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THE INTERRELATIONSHIP OF WEIGHT CHANGE AND CORONARY FLOW IN THE ISOLATED PERFUSED RABBIT HEART

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In the preceding paper (Stubbs & Widdas, 1959*b*), experiments have been described in which the isolated perfused rabbit heart lost weight when stimulated by adrenaline or excess calcium ions. It was shown as the result of these studies that the extravascular fluid of the heart was much more labile than had hitherto been appreciated.

The extensive literature on the subject of the coronary circulation has been reviewed by Anrep (1926) and by Gregg (1946). More recent reports still agree that the coronary flow is chiefly regulated by the oxygen demand and the saturation of the supplying blood (see, for example, Braumwald, Sarnoff, Case, Stainsby & Welch (1958) and Feinberg & Katz (1958)). The importance of systole and the tonic state of the heart was emphasized by Porter (1898) and by Wiggers (1909), and has been studied by many authors since, but the lability of the extravascular fluid is a factor which has not been allowed for in coronary flow studies so far reported.

Although the present work was not primarily an investigation into factors producing variations in coronary flow, it became evident that definite patterns of flow changes accompanied variations in weight. These patterns suggested an interrelationship of some interest.

The present paper describes this interrelationship under different experimental procedures and advances an hypothesis for a new factor in the control of coronary flow. A preliminary account has been given to the Physiological Society (Stubbs & Widdas, 1959*a*).

METHODS

The methods were essentially similar to those described in the previous paper (Stubbs & Widdas, 1959*b*). Hearts weighing 5–20 g were used. In experiments designed to produce cardiac arrest, the heart was perfused with Locke's solution containing potassium citrate, as described by Baker & Dreyer (1956), but a recirculating technique was used.

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RESULTS

The changes which occur in coronary flow when the perfused heart loses or gains weight as a result of various experimental procedures are given in Table 1. The way in which hearts stimulated by adrenaline or excess calcium ions lost weight has been described in the previous paper (Stubbs & Widdas, 1959*b*). Factors contributing to the increased coronary flow in these experiments will be discussed later.

TABLE 1. Relation of coronary flow to changes in weight of the heart

Causes of loss in weight	Nature of weight loss	Changes in coronary flow
Adrenaline	Rapid loss; recovery 3–5 min	Initially reduced or unchanged; increased during recovery stage
Excess Ca^{2+}	Rapid loss; recovery as above	Increase starting with loss of weight and reaching maximum during recovery
Extra-systoles	Small rapid loss; recovery in 0·5–1·5 min	No detectable change
Pitressin	Large rapid loss; slow recovery in 5 min	Marked initial reduction returning with recovery in weight
Stopped perfusion (30 sec)	Rapid loss in weight; rapid recovery on restarting perfusion	Marked reduction. On restarting perfusion may have increase above base line for 0·5–1·0 min
Osmotic transients	Loss initially with hypertonic solution; regained slowly with penetrating non-electrolyte	Increased during loss in weight phase; reduced during gain in weight
Causes of gain in weight associated with cardiac arrest due to	**Nature of weight gain**	**Changes in coronary flow**
Acetylcholine	Rapid gain; slow return over 3 min	Increased with weight gain; returns to base line during recovery
Potassium citrate	Rapid initial gain; slower increase while arrest maintained; rapid loss on resumption of normal beats	Increased initially, falling to base line and below during quiescence; increased on resumption of normal beats

Pitressin

The effect of Pitressin (vasopressin; Parke, Davis) was to cause the heart to lose weight. This, however, differed from the loss in weight caused by adrenaline or excess calcium ions, for there was a marked reduction in coronary flow (Fig. 1). This was indicative of a coronary vasoconstriction and suggested that a large part of the loss in weight was vascular in origin, i.e. that there was a reduction in the capacity of the coronary vascular bed. This corroborates the conclusion of Hanson & Johnson (1957) that Pitressin affects the coronary arterioles. When dye was present, however, there was a significant dilution of the effluent, showing that some extravascular fluid was also lost.

Lowered perfusion pressure

When the perfusion was stopped, there was a loss of weight and almost complete cessation of coronary flow. On starting the perfusion again the coronary flow was at first greater than the previous value, but returned to normal in about 0·5–1·0 min. When dye was present the first effluent showed a dilution of dye which indicated a loss of some extravascular fluid.

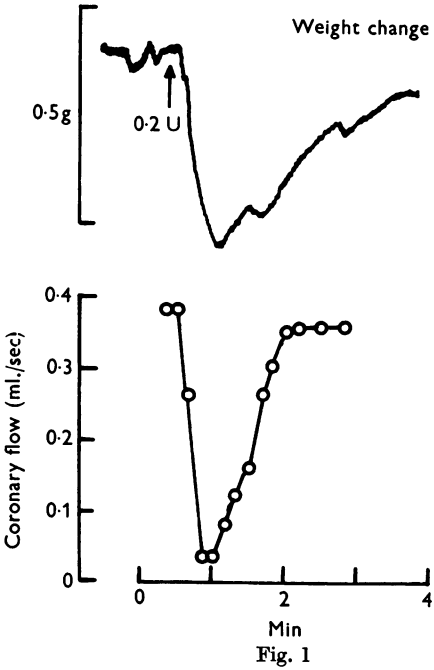

Fig. 1

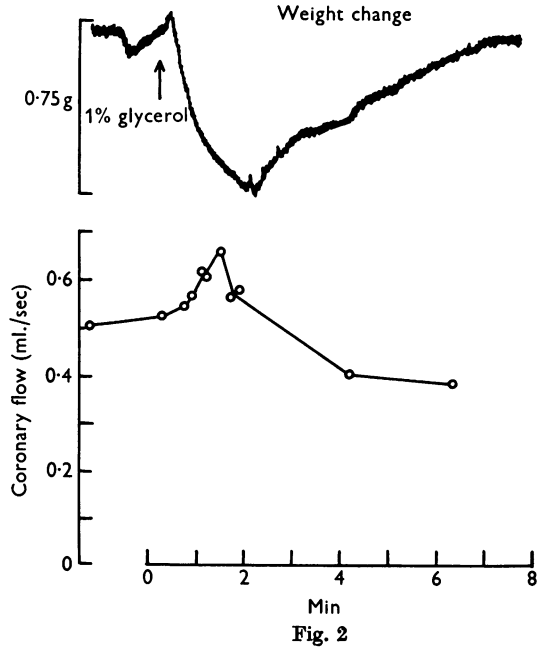

Fig. 2

Fig. 1. Effect of Pitressin on heart weight and coronary outflow.

Fig. 2. Effect of glycerol (1·0 g/100 ml. Locke's solution) on heart weight and coronary flow.

Osmotic transients

Losses in weight produced by changing over to Locke's solution made hypertonic by the addition of non-electrolyte were accompanied by increases in coronary flow. The results of an experiment with Locke's solution containing 1 g glycerol/100 ml. are shown in Fig. 2. Essentially similar results were obtained with glucose and sucrose, though the weight did not return to normal in the way shown for glycerol.

Acetylcholine

An injection of acetylcholine caused the perfused heart to gain weight by as much as 5% of the initial value. A typical result is shown in Fig. 3. The gain in

weight was accompanied by an increase in coronary flow, which returned to the pre-injection value when the weight had returned to normal. Colorimetric monitoring of the outflow while the heart was being perfused with Locke's solution containing dye did not show evidence of a concentrating effect, and this suggested that the gain in weight was largely due to a dilatation of the coronary vascular bed.

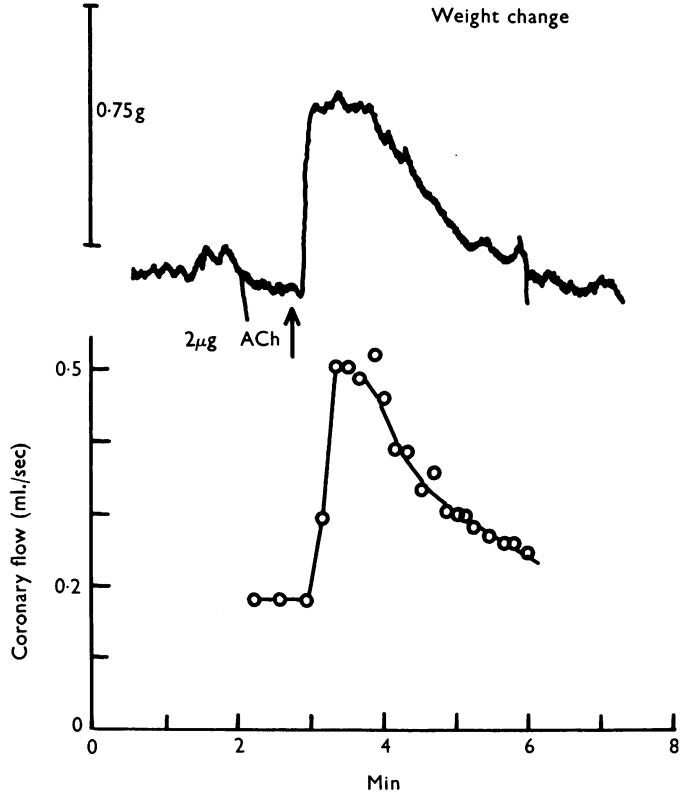

Fig. 3. Effect of acetylcholine on weight and coronary flow. Heart weight 7·0 g.

Potassium citrate

The changes in weight and coronary flow which occurred when a heart was stopped by perfusion with Locke's solution containing potassium citrate (1 mg/ml.) are illustrated in Fig. 4. The weight initially increased in a manner similar to that seen with acetylcholine, but during the quiescence there was a slower persistent increase in weight. The coronary flow, which showed a temporary increase, declined during the quiescence. If the quiescence was prolonged, the flow could diminish to less than half its initial value.

When the perfusion was changed back to normal Locke's solution and beating recommenced, there was a loss of weight and an increase in the coronary

flow toward its former value. When dye was present this loss in weight was accompanied by a dilution, showing that some extravascular fluid was lost.

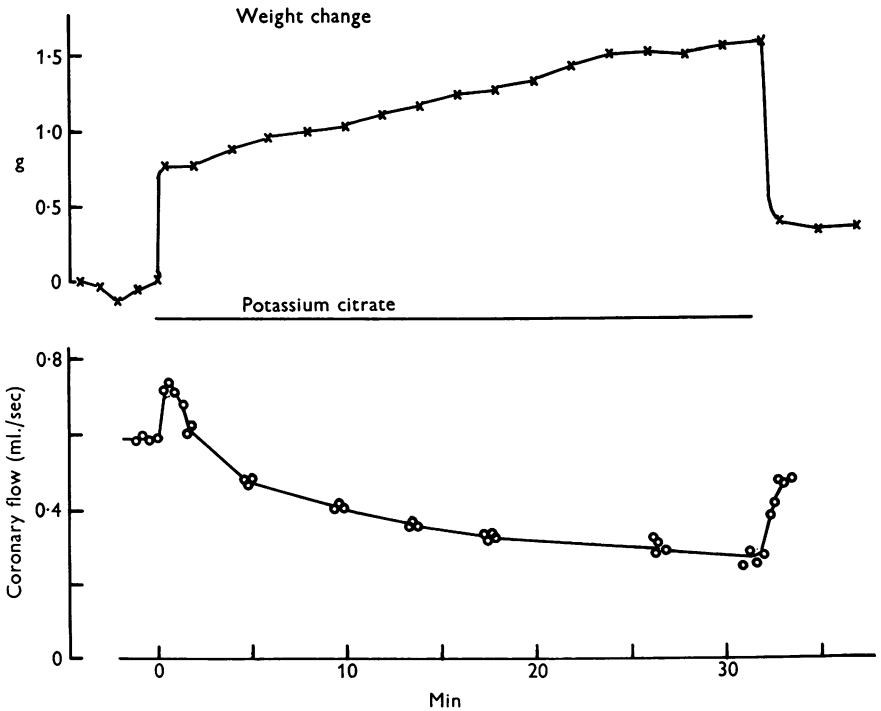

Fig. 4. Effect on weight and coronary flow of cardiac arrest produced by potassium citrate, showing temporary increase in coronary flow followed by progressive decrease.

Adrenaline and calcium ions

When the heart, perfused with Locke's solution containing dye, lost weight owing to stimulation by adrenaline or excess calcium ions, there was a sharp drop in concentration of dye in the outflow, which was indicative of a loss of extravascular fluid. If the heart regained weight by immediately replacing the extravascular fluid lost, one would expect the colorimetric reading to cross the base line in the other direction as the dye or cells became concentrated. Only in the extreme case of a calcium rigor was this reconcentration evident (Fig. 5). Even in this result, the sharp dilution peak to about 65%, corresponding with the rapid weight loss, is in contrast with the blunter curve showing a reconcentration during the weight gain. The dye concentration curve can be seen to approximate to the differential of the weight curve. This suggests that interstitial fluid is lost more rapidly than it is gained in such experiments.

In experiments in which the heart was stimulated by only a moderate excess of calcium ions or by adrenaline, the expected concentration was less evident

and in all such experiments it appeared to be small and drawn out or delayed (see also Stubbs & Widdas, 1959*b*, Fig. 3). Owing to the uncertainty in the base line, accurate quantitative assessment is at present not possible, but the replacement of interstitial fluid could not have been complete when the weight had returned to normal. The results strongly suggest that, in the first place, there must have been an increased capacity of the coronary circulation as the myocardial tone, increased by the adrenaline or excess Ca^{2+} ions, returned to normal levels.

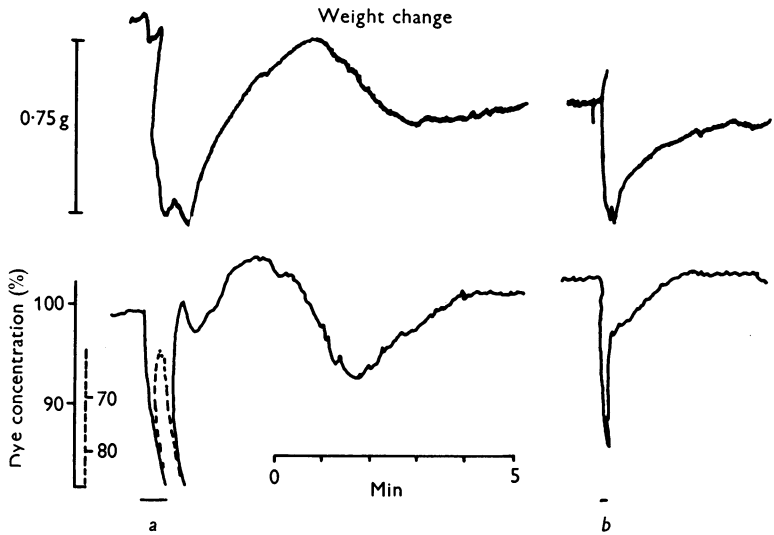

Fig. 5. Simultaneous tracings of heart weight and dye concentration for a heart stimulated by excess calcium ions. In *a* the Ca concentration of the Locke's solution was raised about 10 times for 30 sec. The steep fall in dye concentration to about 65% was recorded by reversing the polarity when the meter came to zero (dotted portion of trace). In *b* an injection of 0·2 ml. 6% $CaCl_2$ was made near the cannula. Heart weight 6·7 g.

With adrenaline, typically the coronary flow increased only when the weight loss was near its maximum. The increase in the flow remained during the whole of the period of gain in weight and slowly declined to the base line. Hammouda & Kinosita (1926) observed a temporary reduction in coronary flow as the rate and force of contraction was increasing, and this has also been seen in the present work in a number of experiments corresponding with the period when the loss in weight was taking place. The increased flow persisted much longer than the inotropic effect on the heart, and corresponded to the period during which the circulatory capacity was deduced to be increased.

With excess calcium ions the increase in flow began as the heart lost weight. It attained a maximum and slowly declined as the heart weight returned to base line. Even when the heart went into rigor, coronary flow was not usually reduced below pre-treatment values.

DISCUSSION

The hypothesis of a mechanical factor in the regulation of coronary flow

Analysis of the results obtained with the perfused heart from measurements of coronary flow, heart weight and dye concentration have indicated an increased circulatory capacity in the acetylcholine and adrenaline responses. The increase with acetylcholine is of sufficient magnitude to point to an involvement of capacity vessels (probably capillaries) and the possible mechanisms are the reduction in myocardial tone or an arteriolar dilatation raising the pressure in the capillaries and, indirectly, their size. The increased capacity in the adrenaline response occurs in a heart which is smaller than normal, and is therefore secondary to the loss of interstitial fluid in the early part of the experiment, which may be presumed to increase available vascular space.

However, in both cases the increased capacity occurs in a heart changing from one level of tone to a lower level. Further, the increases in capacity associated with adrenaline and acetylcholine are so similar to the effect of excess Ca and of the initial action of potassium citrate that it is relevant to inquire if the increased capacity of the circulation might be dependent on changes in the myocardium, and whether these changes could be responsible in part for the changes in the coronary flow.

Indeed, the variations in coronary flow which have been described above can be explained in a relatively simple manner if it is assumed that the calibre and capacity of some resistance vessels depends, in part, on the support of the myocardium mediated through the interstitial fluid. This hypothesis is illustrated schematically in Fig. 6. In the heart perfused with Locke's solution containing no colloid, the balance of interstitial fluid is a temporal one between filtration from the capillaries during diastole and a small backward filtration into the capillaries during systole. Systole may lead to compression and partial emptying of capillaries (a 'kneading' action was suggested by Wiggers (1909)), but their distension in diastole would be limited in part by the external support of the myocardium and interstitial fluid pressure.

If the tone of the myocardium decreased (e.g. owing to acetylcholine), the external support would be reduced and a greater distension would be possible, as is represented in Fig. 6 (*b*). When the heart was beating more forcibly (e.g. on adrenaline stimulation) a greater degree of backward filtration into the capillaries would occur, and in subsequent diastolic periods (particularly as the tone reverted to its former value), additional distension of the capillaries would become possible. This is represented in Fig. 6 (*c*).

In the above response, capillary dilatation would lead to an increased transcapillary pressure gradient. This, in turn, would cause increased filtration with consequent reduction in capillary distension until the equilibrium represented by Fig. 6 (*a*) was again attained.

In a prolonged quiescence, when there were no systoles to promote backward filtration, the outward filtration from the capillaries would proceed until the trans-capillary pressure was reduced to a minimum. This would produce a reduction in calibre and capacity of the vascular bed. This sequence of events represented in Fig. 6 (*d*), would explain the results which were obtained when the heart was arrested with potassium citrate.

Lowering the perfusion pressure or an intense arteriolar constriction (Pitressin experiment) can be visualized as producing effects by lowering the mean capillary pressure. Losses of extravascular fluid brought about by osmotic transients would act similarly to the adrenaline response in making space available for a greater capillary distension.

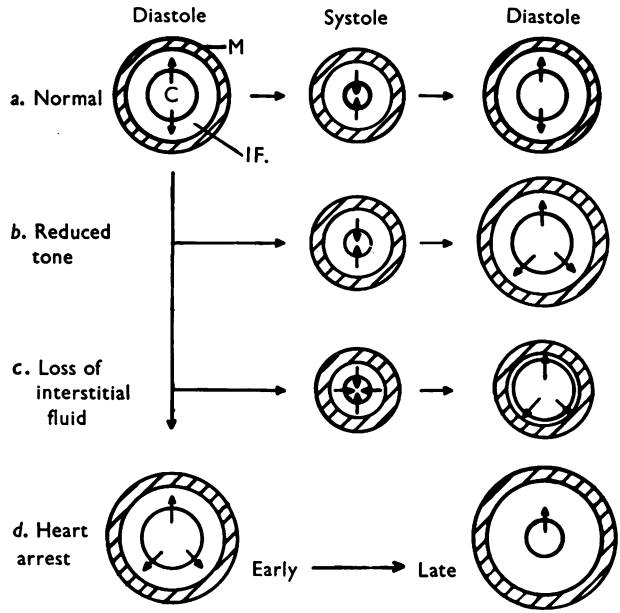

Fig. 6. Schematic representation of the support of a capacity vessel (capillary, C) by the myocardium (M) and interstitial fluid (IF.). *a* The normal balance; *b* effect of decreased muscle tone; *c* effect of loss of interstitial fluid; *d* effect of a prolonged quiescence. For fuller detail see text.

Theoretical extension of the hypothesis

The above hypothesis is limited to the conditions applicable to the heart perfused with a saline free from colloid. For application to a heart or other tissue *in vivo*, the presence of both plasma colloids and the circulating red cells must be taken into account.

The mechanism for the control of the interstitial fluid normally accepted is that based on Starling's hypothesis (Landis, 1934; Ponder, 1949). This postulates that the effective hydrostatic pressure (capillary pressure less tissue-fluid pressure) is opposed by the osmotic pressure of the plasma proteins (less any osmotic pressure due to protein leaking into the tissue spaces). It is further postulated that filtration occurs principally at the arteriolar end of capillaries where the effective hydrostatic pressure exceeds the colloid osmotic pressure, and that reabsorption occurs

at the venous end of capillaries or in collecting venules. Since some capillaries may be at a hydrostatic pressure exceeding the colloid osmotic pressure (Landis, 1926) throughout their whole length, this simplified concept probably only applies to so-called true capillaries (Chambers & Zweifach, 1947). Chambers & Zweifach (1947) also discuss the literature on the pericapillary sheath, and if this sheath or the matrix of surrounding structures offered any resistance to the flow of fluid, it would follow that the tissue-fluid pressure would be highest outside the arteriolar end of a capillary, and, assuming tissue pressure can influence the calibre of the vessel, this part should be narrowed first.

The possible consequences of this on a capillary which is at a critical size, i.e. with a diameter close to that of a red cell, is illustrated schematically in Fig. 7. If filtration produced narrowing sufficient to cause the lumen to be obstructed by a red cell, the pressure gradient along the capillary would be modified, as indicated in Fig. 7 (*b*). This would limit the area available for outward filtration and increase the area for reabsorption. As a result, the tissue fluid would be more rapidly

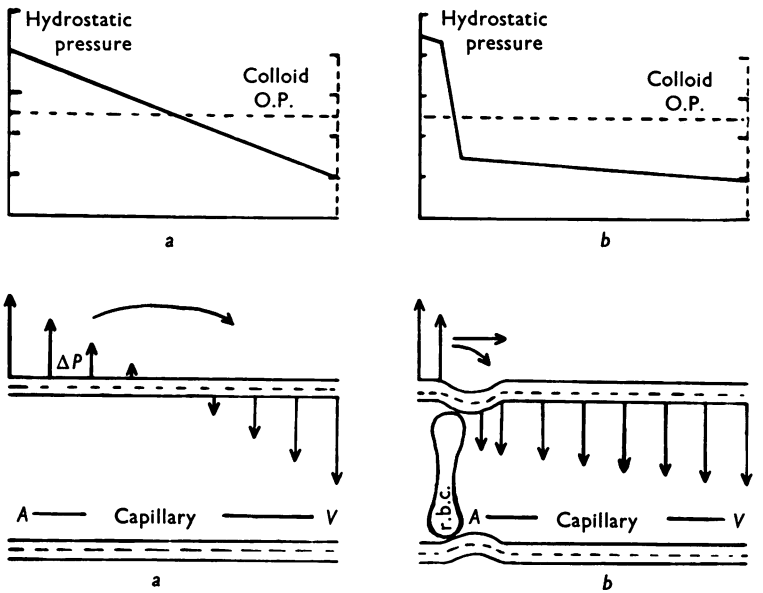

Fig. 7. Pressure gradient and distribution of filtration and reabsorption; *a* in a capillary larger than a red cell diameter; *b* in a capillary which is obstructed by a cell. For further details, see text.

dispersed from the arteriolar end of the capillary, which would be able to expand so that unimpeded flow could recommence. The pressure gradient would then return to that shown in Fig. 7 (*a*) and the whole cycle would repeat itself. If cells could slowly pass the obstruction by a plastic deformation, a condition intermediate between the extremes represented above would result.

The times spent in the different phases of such a cycle would depend on the relative rates of filtration and reabsorption. For instance, the time spent in the condition represented by Fig. 7 (*a*) would be reduced by a high capillary pressure.

In any tissue in which a large proportion of capillaries were of such a critical size, the above cycles, being asynchronous, could form an automatic mechanism for regulating the circulatory capacity and capillary blood flow. A reactive hyperaemia in such a tissue might be caused by allowing reabsorption to occur simultaneously over the whole vascular bed while filtration was stopped (e.g. by arterial occlusion or arteriolar constriction) so that, on re-establishing the circulation, all the capillaries were initially in the state represented by Fig. 7 (*a*) and permitted unimpeded flow.

Even where capillaries were not at the critical size depicted above, a small change in capillary diameter could have a large effect on capillary blood flow. To illustrate this point, the increase in flow with increase in area has been calculated on the basis of an axial stream of uniform velocity (and of diameter equal to the red cell diameter) and assuming streamline flow between this axial column and the vessel wall. Under these conditions, flow is proportional to (a^4-r^4) where a is the radius of the capillary and r the radius of a red cell. The result of this calculation, in which the red cell diameter has been taken as 7μ, is shown in Fig. 8. These considerations suggest that a relatively small change in the distribution of fluid between the interstitial spaces and the circulation could affect blood flow in a significant way in capillaries of 8μ or under if they expanded or contracted reciprocally with the volume of interstitial fluid.

If this aspect of the hypothesis has any more generalized application beyond tissues such as the heart, it would be necessary to take into account other factors which affect the volume of interstitial fluid. Thus glandular secretion and lymph flow, for example, may need to be re-examined to see if they contribute mechanically to some hyperaemic responses.

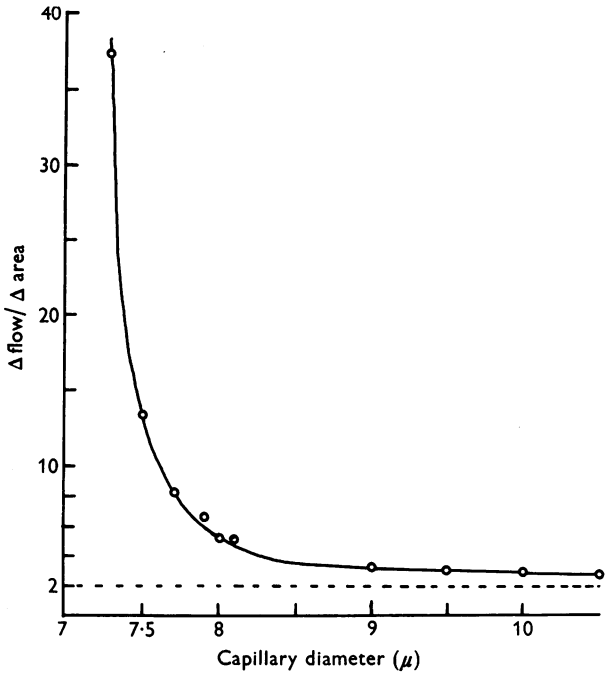

Fig. 8. Percentage change in capillary flow for a 1% change in cross-sectional area of capillary at diameters just above the red cell diameter (taken as 7μ). For basis of calculation see text.

The changes in coronary flow which occur in the perfused heart owing to the effect of adrenaline or acetylcholine normally call for little comment. The adrenaline responses reported correspond closely to those described by Hammouda & Kinosita (1926). These authors regarded the increased flow as due to muscular influences and not to vasodilatation *per se*. The increased coronary flow associated with a heart strongly contracted owing to excess calcium ions is similarly difficult to regard as a vascular effect. The similarity of the weight

changes with those due to adrenaline or excess calcium suggests that the common factor is the myocardial action. In the same way, the effect of acetylcholine is closely paralleled by that of potassium citrate, but the latter only increases the coronary flow initially when the heart weight rapidly increases during the early part of the arrest. The initial increase in coronary flow with arrest of the isolated heart was also shown by Hammouda & Kinosita (1926) who produced cardiac arrest by several methods, all of which differed in detail from that used in the present experiments. The absence of vagal vasodilatation in the heart has recently been re-examined and confirmed by Szentiványi & Nagy (1959), but these authors admit the possibility of vasodilatation caused by large quantities of acetylcholine. Since acetylcholine in large doses produces cardiac arrest and a fall in myocardial tone, these factors may overshadow the vasodilator action.

The occurrence of increased coronary flow with osmotic transients due to a variety of substances, none of which is a pharmacological vasodilator, is further evidence against an interpretation based on vaso-active substances. The accumulation of evidence by the dye and weighing techniques points to increased circulatory capacities in the responses to acetylcholine, to adrenaline, to excess calcium ions, and to the initial effect of potassium citrate perfusion. The effects of adrenaline or acetylcholine on the myocardial action could account for the increases on a mechanical basis just as effectively as by direct vaso-action. The mechanical hypothesis also embraces the responses to procedures not involving any pharmacologically active substance.

In essence, the hypothesis can be divided into two parts. First, it is postulated that the circulatory capacity and peripheral resistance depend in part on the muscle tone. Both these postulates have already been demonstrated in the perfused intestine by Sidky & Bean (1958), who have shown that in that site muscle tonus can augment, mask or even reverse flow changes expected under the influences acting on the intestinal vasculature *per se*. Their demonstration of tonus as an important influence on the large reservoir capacity of the intestinal vasculature is paralleled by the studies on the heart reported here. The effect of the extravascular support on coronary flow has been considered by many workers; for instance, Katz, Jochim & Bohning (1938) visualized that passive changes in calibre may be superimposed on active changes in the coronary vessels.

The difficulties in obtaining a quantitative assessment of the extravascular effects have been emphasized in the important review by Gregg (1946). In a later study, Osher (1953) observed changes in coronary vascular volume with variations in perfusion pressure, and drew attention to such factors as hindrance from extravascular support and anomalous viscosity changes in determining the haemodynamics of the coronary circulation.

Clearly the coronary circulation *in vivo* will involve the integration of many

factors, some acting on the vasculature *per se*, while others are of an extravascular nature. The latter will differ in systole and diastole, so that the strength and duration of systole will be a main variable, as has been brought out more fully in the reviews already mentioned. The same variable, however, is potent in the regulation of interstitial fluid in the isolated heart and could indirectly influence the degree of hindrance in diastole under the second part of the hypothesis. Thus what happens to the interstitial fluid of the heart under different states could be an important new factor in the over-all problem.

The second part of the hypothesis ascribes an important peripheral vascular role to changes in volume of the interstitial fluid as well as to changes in muscle tone. This principle could have applications outside the field of cardiac physiology. A suggestion that tissue pressures may fulfil an appreciable peripheral vascular role has been made by Yamadi & Åstrom (1959) from a study of critical closing pressures in an isolated perfused limb.

The possibility of a backward filtration and loss of interstitial fluid has not so far been investigated in sites such as the intestine, though intramural pressures reported by Sidky & Bean (1958) would appear to justify consideration of this point. It is a logical step to suppose that the support exerted by any structure, muscular or otherwise, must be moderated by changes in the volume of the interstitial fluid. It is in this second respect that the hypothesis offers greater difficulty of experimental confirmation.

The measurement of tissue pressure presents a difficult problem. Indirect evidence led Pappenheimer & Soto-Rivera (1948) to conclude that it was probably zero in the perfused hind limb of the cat. This interpretation, however, applied to an over-all mean value, and may possibly have been influenced by the toneless musculature of the preparation. Theoretically, it may be important to know the pressure in tissue immediately surrounding specific parts of the capillaries, and this could conceivably be different from the average tissue pressure.

Landis (1926) pointed out that some capillaries were at a higher hydrostatic pressure than the colloid osmotic pressure, and may be presumed to permit filtration along their whole length. Others at a lower hydrostatic pressure would favour absorption by osmotic forces. This aspect and the influence of vasomotion on tissue fluid balance has been further developed by Chambers & Zweifach (1947). In tissues with both kinds of capillaries, it is difficult to visualize that the avoidance of oedema is left to a fortuitous occurrence of these capillaries in just the right proportions. An automatic control mechanism based either on physical principles, or involving local reflex or chemical control (Krogh, 1922; Lewis, 1927) of arterioles or capillaries would appear to be essential, and it may be that Starling's (1896) hypothesis should be reviewed from the standpoint of an integration with vasomotor and extravascular

factors affecting capillary pressures and areas available for filtration and reabsorption.

It is interesting to speculate whether the control of coronary flow by oxygen demand could include a mechanical factor, under the hypothesis discussed in this paper. A mechanical component could be involved if the perfusion with fluids of low oxygen tension caused either reduction in tone on the same lines as acetylcholine, or a reflex stimulation, as by adrenaline (Woods & Richardson, 1959), since either could lead to an increased circulatory capacity. Increased cardiac work (and hence oxygen demand) under sympathetic stimulation could affect the balance of interstitial fluid as described in the previous paper (Stubbs & Widdas, 1959*b*).

Eckstein, Stroud, Dowling & Pritchard (1950) found increased coronary flow associated with a reduced heart volume, and attributed the latter to more complete emptying. However, as Johnson (1945) has shown that myocardial compression at any level varies inversely with ventricular size at the end of systole, an additional loss of interstitial fluid would appear to be a possible factor here as well. Even in the isolated heart, where no increase of external work is involved, adrenaline perfusion brings about interstitial fluid and vascular changes of long duration. These factors could also be operative in experiments such as those described by Feinberg & Katz (1958).

It should be emphasized, however, that the lability of the interstitial fluid under the conditions of an isolated perfusion may be exaggerated by the absence of protein, and further investigations will be required to assess the magnitude of this new factor *in vivo*. The pitfalls in the field of cardiac physiology of applying results obtained on isolated preparations to the intact animal have recently been emphasized by Rushmer & Smith (1959).

SUMMARY

1. Variations in coronary flow associated with weight changes in the perfused isolated rabbit heart are described.

2. The flow–weight changes obtained with vaso-active substances can be reproduced with substances or procedures having a similar myocardial action, but which are not ordinarily vaso-active.

3. The hypothesis that the peripheral resistance and circulatory capacity depend in part on the support given by the myocardium and the interstitial fluid would provide a simple explanation of the variations in coronary flow in the isolated heart.

4. A theoretical extension of this hypothesis to conditions *in vitro* is described.

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