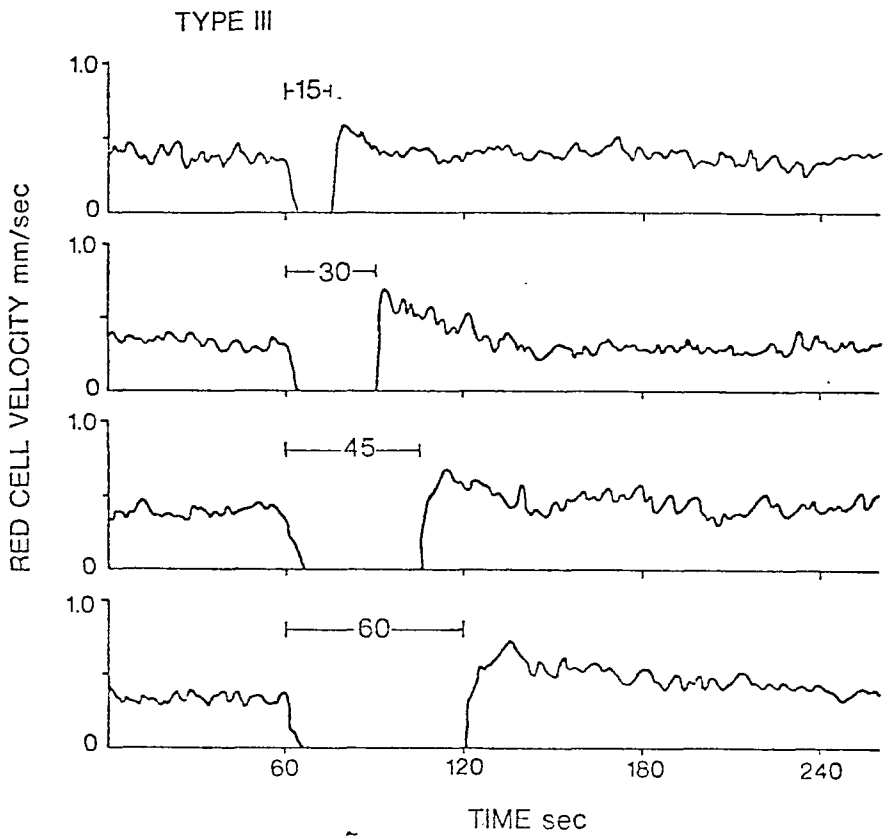

Fig. 9. The responses of a Type III capillary to 15, 30, 45, and 60 second arterial occlusion -- This vessel's hyperemia response was dependent on the occlusion duration.

Table 5. Type III vessel peak flow response (mm/sec). *

Vessel	Occlusion Duration (sec) 15	30	45	60
1	2.17 ± 0	2.16 ± .01	2.41 ± .02	2.38 ± .03†
2	1.80 ± .02	1.92 ± .02	2.14 ± .04	3.16 ± .03*
3	0.60 ± .03	0.65 ± .01†	0.66 ± .03	0.64 ± .01
4	0.72 ± .02	0.66 ± .02	0.78 ± 0 †	0.70 ± .01
5	0.80 ± .01	0.96 ± .02	0.86 ± 0	0.92 ± .03*
6	0.63 ± .02	0.60 ± 0	0.61 ± .01	0.62 ± .01
7	0.42 ± .01	0.60 ± .02	0.71 ± .01	0.71 ± .01*
8	0.56 ± .01	0.58 ± .02	0.78 ± .02	0.86 ± .02*
9	2.17 ± .02	2.16 ± .01	2.41 ± .01	2.28 ± .01*
10	2.10 ± .02	2.04 ± .04	2.18 ± .03	2.16 ± .02
11	0.72 ± .02	0.69 ± 0	0.66 ± .02	0.76 ± .01
12	0.70 ± .01	0.65 ± .01	0.64 ± .01	0.62 ± .01*
13	0.45 ± 0 †	0.45 ± 0	0.42 ± 0 †	0.48 ± .03†
14	0.65 ± .01	0.65 ± .01	0.66 ± 0	0.69 ± 0 †
15	0.90 ± 0	1.20 ± .02	1.25 ± .01	1.34 ± .01*
16	0.57 ± .01	0.68 ± .01	0.68 ± .01	0.72 ± .02*
17	0.55 ± .01	0.64 ± .01	0.86 ± .01	0.70 ± .13*
18	0.44 ± .01	0.42 ± .02	0.38 ± .01	0.22 ± .02*
19	1.42 ± .03	1.50 ± .01	1.47 ± 0	1.56 ± .02†
20	0.42 ± 0	0.60 ± .02	0.70 ± .02	0.70 ± 0 *
21	0.76 ± .02	0.72 ± 0	0.76 ± .02	0.74 ± .01
N=21	0.93 ± .60	0.98 ± .60	1.05 ± .66	1.09 ± .76

* The peak flow responses of each Type III vessel are presented in this table. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†), in which case N=2.

Table 6. Type III vessel time to peak flow (sec) -- the time required to achieve peak flow following arterial occlusion is presented for each Type III capillary. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†), in which case N=2.

Vessel	Occlusion Duration (sec) 15	30	45	60
1	4 ± 0	5 ± .3	5 ± 0	4 ± 0 †
2	5 ± 0	5 ± 0	4 ± .3	4 ± .3
3	23 ± 2.2	20 ± 2 †	24 ± 1.20	27 ± .3
4	5 ± 0	6 ± .3	9 ± 1	9 ± .3*
5	9 ± .3	7 ± .06	8 ± .3	8 ± .3
6	5 ± 0	6 ± .3	6 ± .6	5 ± .3
7	8 ± 0	9 ± .9	8 ± 0	7 ± .6
8	3 ± .3	6 ± .3	10 ± .7	20 ± .9*
9	4 ± 3	5 ± .3	5 ± .3	4 ± .3
10	22 ± 2.0	25 ± 1.5	21 ± 1.5	27 ± 1.2*
11	4 ± .3	5 ± .9	4 ± .3	3 ± 0
12	5 ± .3	7 ± .7	7 ± .6	8 ± .3*
13	3 ± 0 †	2 ± .3	3 ± .5†	4 ± .5†
14	3 ± 0	4 ± 0	4 ± 0	5 ± .5†
15	14 ± .3	17 ± .9	22 ± 1.2	30 ± 2 *
16	4 ± 0	3 ± .6	8 ± .6	15 ± .7*
17	3 ± 0	5 ± 1.5	20 ± 2.5	18 ± 2 *
18	9 ± .3	9 ± 0	11 ± .9	10 ± .3
19	7 ± .5	9 ± 1.0	12 ± .3	12 ± 0 *†
20	9 ± .3	9 ± 0	8 ± 0	8 ± 0
21	5 ± .3	6 ± 1.0	6 ± 1.2	5 ± .3
N=21	7.3 ± 5.7	8.1 ± 5.7	9.8 ± 6.4	11.1 ± 8.5

Table 7. Type III - Peak flow/Control flow ratio.*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	6.76 ± .12	7.08 ± .08	7.06 ± .20	7.12 ± .16†
2	4.28 ± .05	4.72 ± .05	5.99 ± .40	5.59 ± .12*
3	2.66 ± .16	2.72 ± .20†	2.81 ± .04	2.69 ± .15
4	3.89 ± .09	3.51 ± .11	3.92 ± .20	3.63 ± .11
5	2.03 ± .07	2.74 ± .08	2.30 ± .05	2.59 ± .22*
6	2.14 ± .07	1.96 ± .03	1.97 ± .04	1.99 ± .01
7	1.34 ± .07	1.90 ± .06	1.95 ± .15	2.08 ± .03*
8	1.99 ± .05	2.12 ± .04	2.58 ± .07	2.24 ± .09*
9	6.76 ± .06	7.08 ± .08	7.05 ± .03	7.13 ± .08*
10	3.41 ± .04	3.31 ± .06	3.47 ± .05	3.37 ± .05
11	2.44 ± .07	2.44 ± .06	2.36 ± .09	2.65 ± .09
12	2.71 ± .04	2.47 ± .07	2.35 ± .05	2.15 ± .02*
13	1.91 ± .04†	1.87 ± .04	1.91 ± .15†	1.90 ± .19†
14	2.67 ± .03	2.52 ± .09	2.32 ± .05	2.54 ± .05†
15	1.89 ± .02	2.63 ± .07	2.61 ± .01	2.74 ± .03
16	1.47 ± .04	1.74 ± .02	2.08 ± .12	1.84 ± .04
17	1.64 ± .08	1.68 ± .04	2.43 ± .04	1.90 ± .36
18	4.52 ± .39	3.54 ± .16	3.53 ± .19	2.22 ± .14
19	1.77 ± .02	1.82 ± .01	1.79 ± .01	1.88 ± .03†
20	1.22 ± .02	1.44 ± .02	1.91 ± .06	2.05 ± .08
21	2.14 ± .06	2.08 ± .02	2.13 ± .06	2.08 ± .03
N=21	2.84 ± 1.59	2.92 ± 1.58	3.07 ± 1.63	2.97 ± 1.62

* The peak flow to control flow ratio is presented for each Type III capillary. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†) in which case N=2.

Table 8. Type III vessel hyperemia duration (sec) -- the hyperemia response duration is presented for each Type III capillary. Values are expressed as the mean ± S.D. N value is 3, except in those trials marked (†) in which case N=2.

Vessel	Occlusion Duration (sec) 15	30	45	60
1	10 ± 1	10 ± 0	12 ± 1	11 ± 2
2	15 ± 1	9 ± 1	10 ± 1	7 ± 1
3	38 ± 2	34 ± 3	35 ± 3	39 ± 5
4	15 ± 1	19 ± 1	18 ± 1	22 ± 3
5	14 ± 0	14 ± 1	15 ± 1	14 ± 1
6	12 ± 1	14 ± 3	14 ± 1	15 ± 1
7	14 ± 1	15 ± 3	16 ± 1	15 ± 1
8	13 ± 1	16 ± 3	32 ± 2	38 ± 3
9	10 ± 0	10 ± 0	12 ± 1	10 ± 1
10	40 ± 2	45 ± 2	36 ± 4	35 ± 3
11	9 ± 1	12 ± 1	12 ± 0	10 ± 1
12	9 ± 1	10 ± 1	11 ± 1	12 ± 1
13	6 ± 0	8 ± 1	8 ± 1	8 ± 0
14	9 ± 1	12 ± 1	13 ± 2	15 ± 1
15	40 ± 8	31 ± 11	35 ± 2	40 ± 2
16	15 ± 2	34 ± 3	43 ± 4	54 ± 2
17	11 ± 2	30 ± 2	30 ± 1	33 ± 1
18	38 ± 4	22 ± 1	24 ± 2	21 ± 1
19	10 ± 2	15 ± 1	16 ± 0	17 ± 1
20	14 ± 2	21 ± 1	23 ± 1	17 ± 1
21	14 ± 1	16 ± 1	13 ± 2	17 ± 1
N=21	16.9 ± 11.2	18.9 ± 10.2	20.4 ± 10.5	21.4 ± 13.0

Table 9. Type III vessel excess flow.*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	1.05 ± .03	1.19 ± .06	1.20 ± .04	1.12 ± .06†
2	.57 ± .03	1.10 ± .24	2.65 ± .53	1.16 ± .20
3	7.41 ± .28	5.20 ± .49†	6.27 ± .49	6.98 ± .14
4	3.32 ± .11	2.58 ± .45	3.76 ± .25	4.33 ± .08
5	2.66 ± 1.03	3.27 ± .29	3.65 ± .15	4.67 ± 1.2
6	2.31 ± .20	2.59 ± .11	2.44 ± .21	2.76 ± .21
7	1.83 ± .13	1.76 ± .04	1.59 ± .09	1.60 ± .08
8	1.43 ± .06	2.12 ± .29	8.45 ± .40	8.28 ± .47
9	11.2 ± .20	11.5 ± .26	12.1 ± .12	10.9 ± .25
10	3.03 ± .07	3.29 ± .09	2.88 ± .07	2.95 ± .13
11	1.70 ± .07	2.27 ± .03	2.27 ± .07	2.13 ± .07
12	1.63 ± .03	1.75 ± .06	1.99 ± .06	1.90 ± .08
13	.65 ± .06†	.93 ± .03	1.30 ± .07†	1.15 ± .06†
14	1.90 ± .13	2.68 ± .09	2.69 ± .05	3.48 ± .42†
15	4.60 ± .07	7.3 ± .88	13.8 ± 1.00	23.0 ± 1.97
16	1.73 ± .09	3.43 ± .23	4.75 ± .28	5.15 ± .20*
17	1.75 ± .11	2.94 ± .14	3.30 ± .16	3.15 ± .11*
18	5.05 ± .25	3.59 ± .25	3.09 ± .15	2.08 ± .13*
19	1.15 ± .08	1.27 ± .08	1.31 ± .02	1.37 ± .08*†
20	.89 ± .16	1.34 ± .05	2.28 ± .03	1.71 ± .09*
21	3.78 ± .04	3.74 ± .03	3.61 ± .06	3.75 ± .03
N=21	2.84 ± 2.54	3.14 ± 2.43	4.07 ± 3.42	4.46 ± 4.95

* The excess flow for each Type III vessel response is presented. Values are expressed as the mean ± S.D. N value is 3, except in those trials marked (†) in which case N=2.

Type IV Response

Average control red cell velocity in these vessels was .57 mm/sec and was significantly higher than that of Type II and Type III vessels, but was lower than that of Type I vessels. Substantial differences were evident among the individual Type IV vessel hyperemic patterns, as shown in Figure 10. Similarities in the response profile are evident in the top two panels of this figure. These responses, the result of two 30 second arterial occlusions, observed in the same vessel, show identical peak flow responses, but different hyperemia durations. They also demonstrate that different periods of secondary flow stasis, with different recovery times to control level flow, can contribute to a large variance in excess flow values. The bottom two panels (panels 3 and 4, Figure 10) represent Type IV responses from two different vessels. Panel 3 represents a Type IV reactive hyperemia response observed in an on-off type capillary. This particular vessel had a very long secondary flow cessation. This eventually gave way to a secondary reactive hyperemia, evidently caused by a temporary disturbance of the vessel's own regulatory mechanism. Notice in the bottom panel of Figure 10 that an irregular initial hyperemic response occurred. In this particular instance, an almost oscillatory flow behavior can be discerned on the crest of the hyperemia peak. This was

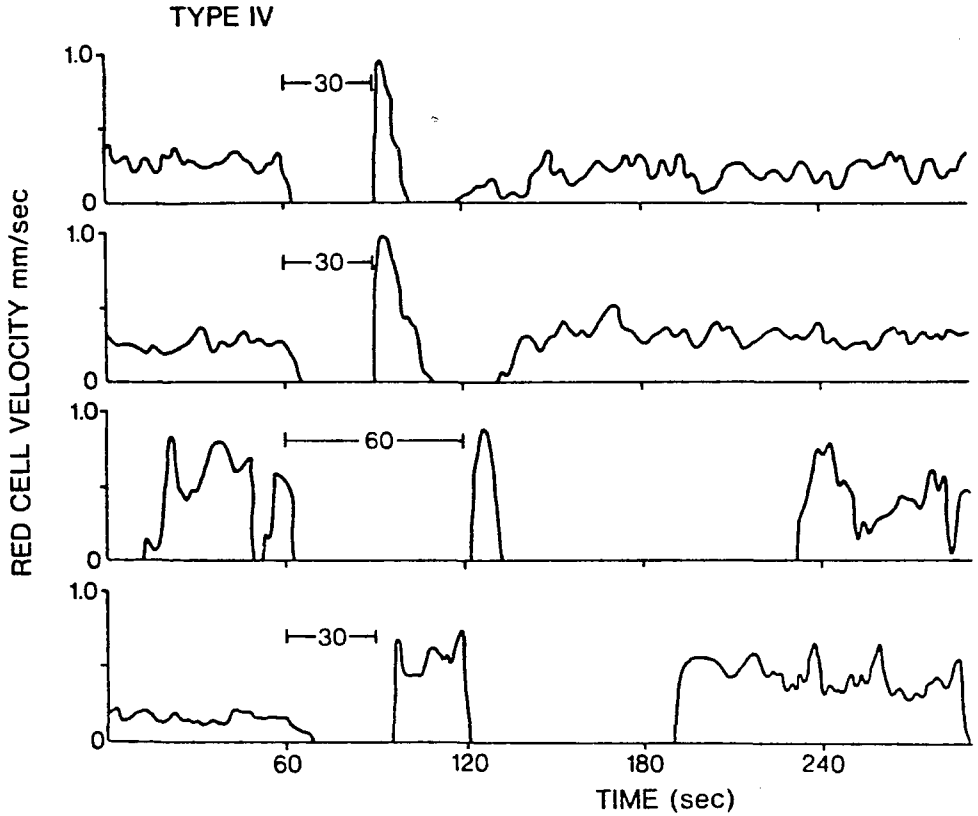

Fig. 10. Representative Type IV capillary reactive hyperemia responses -- The top two panels show two responses of the same vessel to two 30 second arterial occlusions. The bottom two panels emphasize that a secondary hyperemic response frequently was observed in these vessels.

not an uncommon observation. Again, note that the secondary hyperemia following the zero flow period is very evident in this record.

Some Type IV vessels showed increases in peak flow response, time to peak flow, the peak flow to control flow ratio, and the area under the hyperemia peak. Increases in excess flow and the hyperemia duration were also observed. Six of the 16 Type IV vessels observed showed a direct relationship between these increases and longer ischemic periods. Only 4 of these 6 vessels showed increases in all of the parameters examined.

The hyperemic responses of the other 10 Type IV vessels showed no dependency on longer occlusion duration. They displayed very similar responses following 15, 30, 45, and 60 second trials, as shown in Figure 11.

The data of the Type IV vessels are presented in Tables 10, 11, 12, 13, and 14. Vessels whose individual responses were statistically different from those of other vessels are designated by an asterisk. All values represent the mean $\pm$ standard deviation

Distribution of the Four Response Types

The percentage occurrence of these four vessel types is shown in Figure 12. Nine percent of the vessels observed exhibited Type I behavior while Type II vessels represented 20 percent of this population. The Type III and Type IV vessels combined for more than

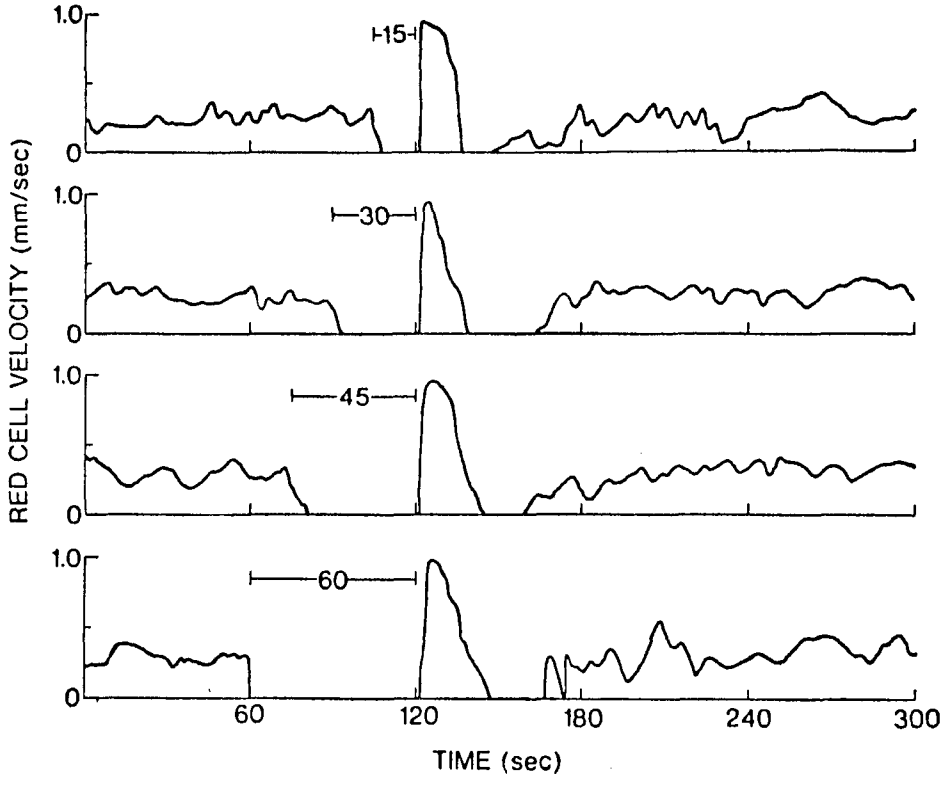

Fig. 11. The reactive hyperemia responses of a single Type IV capillary following 15, 30, 45, and 60 second arterial occlusions -- Peak flow, time to peak flow, the peak flow to control flow ratio, duration of response and area under the hyperemia peak, did not vary with longer occlusion durations.

Table 10. Type IV vessel peak flow response (mm/sec).*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	2.28 ± .02	2.21 ± .02	2.18 ± 0	2.06 ± .03*†
2	0.63 ± 0	0.63 ± .02	0.60 ± 0	0.60 ± 0
3	0.57 ± 0 †	0.66 ± 0	0.66 ± 0 †	0.72 ± .03*†
4	0.62 ± .01	0.60 ± 0	0.66 ± .03†	0.69 ± 0 *
5	0.96 ± .02	0.96 ± 0	0.99 ± 0	0.96 ± .02
6	1.01 ± .02	1.00 ± .02	0.90 ± .05	1.07 ± .02
7	2.57 ± .03†	2.64 ± .02†	2.66 ± .01	2.63 ± .01
8	2.40 ± 0	2.40 ± 0 †	2.52 ± .03	2.70 ± 0 *
9	0.36 ± .01	0.39 ± .01	0.42 ± .03	0.41 ± .01
10	0.39 ± .01	0.50 ± .02	0.60 ± .01	0.64 ± .01*
11	0.46 ± .02	0.60 ± .02	0.57 ± .05	0.64 ± .01
12	1.62 ± .10	1.20 ± .09	1.92 ± .20	1.38 ± .09
13	1.71 ± .03	1.70 ± .01	1.67 ± .01	1.64 ± .01
14	0.46 ± .01	0.50 ± .01	0.45 ± 0	0.46 ± .01
15	2.40 ± .02	2.41 ± .01	2.42 ± .01	2.40 ± .01
16	0.90 ± .05	0.84 ± .02	0.81 ± 0 †	0.88 ± .01

* The peak flow responses of each Type IV vessel are presented in this table. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked ( ) in which case N=2.

Table 11. Type IV vessel time to peak flow (sec).*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	8 ± .3	10 ± .6	12 ± 1.2	14 ± 0 *†
2	4 ± .3	5 ± .3	7 ± 0	3 ± .3
3	3 ± 0 †	3 ± 0	8 ± .5†	21 ± 4 *†
4	5 ± .3	35 ± 10	16 ± 1.5†	24 ± 1
5	4 ± .3	3 ± .3	3 ± .3	5 ± .3
6	5 ± 0	4 ± .3	6 ± .3	10 ± 1.7*
7	35 ± 1.5†	42 ± .5†	40 ± 1.7	41 ± .7
8	10 ± 3	12 ± 1 †	16 ± .3	17 ± 0 *
9	3 ± 0	5 ± .3	5 ± 0	5 ± .3
10	2 ± 0	2 ± 0	9 ± .6	8 ± .9*
11	12 ± .9	15 ± .3	17 ± .7	22 ± 5 *
12	18 ± .9	25 ± 3	17 ± .7	21 ± .9
13	24 ± 1.5	28 ± 1.5	28 ± 2	30 ± 2.6
14	6 ± 0	6 ± 0	7 ± .3	9 ± 2
15	5 ± .3	6 ± .3	6 ± .3	5 ± .3
16	4 ± .3	5 ± .3	7 ± .5†	8 ± 0 *
N=16	9.25 ± 9.11	12.9 ± 12.6	12.8 ± 9.7	15.2 ± 10.7

* The time required to achieve peak flow following arterial occlusion is presented for each Type IV capillary. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†) in which case N=2. Significance (*) was tested at the .01 level.

Table 12. Type IV vessel peak flow to control flow ratio.*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	3.83 ± .07	3.93 ± .01	3.79 ± .03	3.72 ± .09*†
2	2.03 ± .02	2.05 ± .07	1.90 ± .02	2.00 ± .02
3	3.94 ± .14†	3.98 ± .06	4.22 ± .12†	3.95 ± .22*†
4	1.94 ± .01	2.35 ± .01	2.36 ± .04†	2.36 ± .04*
5	3.64 ± .09	3.45 ± .03	3.68 ± .07	3.49 ± .05
6	3.82 ± .06	3.91 ± .05	3.39 ± .20	3.65 ± .02
7	2.19 ± .02†	2.08 ± .07†	2.01 ± .02	2.16 ± .06
8	1.98 ± .02	1.76 ± .13†	1.91 ± .02	2.16 ± .04*
9	6.40 ± .02	6.71 ± .08	6.66 ± .18	6.47 ± .05
10	1.60 ± .03	2.03 ± .08	2.26 ± .08	2.53 ± .03*
11	1.71 ± .05	2.12 ± .10	2.25 ± .11	2.72 ± .03
12	3.09 ± .23	3.25 ± .17	2.59 ± .24	2.26 ± .49
13	2.82 ± .03	2.42 ± .06	2.21 ± .03	2.77 ± .28
14	1.35 ± .05	1.36 ± .04	1.31 ± .03	1.33 ± .03
15	2.89 ± .03	2.98 ± .06	2.93 ± .01	2.85 ± .01
16	2.07 ± .16	2.03 ± .05	1.88 ± .01†	2.09 ± .03
N=16	2.83 ± 1.29	2.90 ± 1.31	2.83 ± 1.30	2.96 ± 1.22

* The peak flow to control flow ratio is presented for each Type IV capillary. Values are expressed as the mean ± S.D. N value is 3, except in those trials marked (†) in which case N=2.

Table 13. Type IV vessel hyperemia duration (sec).*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	10 ± 1.7	14 ± 1	15 ± 1	20 ± 3*†
2	10 ± .3	12 ± 1	13 ± .3	14 ± 2
3	15 ± .5†	23 ± .3	21 ± .5†	22 ± 2†
4	15 ± .9	45 ± 10	40 ± 5 †	48 ± 4
5	5 ± 1.0	11 ± 1	9 ± .3	12 ± 1
6	12 ± .3	15 ± .3	16 ± 1	15 ± .3
7	35 ± 2.0†	48 ± 4 †	42 ± 1	49 ± 2
8	24 ± .3	28 ± 2 †	33 ± 1	37 ± 9*
9	18 ± 1.2	25 ± 2	32 ± .3	34 ± 1*
10	4 ± .3	9 ± 1	11 ± .3	12 ± 1*
11	43 ± 1.5	41 ± 1	44 ± 1	40 ± 1
12	26 ± .6	27 ± 1	33 ± 2	33 ± 1
13	32 ± .9	34 ± 2	38 ± 3	39 ± 3
14	11 ± .3	12 ± 0	14 ± 1	14 ± 1
15	7 ± .3	8 ± 0	10 ± 2	12 ± 3
16	9 ± .3	10 ± 0	9 ± 0†	10 ± 1
N=16	17.2 ± 11.5	22.6 ± 13.5	23.8 ± 13.1	25.7 ± 13.9

* The hyperemia response duration is presented for each Type IV capillary. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†) in which case N=2.

Table 14. Type IV vessel excess flow (mm).*

Vessel	Occlusion Duration (sec) 15	30	45	60
1	- .10 ± .07	- .20 ± .02	- .28 ± .03	- .34 ± .10*†
2	-1.16 ± .34	-1.28 ± .23	-1.37 ± .03	-1.53 ± .15*
3	- .30 ± .04†	- .38 ± .10	- .39 ± .08†	- .46 ± .09*†
4	.09 ± .09	.25 ± .09	.17 ± .22†	.21 ± .09*
5	- .38 ± .02	- .46 ± .03	- .51 ± .02	- .58 ± .03*
6	- .27 ± .03	- .39 ± .02	- .45 ± .02	- .51 ± .02*
7	.88 ± .13†	.49 ± .09†	.32 ± .08	.13 ± .10*
8	.61 ± .19	.56 ± .22†	.30 ± .16	.21 ± .24*
9	.32 ± .01	.21 ± .01	.13 ± .01	.05 ± .01*
10	- .11 ± .02	- .26 ± .03	- .39 ± .05	- .52 ± .02*
11	.20 ± .01	.12 ± .01	.08 ± .03	.04 ± .01*
12	.48 ± .07	.11 ± .11	- .10 ± .07	- .30 ± .25
13	.90 ± .06	.60 ± .10	.35 ± .10	.43 ± .32
14	.17 ± .03	.12 ± .04	.02 ± .04	- .08 ± .01
15	1.60 ± .05	1.49 ± .04	1.28 ± .13	1.07 ± .11
16	.34 ± .07	.13 ± .15	.12 ± .16†	.03 ± .03
N=16	0.20 ± .64	0.07 ± .60	-0.05 ± .56	-0.13 ± .56

* The excess flow for each Type IV vessel response is presented. Values are expressed as the mean ± S.D. N value is 3, except for those trials marked (†) in which case N=2.

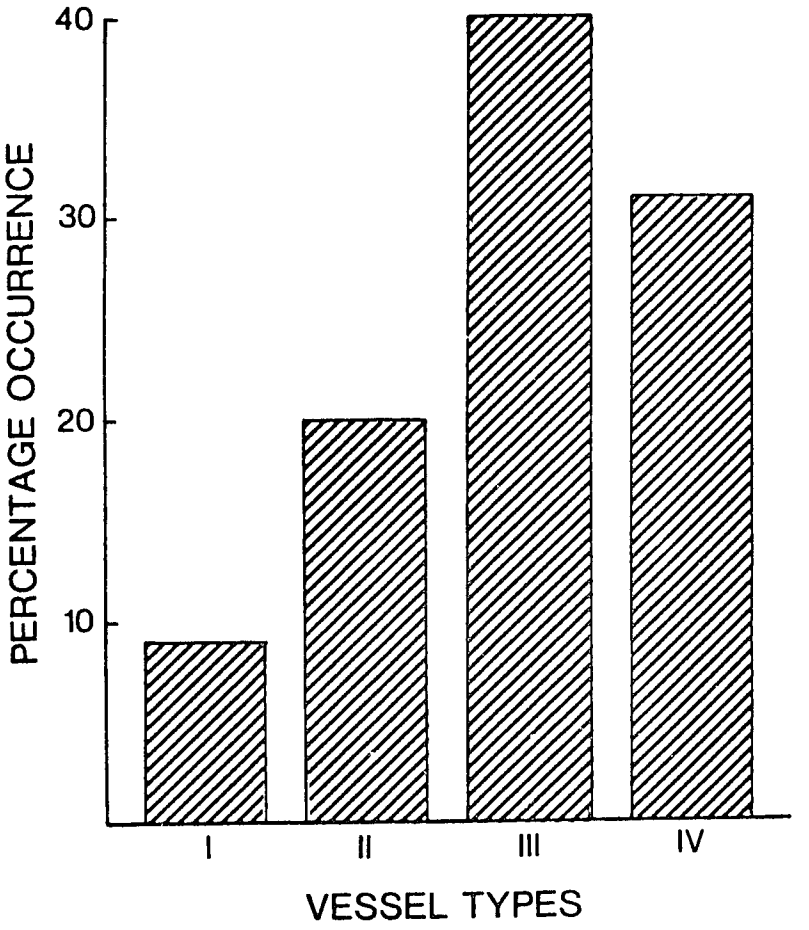

Fig. 12. Histogram showing the percentage occurrence of the four reactive hyperemia response types.

70 percent of the vessels evaluated. The item of primary significance in this study was the hyperemia which followed an arterial occlusion. Therefore, the vessels which showed this response were the ones of primary interest. If all of the vessels which were originally selected for observation had been studied with four durations of occlusions, the Type I vessels would have represented a larger portion of the mesentery capillary population.

Evaluation Parameters

The six parameters selected to evaluate the reactive hyperemia responses of the Type III and Type IV vessels are depicted diagrammatically in Figure 13. A period of control flow (C) was measured for at least 60 seconds prior to an occlusion. Following release of the arterial occlusion, flow increased to a maximum peak velocity (P). The amount of flow in excess of mean control flow was termed excess flow. The time to peak flow (T) and the duration of the hyperemia (D) were measured. The ratio of peak flow to control flow was computed.

Comparison of Gross Flow and Type III Hyperemia Responses

Since the gross flow and the Type III response were similar in profile, a comparison seemed to be in order. The time to peak flow averaged about 9 seconds in the Type III vessels and was 8 seconds for the gross blood flow response. This parameter did not vary with occlusion duration in 15 of 21 of the Type III capillaries, nor did it vary

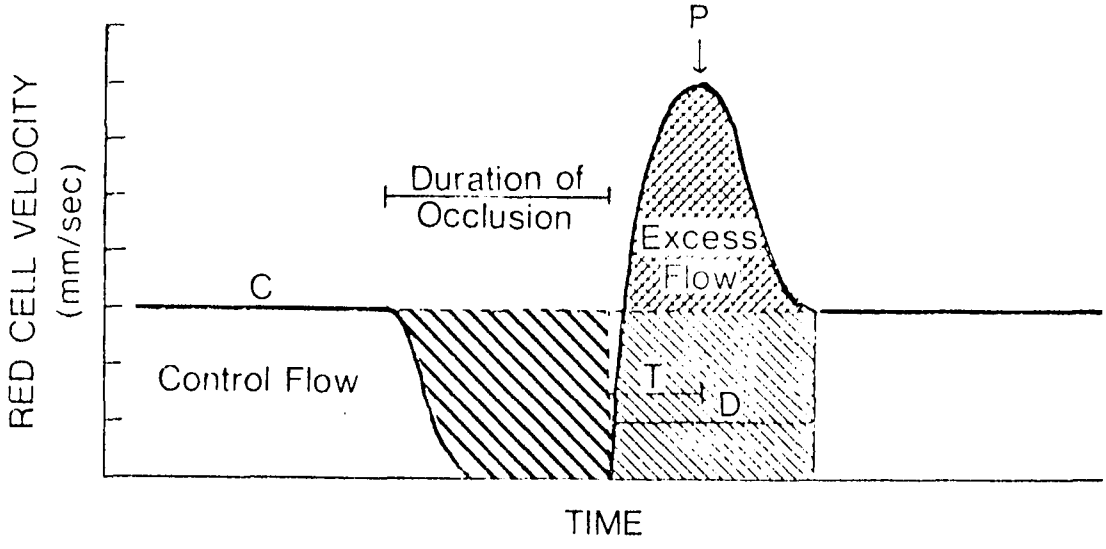

Fig. 13. Diagram which shows the parameters used to evaluate the reactive hyperemia responses -- A period of control flow (C) preceded the occlusion. The post-occlusion response was evaluated for peak flow (P), the time to peak flow (T), and the duration (D) of hyperemia. Excess flow was defined as the red cell velocity in excess of control velocity.

in the gross flow. The duration of hyperemia of 12 of 21 capillaries and the peak velocity to control velocity ratio of 13 of 21 vessels remained constant for the Type III capillaries. These parameters were found to increase as a function of longer occlusion in the gross flow studies.

Pressure Pulse Study

The study of reactive hyperemia produced evidence suggesting that a myogenic control mechanism indeed exists in the mesenteric microcirculation. However, it was felt that even stronger supportive evidence of this mechanism might be obtainable. Therefore, it was decided to investigate the converse aspect of the myogenic mechanism. That is, that vasoconstriction occurs in response to a pressure elevation.

With the purpose in mind to observe this response, ten preparations were used to study the effects of brief pressure elevations on capillary blood flow. Sixteen vessels were observed in these experiments. All of them showed a reactive hyperemia response characteristic of either the Type III or Type IV vessels described previously. All of these vessels also autoregulated when arterial pressure was lowered by a partial arterial occlusion. Autoregulation, for these experiments, was defined as maintained control red blood cell velocity when perfusion pressure was reduced below control level.

The procedure followed was to lower arterial pressure to some value between 60 and 100 mm Hg, and then to determine if capillary blood flow returned to approximately control level. If red cell velocity in the vessel did not respond in this manner, within two or three trials, another vessel was sought for examination. When a responsive vessel was found, the arterial pressure was quickly elevated and then returned to the previously established autoregulatory pressure. Pressure pulses of 1 to 20 seconds were created in this way. It was also possible to alter the rate of pressure rise. In some instances vessels autoregulated over a wider pressure range and, therefore, permitted a greater latitude for their examination. When possible, these vessels were pulsed with more than one magnitude of pressure. Four of the 16 vessels studied were observed for over four hours each. The vessels which exhibited Type IV reactive hyperemia behavior on test occlusion trials, also responded to quick pressure pulses (4-20 sec duration) by displaying periods of flow stasis. Their general pattern was an initial hyperemia and then a period of zero flow. It is significant that the magnitude of this hyperemia was less than that shown during total arterial occlusion.

Four of the 16 vessels studied responded in the above fashion. One of these vessels is presented in Figure 14. Pressure pulses of 80 mm Hg, and 4 to 20 seconds duration, were effective in causing flow cessation in this vessel. Pulses of shorter duration (1 to 3 sec) did not cause flow to stop. Note that the red cell velocity diminished to zero, even though perfusion pressure was still elevated.

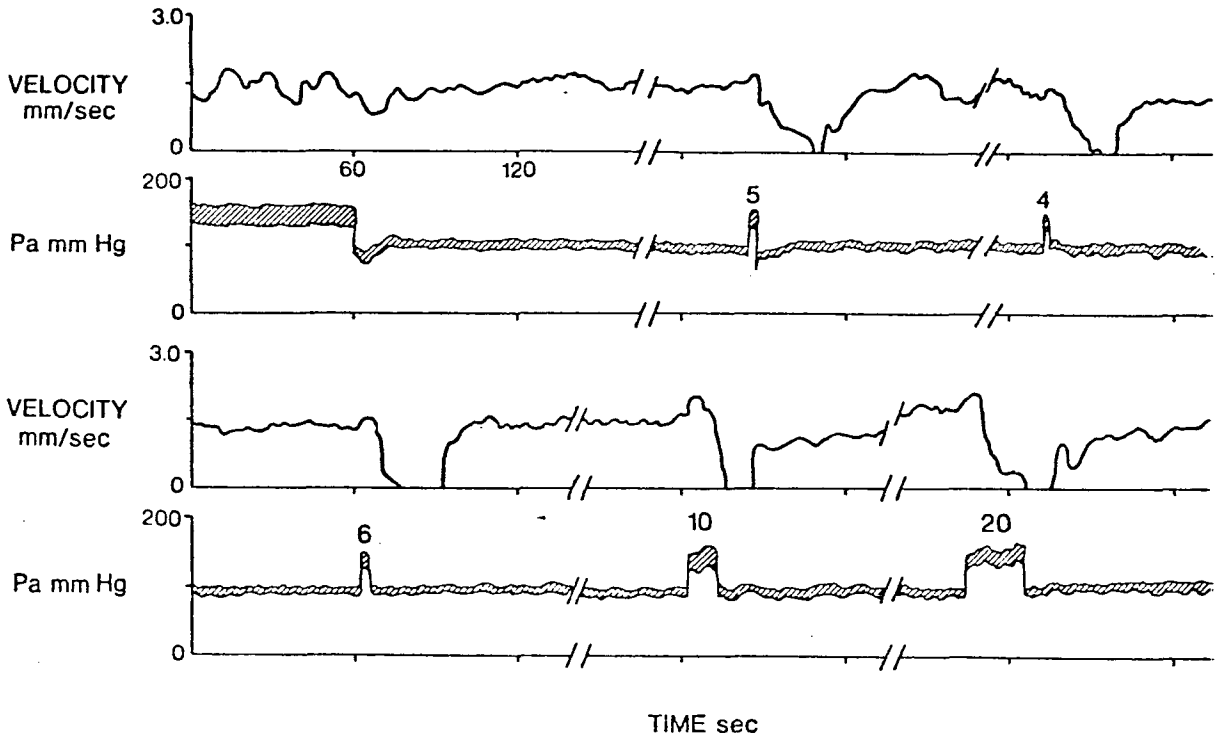

Fig. 14. Effect of 4 to 20 second duration pressure pulses on the red cell velocity of a Type IV vessel -- The magnitude of the pressure pulses was 80 mmHg. The zero flow periods following these pulses suggests a precapillary constriction in response to the pressure elevation.

Figure 15 demonstrates that flow again ceased just as it did during post-occlusion trials, when arterial pressure was restored and maintained. The oscillatory behavior seen when the flow returned was not unusual. This activity was not associated with either intestinal motility or venous pressure fluctuations. The cause of this flow cessation is considered to be the result of a constrictor response of the precapillary sphincter of this vessel. For the ease of describing these pressure pulse responses, a decrease in red cell velocity also will be described as a constrictor response.

Effect of the Pressure Pulse Magnitude

Pressure pulses of various magnitude were tested to see if they altered the constrictor response of a given vessel. Figure 16 shows the effect of a smaller pressure pulse (60 mm Hg) on the flow in the same capillary seen in Figures 14 and 15. Notice that the constriction occurred at the same time after the pressure pulse, but that total constriction was not induced. In the bottom panel of Figure 16, it is evident that flow in the capillary was much higher at that time of the experiment, but that the constrictor response still existed. In addition, the constrictor mechanism was not altered by the pressure pulse manipulations, or affected by preparation degradation, because an 8 second pressure pulse of the original test magnitude (80 mm Hg) still induced total constriction. This last response was observed almost 3 hours after the responses shown in

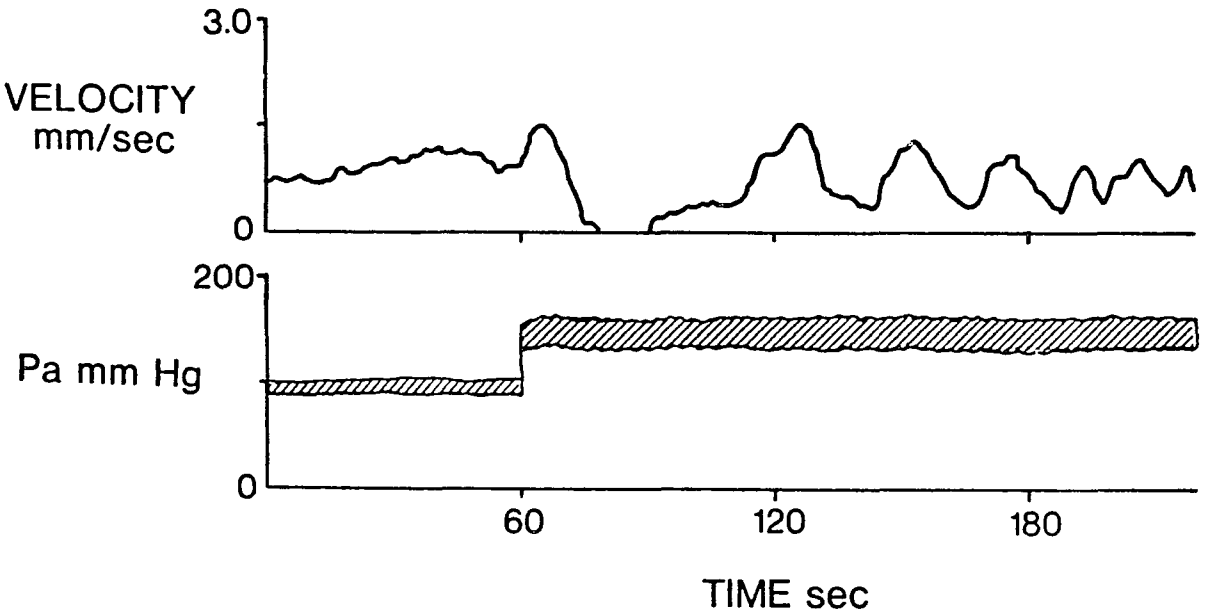

Fig. 15. Red cell velocity decreased to zero when arterial pressure was restored to control -- Notice too, that red cell velocity tended to oscillate for a period of time. This record comes from the same vessel shown in Figure 14.

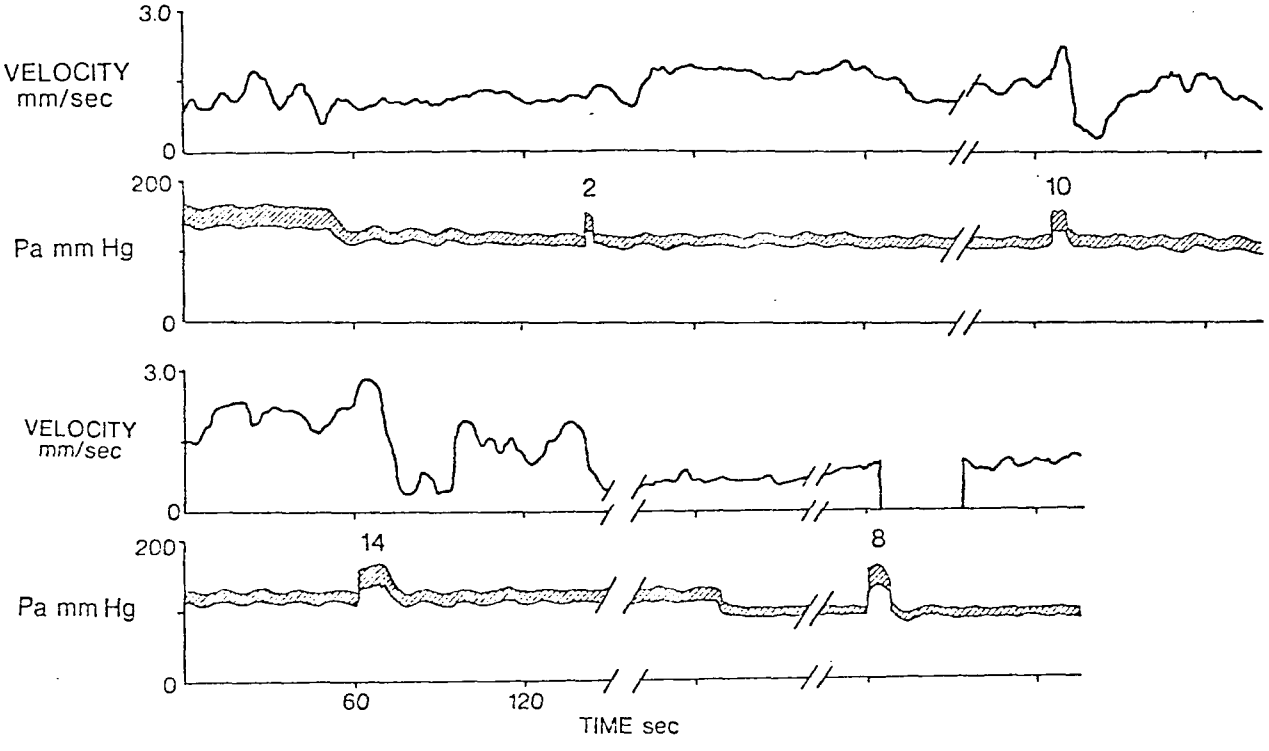

Fig. 16. The response of the capillary shown in Figures 14 and 15, to 60 mm Hg pressure pulses.

Figure 14. Eleven of 16 vessels studied showed a variable constrictor response to different magnitudes of pressure pulse. Only 4 of these 11 exhibited zero flow periods following pressure pulses of any magnitude.

Ramp Pressure Changes

A second type of pressure manipulation was produced in 14 capillaries observed in 6 preparations. The rate at which pressure elevation occurred (dP/dt) was varied over a range of 21 mm Hg/sec, to less than 1 mm Hg/sec. As seen in Figure 17, when the pressure was raised quickly (dP/dt = 12 mm Hg/sec) a constrictor response developed which caused red cell velocity to diminish to zero. When the dP/dt was limited to less than 1 mm Hg/sec, no initial hyperemia, and no secondary flow reduction was observed. Figure 18 shows a similar response, of the same vessel, to a 100 mm Hg pressure change which was effected over a 5 minute period of time. This vessel autoregulated very well, approximately control velocity, at 60 mm Hg perfusion pressure. Although transient periods of flow change were seen (at 60, 120, and 300 second marks on the record), red cell velocity remained relatively unchanging during this period.

Only 2 of the 14 capillaries studied in this way showed the extreme variability of the vessel shown in Figures 17 and 18. It should be emphasized, though, that only 4 of these 14 exhibited behavior characteristics of Type IV vessels following both occlusions

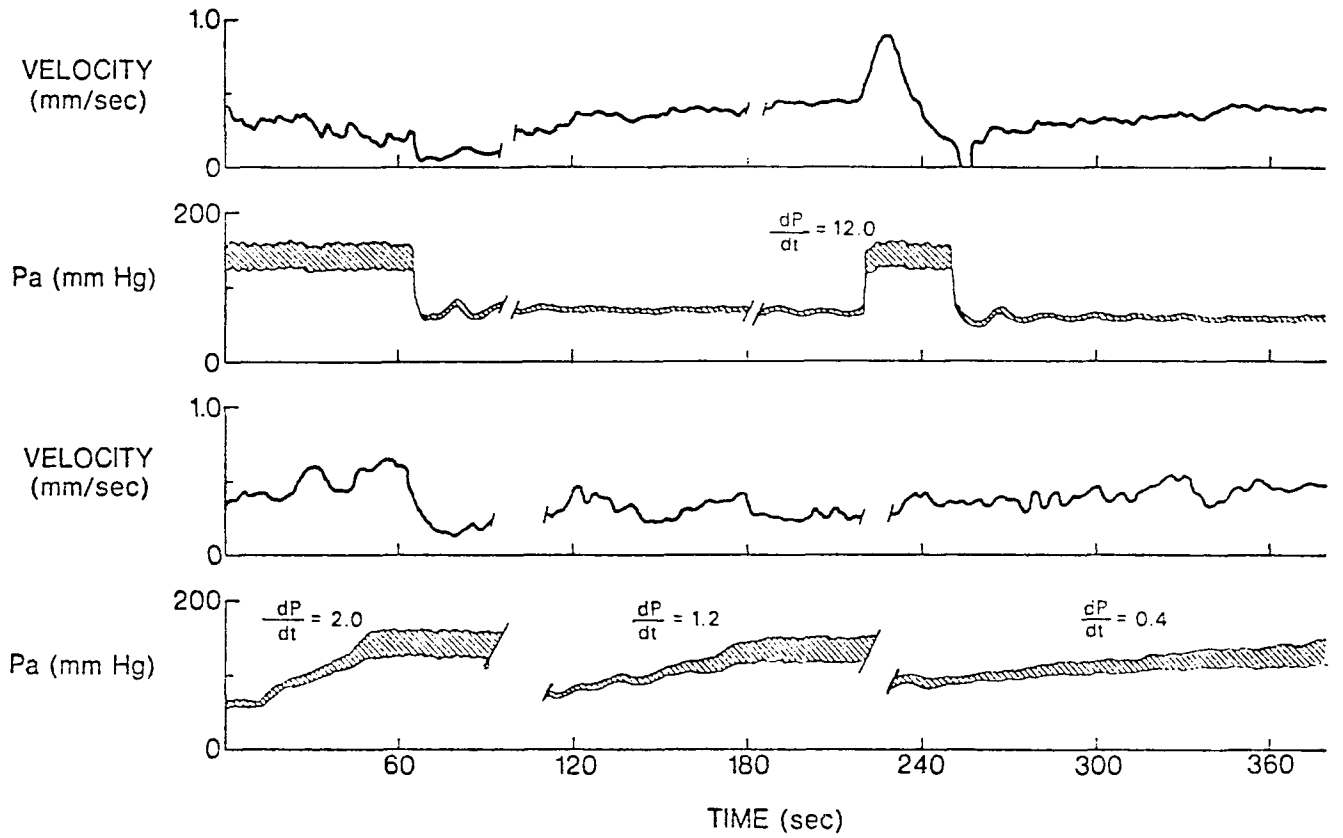

Fig. 17. The effect of varying the rate of pressure elevation (dP/dt) on capillary red cell velocity -- A dP/dt of 12 mmHg/sec caused a zero flow period (top panels) and slower pressure increases did not cause related changes in red cell velocity.

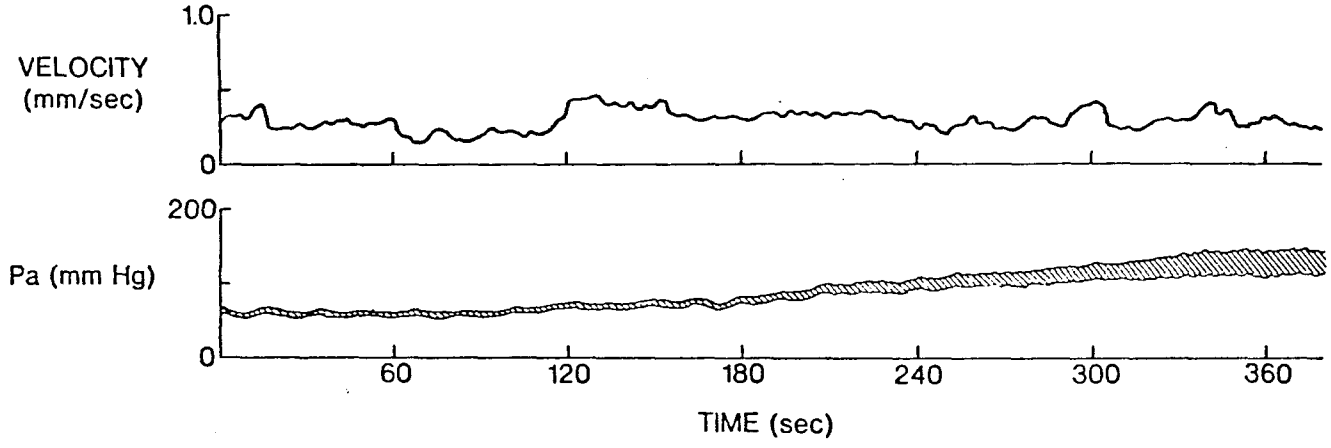

Fig. 18. Record shows a pressure change of over 100 mm Hg magnitude which took place over a 5 minute time period -- No evidence of pressure induced constriction was observed.

and quick pressure pulses. Nevertheless, these results indicate that the mechanism which regulates the Type IV vessels is sensitive to more than one aspect of pressure alterations.

The percent change in red cell velocity is shown as a function of dP/dt in Figure 19. The open circles represent the two capillaries which showed a graded response with different rates of pressure increase. Only these two vessels (vessels 1 and 2) showed the ability for graded response, ranging from zero flow stoppage with large dP/dt, to no change in flow with a small dP/dt. Vessels 3-7 did respond to variable dP/dt but constricted to the same extent if they responded at all. The remaining vessels were less consistent than these seven. As seen in the upper half of Figure 19., some vessels exhibited flow increases when even small dP/dt tests were attempted. This was not a consistent response of any one vessel and possibly reflects an artifact induced by the experimental procedure. Five out of the 14 vessels observed, exhibited the same decrease in velocity no matter what rate of pressure change was used. Individual vessel responses are labeled by the same number in Figure 19.

Figure 20 demonstrates the responses observed in one vessel with different rates of pressure change. In this vessel dP/dt did not appear to be an effective stimulus for its constrictor mechanism. Possibly a pressure threshold initiated the velocity reduction observed in this vessel.

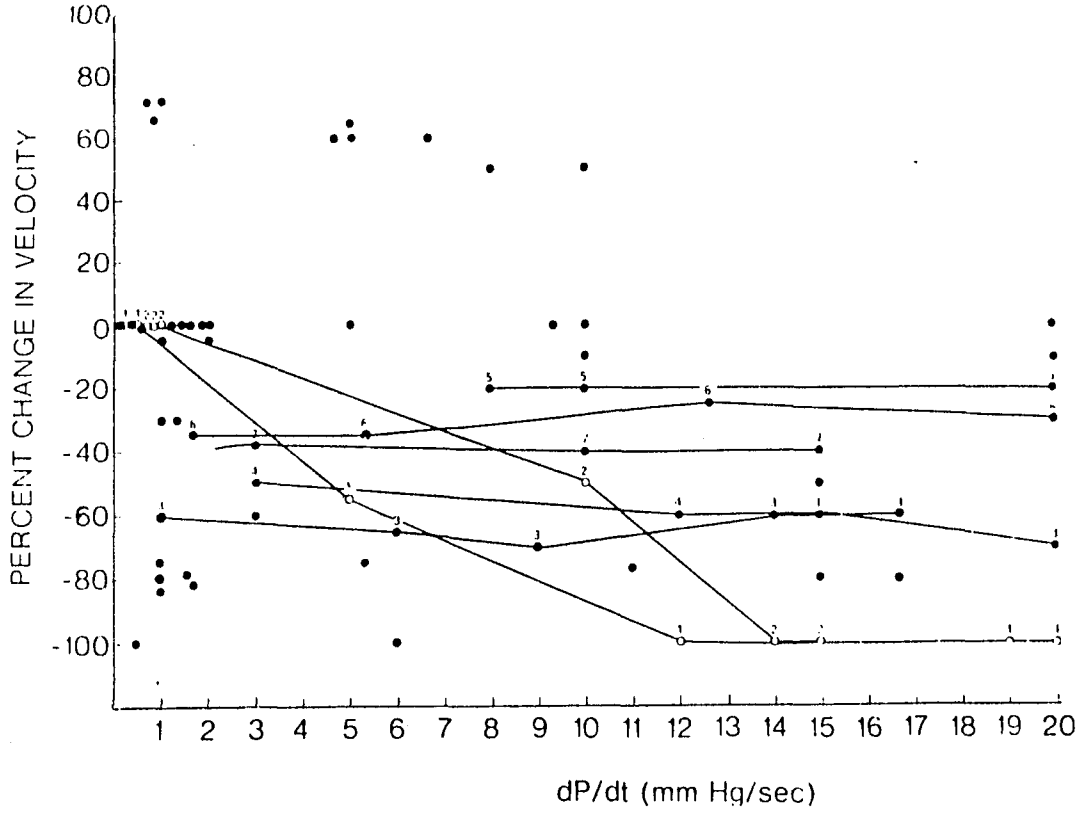

Fig. 19. The percentage change in red cell velocity as a function of dP/dt for 14 cat mesentery capillaries -- Open circled vessels represent the two vessels which showed the most variable responses with different dP/dt. The other numbered vessels 3-7 represents 5 vessels of the 14 which showed no response to dP/dt over the range studied.

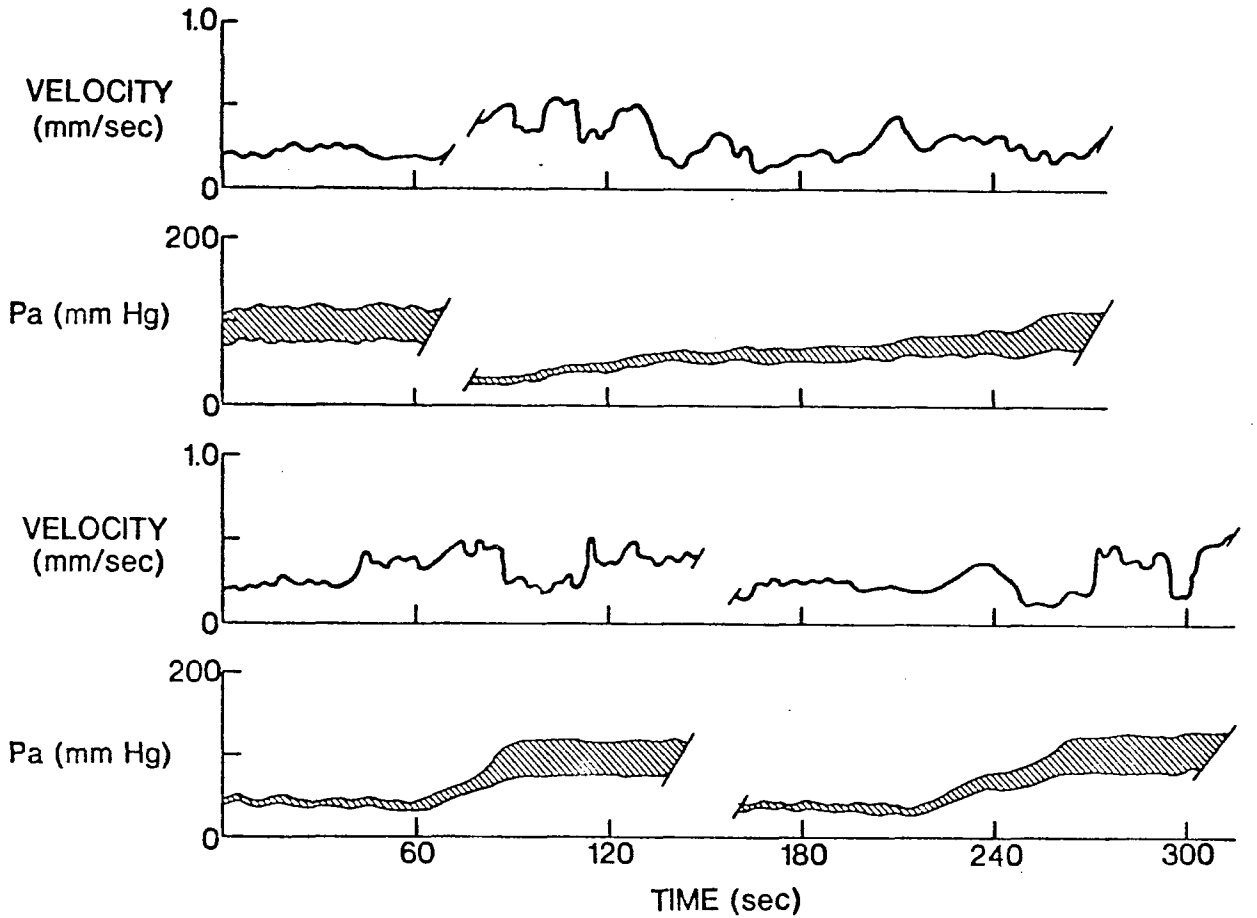

Fig. 20. A vessel which did not respond to variable dP/dt but was responsive to the magnitude of pressure increase.

A latent period was observed to exist between the start of pressure elevation and when the flow decrease was initiated. This is demonstrated in the pressure pulse responses shown in Figure 14. Approximately 6 seconds elapsed in this instance before flow dropped to zero. This latent period ranged from 6-12 seconds for the four capillaries which developed zero flow periods. The mean for all vessels observed was 9 ± 5 (S.D.).

DISCUSSION

General Considerations

In these studies, two theories were considered sufficiently valid that they might explain reactive hyperemia. These were the metabolic and myogenic theories.

The metabolic theory postulates that accumulation of vasodilator metabolites, or depletion of local oxygen supply, occur during periods of vascular occlusion. As a result of these events, vasodilatation of resistance vessels then develops and allows reactive hyperemia when flow is restored. If reactive hyperemia results from this mechanism, certain changes might be expected. For example, increased periods of flow stagnation would result in a more extensive vasodilatation and allow a proportionately greater magnitude of hyperemia. This is based on the assumption that metabolite concentrations accumulate as a function of occlusion duration until their maximal dilatory effect is realized. Beyond this concentration, the major effect would be realized as an increased response duration, as longer periods of elevated flow become necessary to remove the accumulated dilators, or reestablish depleted oxygen stores. An exponential return of blood flow to control level might also be expected to be revealed in the hyperemia profile. Furthermore, an increase in the excess flow might be predicted since increases in both the peak flow

and the response duration would be likely. Since vessel dilation occurs during the occlusion period, the time to peak flow would be predicted to be a matter of a few seconds. No increase in this parameter with occlusion duration is expected according to metabolic theory.

Classical myogenic theory also considers that vasodilatation of resistance vessels occurs during periods of vascular occlusion. During an occlusion, reduction of intraluminal pressure effectively removes the stimulus for maintaining normal vascular wall tension and vasodilatation occurs. Again a quick rise to peak flow would be predicted. Progressive increases in the peak flow values would not be expected when occlusion durations longer than those required for complete myogenic relaxation are used. This assumes that arterial pressure is independent of the occlusion durations used in this study. Therefore, the time to peak flow and the magnitude of the peak flow would be predicted to be independent of occlusion duration. Myogenic theory would also predict that peak-flow to control-flow ratios, excess flows, and the hyperemia response duration would all be constant for the different occlusion durations used in this study. Vasoconstriction would be expected when perfusion pressure was increased.

Gross Blood Flow Reactive Hyperemia Response

Control level gross blood flow in these preparations was found to be comparable to other values reported in the literature. Folkow

(1952) and Richardson and Johnson (1969) reported resting cat intestinal blood flows to be 20 to 40 ml/min/100 g of tissue. The average value was 24.4 ml/min/100 g of tissue in the preparations of the present study.

Only Selkurt et al. (1964) specifically studied reactive hyperemia in the isolated intestinal preparation. Their work was done in dogs and, therefore, species differences must be accounted for before comparisons with cat intestinal data can be made. Nevertheless, the trends they observed in gross flow reactive hyperemia were confirmed in this study. Examination of their published data revealed peak flow was reached approximately 10 seconds after occlusion release, as compared with 8 seconds in this study. An increase in the duration of gross flow hyperemia with occlusion time was seen in both the Selkurt study and this study, but the mean value of 35 seconds hyperemia duration for a 15 second occlusion in the dog was approximately twice that observed in cat preparations (15 seconds). In the cat intestine, it appeared that the duration of reactive hyperemia was almost comparable to the occlusion duration, being 15, 34, 40, and 70 seconds for 15, 30, 45, and 60 second occlusions respectively.

Selkurt and his coworkers postulated a metabolic origin of gross flow intestinal hyperemia. They found that both the duration of reactive hyperemia and the total hyperemia response increased as a function of occlusion duration. Furthermore, they reported evidence

which, they said, argued against a myogenic mechanism. They observed that reactive hyperemia still occurred following occlusions during which arterial pressure was maintained at or above control level by infusing dextran solutions. The conclusions drawn from these experiments are subject to criticism because artificial perfusates have been shown to be detrimental to myogenic activity of intestinal preparations (Folkow 1952). Furthermore, when dextran infusions were used to maintain arterial pressure in the cat mesentery experiments, they were found to be detrimental to the general physiological state of the animal, and specifically altered vascular reactivity.

However, the data obtained in these experiments do suggest that metabolic factors play a significant role in the development of the gross flow reactive hyperemia response in the cat intestine. For example, when the occlusion duration was increased from 15 to 60 seconds, the peak flow increased from 53 to 66 ml/min/100 g of tissue, the peak-flow to control-flow ratio increased from 2.2 to 2.7, the duration of hyperemia increased from 15 to 70 seconds and the excess flow also increased from 3 to 10 ml of blood. All of these changes might be predicted to occur if a metabolic mechanism acted to control reactive hyperemia.

Oxygen consumption of the intestine is 0.82 ml/min/100 g of tissue (Johnson 1960). It can be calculated that oxygen stores of the intestine would be depleted during a one minute period of ischemia.

A progressive accumulation of anaerobic metabolites might then occur in the vicinity of the intestinal resistance vessels with longer occlusion durations. Since 85 percent of the venous effluent in the mesenteric vein originates in the intestine (Grim 1963), the effects of such a metabolic accumulation might contribute to the gross flow hyperemia response. It seems unlikely that any significant contribution of this nature would be made by the mesenteric tissue because of its small contribution to the venous effluent and its low metabolic activity (Diem and Lintner 1972).

As previously mentioned, Selkurt et al. (1964) did not find direct evidence that myogenic activity played a significant role in the development of intestinal reactive hyperemia. No direct evidence of a myogenic involvement in cat intestinal reactive hyperemia was obtained in this study either. While this does not support Folkow's (1949) suggestion that myogenic activity is strongly involved in the origin of this phenomenon, neither does it contradict Folkow's suggestion of myogenic involvement in vascular responses to arterial pressure variation. His conclusions were later strongly supported by the observations of Selkurt and Johnson (1958) who found a large increase in vascular resistance when intestinal venous pressure was elevated. It is also important to acknowledge the possibility that metabolic factors might dominate over myogenic control when conditions exist which force these two mechanisms to compete (Folkow 1952). If this is true, it is possible that the myogenic contribution to the

intestinal post-ischemic response was masked by an overwhelming metabolic effect. Furthermore, an averaging effect, involving flow in many capillaries simultaneously, would also tend to conceal the myogenic response.

Red Cell Velocity as a Measure of Volume Flow

Variations in volume flow were measured by capillary red cell velocity fluctuations in these studies. This assumes that the cross-sectional area of capillaries is constant under these experimental conditions. As mentioned previously, capillaries are devoid of any contractile investment. Mesentery capillaries have also been shown to maintain constant diameter over a wide range of pressures (Baez, Lamport, Baez 1960) which includes the pressure range used in these experiments. Therefore, the changes in red cell velocities observed in these studies are considered to reflect changes in the precapillary resistance elements of the mesentery circulation, and not dimensional changes in the capillaries. A more detailed discussion of this point follows.

Flow Patterns Observed in Mesentery Capillaries

The four patterns of red cell flow observed in this mesentery study were similar to the patterns described by Johnson and Wayland (1967). Reactive hyperemia was observed in vessels representative of all four flow patterns. Each capillary had its own characteristic pattern of flow and did not deviate from this pattern during the course

of an experiment. It was not unusual to see a different flow pattern in two capillaries which branched from the same parent arteriole. Assuming that the flow pattern shown by individual capillaries is a reflection of precapillary smooth muscle activity, it follows that different frequencies of contraction exist in this smooth muscle along the length of arterioles. It also appears that the smooth muscle activity in one region is independent of the activity in adjacent regions.

Whenever periodic flow was seen in one capillary of a preparation, this seemed to be the predominant flow pattern in the vascular bed. Visual observations indicate that the type of flow pattern shown by a vessel is determined by the activity at the branch point of the capillary, and is not a reflection of diameter changes of the arteriole itself. This is in agreement with observations made by Chambers and Zweifach (1944), Johnson and Wayland (1967), and Nicoll and Webb (1946).

Reactive Hyperemia in Mesentery Capillaries

Reactive hyperemia has not been studied extensively in the microvasculature. Johnson and Wayland (1967) reported that a hyperemic response followed periods of reduced perfusion pressure in cat mesentery capillaries. But the response was not studied in detail at that time. Quantitative evaluations have been made in two skeletal muscle preparations. In one of these, the frog pectoralis muscle, only

metabolic factors were thought to be responsible for the hyperemia (Gentry and Johnson 1972). The other study revealed that four distinct populations of capillaries, based on their reactive hyperemia profiles, existed in the cat sartorius muscle (Burton and Johnson 1972). The responses were suggested to be controlled by either metabolic or myogenic mechanisms, singly or in combination. Since these same response patterns were observed in the cat mesentery capillaries of this study, a comparison of the results of the two studies seemed in order. This comparison is somewhat limited since only 60 sec occlusions were used in the cat muscle study.

There were four types of responses which followed periods of arterial occlusion. The Type I response showed no hyperemia but just returned to control level flow. Type II vessels displayed a long period of hyperemia which was followed by control level flow. A quick rise to peak flow followed by return to control typified the Type III vessels. A similar rise to peak flow was also seen in the Type IV response, but this was followed by a period of zero flow in these vessels.

The frequency of occurrence of these responses in the sartorius and mesentery studies were Type I -- 28 percent in muscle vs. 9 percent in mesentery, Type II -- 14 percent in muscle vs. 20 percent in mesentery, Type III -- 21 percent in muscle vs. 40 percent in mesentery and Type IV -- 37 percent in muscle vs. 32 percent in mesentery.

Both studies revealed that Type I vessels had the highest control velocities, but the group average was slightly lower in skeletal muscle (0.63 mm/sec) than in mesentery (0.83 mm/sec). The post-occlusion rise time to control velocity was 14 seconds in the cat muscle while mesenteric capillaries required 75 seconds, on the average, to reach control.

Type II vessels in the two studies had control velocities of 0.40 mm/sec in skeletal muscle and 0.28 mm/sec in the mesentery. A large difference was apparent in the duration of hyperemia in the two studies. Within 60 seconds after occlusion release, the Type II hyperemia was gone in muscle, but in many cases the mesentery capillary flow was still increasing at 60 seconds. The total response lasted an average of 54 seconds in muscle and 170 seconds in mesentery. Peak velocity to control velocity ratios were 2.7 in muscle and 3.9 in mesentery.

It is interesting to consider the possible cause of such sustained periods of hyperemia. Burton and Johnson (1972) suggested that neither the metabolic nor myogenic theories provided plausible explanations for such a sustained response. Neither theory would seem to predict such a prolonged rise to peak flow following occlusion release nor such a prolonged response duration. From a metabolic standpoint, an extremely slow washout of metabolites would be necessary for such an extended hyperemia. But response durations of this length were observed in the mesentery following even a 10 second

arterial occlusion, which further argues against a metabolic cause. In addition, an exponential decay of the hyperemia, which might be expected according to metabolic theory, was not seen. Furthermore, such extreme variability of the response was seen in individual vessels with fixed occlusion durations, as well as with different occlusion durations, that a metabolic mechanism again seems unlikely.

The possibility exists that the Type II response might be due to a total relaxation of the vascular smooth muscle. This may have been induced by the sudden restoration of perfusion pressure to the system following an arterial occlusion. An inhibitory response similar to this was described by Burnstock and Prosser (1960) in guinea pig taenia coli. When a quick stretch was applied to a spontaneously active strip of taenia coli, relaxation of the smooth muscle occurred simultaneously with inhibition of spike activity. This period of inhibition lasted for 10-40 seconds but was followed by return of normal tension and spike activity. The cause of this behavior is not known. But, a vasodilatation which had a similar duration (25 sec) was observed in dog gracilis muscle and was explained to be of myogenic origin (Smiesko 1971). Although the Type II mesenteric response lasted 7 times longer, it might be of similar myogenic origin. However, according to this interpretation, the Type II response would result from a relaxation induced by the sudden pressure increase rather than the preceding pressure reduction.

Comparison of the Type III capillaries of cat skeletal muscle with those of the mesentery revealed that their average preocclusion

velocities were quite similar (0.38 and 0.35 mm/sec respectively). More variability was seen in the rise time to peak velocity of the mesentery capillaries (10 $\pm$ 4 seconds in muscle vs. 10 $\pm$ 7 seconds in mesentery), but their average value (11 seconds) was similar to that found in muscle (10 seconds). Comparable response durations in the Type III patterns were also found with these values being 22 seconds in muscle and 21 seconds in mesentery. Peak velocity to control velocity ratios were 3.3 for muscle and 2.8 for mesentery capillaries.

Average control velocities for Type IV capillaries in skeletal muscle were 0.27 mm/sec, but were twice as great, 0.57 mm/sec, in mesentery vessels. Muscle capillaries reached their post-occlusion peak velocity in 5 seconds, which was three times faster than the mesentery vessels (15 sec). Total response durations were 20 seconds for muscle and 21 seconds for mesentery. Skeletal muscle Type IV vessels had a peak to control velocity ratio of 4.2 while a value of 2.8 was found in the mesentery. The mesentery capillaries had much longer average periods of zero flow (27 seconds) than the muscle capillaries (7 seconds).

Both the metabolic and myogenic concepts would predict that resistance vessel relaxation would be maximal at the time of occlusion release. This would conceivably allow peak flow to be achieved in a matter of a few seconds. Although peak flow was found to be reached in approximately 2-3 seconds in kidney gross flow experiments (Honda, Aizawa, and Yoshitoshi 1968), analysis of published data revealed that

considerably longer times to peak flow were observed in skeletal muscle (>30 sec) (Fairchild et al. 1966) and the intestine (10 seconds) (Selkurt et al. 1964). Longer times to peak flow were also found in these experiments. The question why flow does not reach peak value almost immediately following release of an arterial occlusion remains unanswered.

Although some differences were found between the Type III and Type IV vessels, the values for the duration of response and peak to control ratios were similar. It is conceivable that the difference in the two vessel response types is a matter of response intensity rather than mechanism, at least in some vessels. A myogenic mechanism could account for both flow profiles and be explained in the following manner. Control flow is maintained at a submaximal level by a myogenically regulated vasoconstriction. The degree of this constriction is a function of the intraluminal pressure stimulus which regulates the contractile state of resistance vessel smooth muscle. As this pressure stimulus decreases during the period of arterial occlusion, the smooth muscle relaxes. When pressure is restored, this relaxation leads to a larger vessel diameter which accounts for the post-occlusive hyperemia. During the period of increased flow, the intraluminal pressure in the arterioles is very likely greater than during the control state. Under such conditions, the arteriolar smooth muscle may be strongly stimulated to constrict by the myogenic mechanism which reduces flow towards control

level. As flow falls, the arteriolar pressure also falls and reduces the myogenic stimulus to some extent. This explanation is applicable, to some extent, for 57% of the Type III and 62% of the Type IV vessels studied.

The results of the remaining 43% of the Type III and 38% of the Type IV were not in complete agreement with the predictions outlined for a myogenically regulated reactive hyperemia response. For instance, some of both the Type III and the Type IV vessels showed increases in either the peak flow, the P/C ratio, the duration, or the total hyperemia response. A few of these vessels showed a behavior which was 100% consistent with that predicted for a metabolic control mechanism. These vessels, 24% of the Type III and 25% of the Type IV vessels, showed increases in the above-mentioned parameters. The excess flow, which was an exception, was generally found to be an inverse function of occlusion duration. This is not consistent with the gross flow data found in other tissues.

In regard to the excess flow observed in the Type IV vessels, their negative excess flow values are particularly interesting. Recall that Lewis and Grant (1925) suggested that reactive hyperemia occurred to repay the flow debt incurred during arterial occlusion. Although this hypothesis has since been proven incorrect (Olsson and Gregg 1965; Konradi and Levtov 1970), even these studies reported positive excess flows. Half of the Type IV capillaries had a negative

excess flow because of their intrinsic ability for a post-hyperemic flow cessation. This finding suggests that flow debt repayment is not important in certain capillaries.

Folkow (1952) suggested that the myogenic mechanism might be masked by the metabolic control mechanism during a competitive situation. This may be correct for gross flow responses, but some of the individual capillary responses argue against this concept. For instance, 38% of the Type III and Type IV vessels showed increased peak responses with longer occlusions. However, of the vessels which responded in this way, only 5 of the 8 Type III, and 4 of the 6 Type IV vessels, also showed an increased response duration. This suggests that some capillaries, 13% of the Type III, and 14% of the Type IV vessels, are influenced by metabolic factors. However, it also suggests that both mechanisms are functional in some capillaries. Furthermore, since significant increases in peak flow followed longer ischemic periods, but the response duration was unchanged, this suggests that the hyperemia response was terminated by a dominant myogenic constriction.

The behavior of the capillaries observed in this study is thought to be a reflection of the activity of either precapillary sphincters, or the vasomotor activity of the parent arteriole. Although Johnson (1968) reported arteriolar diameter changes in response to pressure alterations, it was not possible to determine that arteriolar activity caused the capillary responses of this study.

In fact, on the basis of some observations, it is more likely that precapillary sphincters are the responsible element. For instance, different capillaries which branched from the same arteriole, did not always have the same control flow pattern, nor did they have the same hyperemia response type. In Table 2, the Type I vessel, and one of the Type IV vessels of Experiment 3 branched from the same arteriole. The most extreme case was Experiment 11, where one arteriole gave rise to a Type I, a Type III, and a Type IV capillary. This suggests that capillary flow is controlled by a local smooth muscle segment, and is not a reflection of the entire smooth muscle investment of a single arteriole.

On other occasions, another important observation was made. It was possible, in some Type IV capillaries, and some of those vessels which had an on-off flow pattern, to discern plasma flow in the absence of red cell flow. The plasma flow occurred in the same direction as the control blood flow, and caused trapped red cells to be carried out of the capillary. In some instances, plasma flow persisted for several seconds before red cells again entered these vessels. It is known that red cells can deform very well and can squeeze through an opening less than 2μ in diameter (Braasch 1971). Therefore, this suggests that the capillary entrance was initially so constricted that only plasma could enter, but that it gradually dilated and allowed red cell entry. The Type IV zero flow response, and maybe the on-off and periodic flow patterns as well, might result

from such precapillary sphincter activity. Since plasma flow was detected going in the normal flow direction, this also argues against pressure redistribution as the cause of any of these responses.

Burton and Johnson (1972) postulated that the muscle fiber type a capillary was associated with might determine the reactive hyperemia profile shown by that vessel. For example Type I capillaries, which had high control velocities and showed no hyperemia response were suggested, possibly, to be near slow twitch muscle fibers. Type III and Type IV capillaries were suggested to be associated with white muscle fibers which would be affected by ischemic periods to a greater extent. We believe that a very similar metabolic environment existed for the vessels observed in our study because, by necessity, they were selected from fat free areas and, furthermore, the mesentery is a more homogeneous tissue than skeletal muscle. Since mesentery capillary responses were similar to those found in cat sartorius muscle, we find it unlikely that the metabolic environment of a capillary completely determines how it responds to ischemia.

Pressure Pulse Effects on Capillary Flow

Myogenic constrictor responses were observed following arterial pressure elevations [Bayliss (1902) and Folkow (1949)]. Most other attempts to study this response have resulted in passive increases in flow with perfusion pressure [Jones and Berne (1962) and Zsoter (1961)].

Pressure pulses of 1 sec duration applied to the dog gracilis muscle resulted in what Smiesko (1971) termed an active myogenic vasodilatation.

This is the first study of capillary flow changes in response to quick pressure pulses. Short duration pressure elevations were found to effectively induce a vasoconstrictor response which caused either reduction, or cessation, of capillary blood flow. The duration of the pressure increase was of critical importance and had to be longer than 4 sec before the constrictor response occurred. Pressure pulses of shorter duration caused neither vasoconstriction nor vasodilatation. In most instances, a brief hyperemia preceded the constrictor response but was considerably shorter in duration (5 to 10 sec) than the vasodilatation seen by Smiesko (1971) in the dog gracilis muscle (25 sec).

Only those vessels which showed Type III and Type IV hyperemia responses during selection tests were studied during the pressure pulse experiments. It is a significant finding that the post-hyperemic flow change characteristic of a given vessel (Type III or Type IV) was also seen following pressure pulses. The Type III vessels responded to pressure pulses in an all-or-none fashion and rarely exhibited a hypoemic post-hyperemia flow. The post-hyperemic flow pattern of the Type IV vessels was modified by pulsing the preparation with lesser magnitudes of pressure. By manipulating the pressure pulse magnitude

in this way, the flow profile of Type IV vessels could be changed to that of a Type III vessel.

Type III vessels did not show an ability to vary their response with different magnitudes of pressure pulse. Occasionally, Type III vessels responded to a pressure pulsation and showed a prolonged dilatation similar to a Type II vessel hyperemia response. This unusual behavior occurred more frequently when the pressure was elevated very slowly. It should also be mentioned that this change in character of the Type III vessel to that of Type II was never seen following total occlusion, but was only seen during pressure pulse experiments under conditions of autoregulation. Some of these vessels resumed their Type III behavior on subsequent trials, but others never regained their original character during the period of observation. No Type IV vessel was ever observed to respond in this fashion.

The experimental conditions for these pressure pulse studies are considered critical to the interpretation of the results. Although the perfusion pressure of the preparation was reduced by partial arterial occlusion, autoregulation of flow was such that the test capillary was perfused by a normal quantity of blood. Under these conditions, it is assumed that metabolites were removed at a normal rate and did not contribute to the post pressure pulse response. It is possible that the hyperemia which followed a pressure pulse was a passive response, but the flow cessation which occurred in Type IV

vessels cannot be explained in this way. The fact that the constrictor response was initiated while the pressure was still elevated during pulse trials, and also that it occurred when normal perfusion pressure was restored and maintained, eliminates this possibility.

Effects of Rate of Change of Perfusion Pressure on Capillary Flow

Although Folkow (1949) found that rapid increases in arterial pressure were necessary to reduce myogenic vasoconstrictor responses in dog hindlimb preparations, no attempt was made to evaluate flow changes as a function of rate of pressure change (dP/dt). Smiesko (1971) determined that a myogenic vasodilatation which existed in dog gracilis muscle was proportional to the dP/dt imposed. But this is the first study of capillary flow changes as a result of variations in the rate of change of perfusion pressure.

Only two of the 14 vessels studied in this way responded in a graded fashion with different dP/dts. That is, vasoconstriction was severe enough to completely stop flow when the dP/dt was 12 mm Hg/sec or greater, and no perceptible change in flow resulted from dP/dts of less than 1 mm/Hg sec. These vessels represented two of the four Type IV vessels observed in this portion of the study. Five of 14 vessels responded only to specific magnitudes of pressure change, since constrictor responses occurred at specific pressures regardless of the dP/dt. The remainder of the vessels showed no consistency in their response to dP/dt, including the remaining two Type IV vessels.

The graded response was repeatable in the two vessels depicted as numbers 1 and 2 in Figure 19. Data of this kind were exceedingly difficult to obtain. This might be related to the long periods of autoregulation which had to be imposed on the preparation in order to obtain pressure pulse data. The aberrant behavior of Type III vessels which changed to Type II vessel behavior may indicate that the mesentery preparation is adversely affected by the long periods of reduced arterial pressure which had to be used in these studies.

The pressure pulse studies in conjunction with the previously discussed reactive hyperemia responses revealed some characteristics of the control mechanisms of the Type III and Type IV vessels.

It seems that the Type III vessels react in an all-or-none manner, to either pressure reduction or elevations. Therefore, the response of these vessels is critically damped. Thus, their reactive hyperemia patterns rarely showed an undershoot following the initial hyperemia and their red cell velocity returned to control level without exhibiting oscillations. The Type IV showed an underdamped response characterized by a period of zero flow. Also, some of the zero flow periods were followed by a secondary reactive hyperemia which was not induced by arterial occlusion, but which the concept of an underdamped myogenic response suggested here. Additional evidence in support of this concept was seen in both hyperemia and pressure pulse studies when flow tended to be periodic when normal perfusion pressure was restored. A receptor capable of responding in this way would be analogous to carotid sinus baroreceptors which increase

their firing rate in response to absolute pressure increase, as well as the rate of pressure rise. Receptors of this type with appropriate time delay could induce a response similar to that seen in Type IV hyperemia and pressure pulse studies. Evidence in support of this latter concept was found in those Type IV vessels which could be manipulated by variations in either the mangitude of the pressure pulse or the rate of pressure change. These vessels responded to high dP/dt with zero flow periods, at intermediate dP/dt showed a reduced but not zero flow, and at very slow dP/dt showed no change in flow. None of the Type III vessels studied showed this variable type of response to different rates of pressure change. But, as mentioned previously, when slow rates of pressure change were imposed, the character of some of these vessels changed to that of Type II activity.

CONCLUSIONS

Reactive hyperemia of individual cat mesentery capillaries was studied. This response was induced by occluding the arterial supply to the isolated autoperfused, denervated ileum preparations. The changes in capillary blood flow caused by quick pressure pulses were also studied. The following questions were studied:

1. Do all capillaries in the cat mesentery demonstrate reactive hyperemia?

2. Is reactive hyperemia associated with a particular pattern of flow in capillaries?

3. Do all capillaries branching from the same parent arteriole exhibit reactive hyperemia?

4. For those capillaries which show reactive hyperemia, do they all show the same post-occlusion flow pattern?

5. Does capillary blood flow vary when the arterial perfusion pressure is quickly elevated? Is the change passive or active?

6. Are capillary flow variations which are caused by perfusion pressure alterations dependent upon time, rate of pressure change, and magnitude of pressure change?

The following conclusions were reached:

1. A population of cat mesentery capillaries exists in which the blood flow is not actively regulated. These vessels do not

demonstrate post-occlusion hyperemia. These vessels have high control flow velocities and steady flow patterns.

2. Reactive hyperemia in mesenteric capillaries is independent of control flow pattern. The response was seen in vessels which had steady, irregular, on-off, and periodic flow patterns.

3. Periodic flow capillaries demonstrate reactive hyperemia more frequently than any other vessels. The hyperemia response type shown by these vessels is of Type III or Type IV. The response type is consistent for individual vessels.

4. Capillary flow appears to be controlled at discrete regions of arterioles. It is possible that these control sites are precapillary sphincters. Evidence in support of this conclusion was found where a Type I, Type III, and Type IV response was observed in three separate capillaries which branched from the same parent arteriole.

5. Reactive hyperemia responses are the result of local control mechanisms. These mechanisms appear to involve myogenic and metabolic regulations, singly in some vessels, and in combination in others.

6. The adequate stimulus for the myogenically controlled vessels appears to include a pressure change of specific magnitude and duration. In addition, the control mechanism of some vessels includes a sensitivity to the rate of pressure change.

APPENDIX A

RESPONSES OF TYPE II VESSELS

Table A-1. Type II vessel control velocity data (mm/sec).

Vessel	Occlusion Duration (sec) 15	30	45	60
1	.41 ± .01	.40 ± .01	.38 ± .01	.41 ± .01
2	.49 ± .01	.46 ± .01	.47 ± .01	.47 ± .01
3	.38 ± .01	.38 ± .01	.36 ± .01	.37 ± .01
4	.17 ± .02	.14 ± .02	.15 ± .01	.14 ± .02
5	1.32 ± .03	1.35 ± .01	1.35 ± .02	1.30 ± .06
6	.47 ± .01	.46 ± .01	.54 ± .05	.51 ± .02
7	.56 ± .01	.54 ± .01	.54 ± .01	.56 ± .01
8	.37 ± .01	.36 ± .01	.35 ± .02	.33 ± .02
9	.12 ± .02	.12 ± .01	.11 ± .01	.12 ± .01
N=9	.48 ± .35	.47 ± .36	.47 ± .36	.47 ± .35

Table A-2. Type II vessel peak hyperemia response (mm/sec).

Vessel	Occlusion Duration (sec) 15	30	45	60
1	.74 ± .02	.83 ± .02	.66 ± .08	.90 ± .05
2	1.08 ± .04	1.12 ± .06	1.05 ± .03	.99 ± .08
3	.96 ± .01	.69 ± .14	.99 ± .03	.98 ± .53
4	.66 ± .03	.63 ± .06	.63 ± .03	.66 ± .03
5	2.46 ± .04	2.52 ± .13	2.59 ± .03	2.20 ± .54
6	.63 ± .03	.99 ± .03	.84 ± .06	.90 ± .08
7	1.61 ± .05	1.56 ± .05	1.47 ± .08	1.50 ± .12
8	.82 ± .05	.72 ± .05	.78 ± .06	.82 ± .07
9	.74 ± .05	.96 ± .08	.85 ± .16	.76 ± .05
N=9	1.07 ± .60	1.11 ± .60	1.10 ± .61	1.08 ± .48

Table A-3. Type II vessel time to peak flow (sec).

Vessel	Occlusion Duration (sec) 15	30	45	60
1	8 ± 2	12 ± 1	6 ± 0	15 ± 2
2	127 ± 15	110 ± 9	93 ± 7	115 ± 8
3	5 ± 1	9 ± 3	8 ± 2	10 ± 3
4	110 ± 5	117 ± 9	123 ± 10	128 ± 11
5	29 ± 1	37 ± 8	15 ± 4	27 ± 16
6	64 ± 15	105 ± 11	100 ± 15	94 ± 18
7	50 ± 3	48 ± 2	44 ± 3	60 ± 20
8	63 ± 5	62 ± 1	71 ± 7	85 ± 33
9	10 ± 1	3 ± 2	5 ± 1	14 ± 3
N=9	51.8 ± 44.3	55.9 ± 45.4	51.7 ± 46.2	60.9 ± 46.3

Table A-4. Type II vessel peak flow to control flow data.

Vessel	Occlusion Duration (sec) 15	30	45	60
1	1.84 ± .06	2.11 ± .04	1.74 ± .22	2.16 ± .16
2	2.23 ± .06	2.45 ± .03	2.24 ± .10	2.09 ± .15
3	2.24 ± .03	1.83 ± .37	2.79 ± .05	2.22 ± .10
4	3.99 ± .35	4.58 ± .60	4.26 ± .07	4.63 ± .65
5	1.86 ± .04	1.87 ± .09	1.92 ± .05	1.70 ± .49
6	1.33 ± .04	2.19 ± .13	1.57 ± .07	1.70 ± .15
7	2.88 ± .13	2.10 ± .13	2.72 ± .17	2.71 ± .17
8	2.23 ± .10	2.01 ± .17	2.22 ± .14	2.48 ± .07
9	5.88 ± .99	8.31 ± .78	7.65 ± 1.58	6.39 ± .47
N=9	2.72 ± 1.40	3.14 ± 2.12	3.01 ± 1.90	2.95 ± 1.56

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