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THE ABSENCE OF AN ARTERIAL PRESSURE EFFECT ON FILTRATION BY PERFUSED GLOMERULI OF THE HAGFISH, *EPTATRETUS STOUTI* (LOCKINGTON)

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SUMMARY

Single renal corpuscles of hagfish were perfused with a Ringer solution containing Ficoll 70 to simulate the colloid osmotic pressure of hagfish plasma. Simultaneous measurements were made of single glomerulus filtration rate (SGFR), perfusion pressure and the pressure in a vessel of the renal vasculature. The results confirm that SGFR is independent of pressure in the glomerular capillaries (P_{GC}). The results also suggest that flow through glomeruli and SGFR are closely linked. Studies of the pressures in glomerular capillaries during periods when the perfusion rate was varied indicate that P_{GC} reflects the area of the active capillaries and the rate of perfusion. Therefore, in the hagfish, P_{GC} appears to be an effect of factors that cause glomerular filtration, not the main cause of that process.

INTRODUCTION

It is widely believed that arterial pressure filtration, as suggested by Starling, underlies primary urine formation in vertebrates (e.g. Renkin & Gilmore, 1973; Arendshorst & Gottschalk, 1985). Despite the possession of glomeruli which are very similar in form and function to glomeruli of other vertebrates, arterial pressure does not seem to underlie primary urine formation in hagfish. As demonstrated recently (Riegel, 1986*b*), maximum hydrostatic (arterial) pressure in glomerular capillaries is about 0·4 kPa; the colloid osmotic pressures (COPs) of the blood and glomerular fluid are, respectively, about 1·4 kPa and nil. Either hagfish glomeruli function very differently from those of other vertebrates or understanding of the latter is not as complete as recent reviews (e.g. Brenner, Baylis & Deen, 1976; Arendshorst & Gottschalk, 1985) would suggest.

As shown by Riegel (1986*b*), blood flow through renal corpuscles of hagfish is more complex than indicated by previous studies (e.g. Grodziński, 1926; Heath-Eves & McMillan, 1974). The renal artery serves both the low-presure capillaries of

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the glomerulus and a high-pressure shunt to the glomerular capillaries. One consequence of this is that vessels efferent to the renal corpuscle are of two kinds. (1) One kind of vessel shunts the glomerular capillaries. In these vessels pressure can be as high as the pressure in the renal artery, and a fully developed arterial pulse is seen. These vessels are designated 'high pressure efferent vessels' (HPEVs). (2) A second type of efferent vessel is one in which the pressure is lower than in the glomerular capillaries and the arterial pulse is barely discernible. These vessels are termed 'low pressure efferent vessels' (LPEVs). It is likely that the LPEVs are efferent to (downstream from) the glomerular capillaries.

The present paper reports the results of studies in which a perfusion technique has been used to study pressure and flow relationships in hagfish kidney. This method was used for two main reasons. First, the present state of knowledge does not permit indirect estimates of blood flow through the kidney of hagfishes. Second, most vessels of the renal vasculature react to damage by promoting localized clotting of the blood (Riegel, 1986*b*), thus discouraging the long-term penetration of such vessels with pressure-sensing or infusion micropipettes. However, hagfish renal corpuscles are relatively easily isolated and individually perfused; during perfusion they produce urine at rates characteristic of glomeruli through which blood is flowing (Stolte & Eisenbach, 1973; Riegel, 1978). Consequently it seems probable that perfused renal corpuscles can serve as a model of glomerular function in intact hagfish. The results of studies of changes in perfusion pressure and the rate of perfusion on single glomerulus filtration rate (SGFR) and pressures in the renal vasculature are presented here.

MATERIALS AND METHODS

Specimens of a Pacific hagfish, *Eptatretus stouti* (Lockington), were studied at the Hopkins Marine Station of Stanford University in Pacific Grove, California, USA. With the exceptions that will be noted, methods of study were closely similar to those described previously (Riegel, 1978, 1986*b*). All experiments were performed on anaesthetized animals which were killed prior to recovery. The temperature of the experiments was 5 °C which approximates the temperature of the deep-water habitat of hagfish.

Perfusion technique

Single glomeruli were perfused through a microcannula tied into a segmental artery. The junction of the segmental artery with the dorsal aorta and all other branches of the segmental artery, except the renal artery serving the renal corpuscle under study, were ligated (see Fig. 1). The microcannulae were made from 1·5 mm o.d. sodium-glass capillary. They were pulled and then bevelled to a sharp tip by grinding on two sides with a Chang (1975) grinder which had been fitted with a coarse grinding surface (Riegel, 1986*b*). The diameters of the tips of the microcannulae varied from about 150 μm to 200 μm. Microcannulae were connected by 2 mm o.d. polyethylene manometer tubing (Portex Ltd, Hythe, England) to a

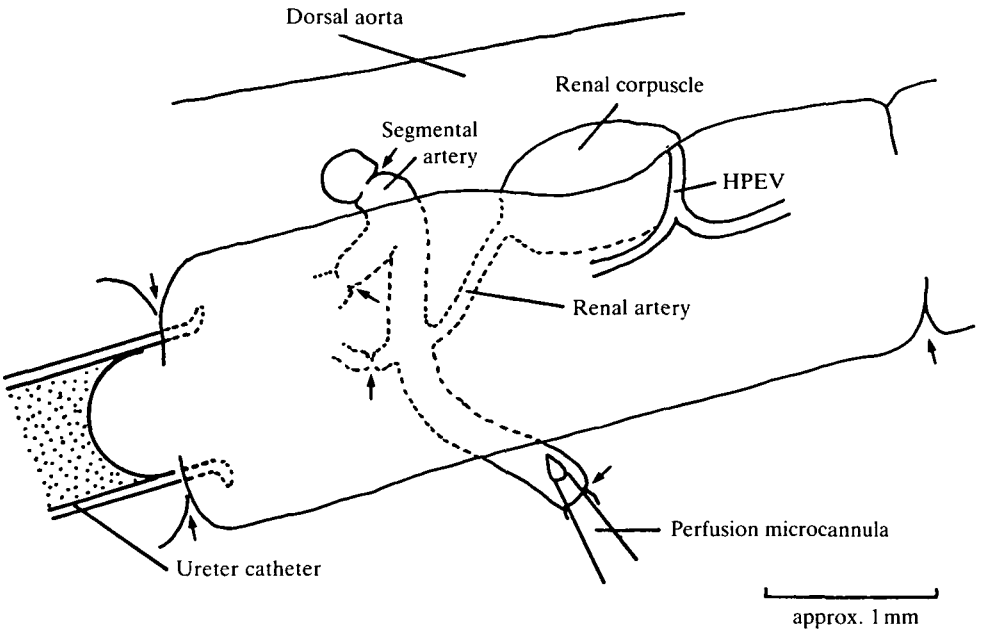

Fig. 1. Diagrammatic representation of the perfusion arrangement. Arrows represent points where ligatures were applied. HPEV, high pressure efferent vessel.

stepping-motor-driven glass syringe. The speed of the motor, hence the rate of perfusion, was controlled precisely with an electronic timer-controller.

The SGFR of perfused glomeruli was measured by a method similar to that described by Riegel (1978) which is accurate to at least 10%. Simultaneously with the SGFR measurements, perfusion pressure and pressure in a vessel of the renal vasculature were monitored. Perfusion pressure was measured by a blood-pressure transducer (EM 750, Elcomatic Ltd, Glasgow, Scotland) in the perfusion line. Perfusion pressures measured after cannulation of the segmental artery were corrected by subtracting pressures measured prior to cannulation with the tip of the microcannula adjacent to the site of cannulation. Even at the highest rates of perfusion used ($12\,\mu l\,min^{-1}$) the correction necessary was small (0·01–0·02 kPa) compared to the perfusion pressures measured (1–3 kPa) at those rates of flow. Resolution of the perfusion pressure transducer was at least 0·03 kPa except when measuring pressures greater than 1·5 kPa, in which case the resolution was at least 0·1 kPa.

Pressure in a vessel of the renal vasculature was measured using a servo-nulling microtransducer. The instrument used was an improved version (Intaglietta, Pawula & Tompkins, 1970) of the device first described by Wiederhielm, Woodbury & Rushmer, 1964). The procedure for measuring pressure in perfused vessels of the vasculature was identical to that described by Riegel (1986*b*); the resolution of the pressure microtransducer was at least 0·02 kPa for pressures less than about 0·8 kPa and at least 0·04 kPa for pressures greater than about 0·8 kPa. Output from the perfusion-line pressure transducer and the pressure microtransducer was monitored

on a dual-channel oscillographic recorder (MD 400/2, Bioscience Ltd, Sheerness, England).

Glomerular fluid collected during the perfusions was stored in a freezer under liquid paraffin. When sufficient samples had been accumulated, the COPs of the samples were determined using the miniature membrane electro-osmometer described by Riegel (1986*a*). The osmometer was fitted with a small disc of ultrafiltration membrane, type PTGC (10000 Da cut-off, Millipore Ltd, Harrow, England). Storage of samples frozen under liquid paraffin did not alter the COP of either standards or blood plasma (Riegel, 1986*b*). It was assumed, therefore, that the COP of glomerular fluid was not altered by such storage.

RESULTS

The discussion below is based on data derived from 15 perfusions which yielded results considered to be reliable.

Relationship between perfusion rate, perfusion pressure and single glomerulus filtration rate

The pressure generated in the perfusion line appeared to depend entirely upon the flow resistance of the perfused preparations. Fig. 2 shows the resulting pressures when perfusion rates were varied between about 1 and 12 μl min^{-1}. The line of best fit through the data points follows a parabolic course. (The line was fitted by a least-squares approximation: $r = 0{\cdot}794$, $P \ll 0{\cdot}001$, $N = 227$). The shape of the line suggests that no marked adjustment of the flow resistance occurred. That is, the perfused renal vasculature appears to conform to the 'passive' system described by Green, Rapela & Conrad (1963) which lacks a marked autoregulatory response.

Ninety-eight measurements of SGFR were made simultaneously with measurements of perfusion pressure and perfusion rate. Treating the data of the individual perfusions as a whole, no statistically significant correlation between SGFR and perfusion rate was discernible. However, of the 15 perfusions, data from 11 were adequate for a least-squares analysis, and in eight of these a statistically significant ($P < 0{\cdot}01$) positive correlation existed between SGFR and perfusion rate. (This positive relationship is illustrated clearly by Fig. 7.)

A plot of all values of SGFR against all values of perfusion pressure yielded a scatter diagram to which several lines of best fit, all of low probability ($P < 0{\cdot}001$), could be fitted by the least-squares approximation. This probably indicates two things: (1) there was considerable variation between the various perfused preparations; (2) SGFR does not bear a simple relationship to perfusion pressure because there are differential changes in flow and pressure in the various components of the perfused renal vasculature.

Although it is not possible to measure flow rates in individual vessels of the renal vasculature, pressure changes measured in those vessels could perhaps yield useful information in this regard. Pressures were measured in 23 renal blood vessels: three renal arteries, seven glomerular capillaries, four LPEVs and nine HPEVs. The ratios

of the pressures in the various renal vessels to the perfusion pressures measured simultaneously were plotted against the perfusion pressure. The results are shown in Fig. 3, where it can be seen readily that pressure in both renal arteries and HPEVs remains relatively high at all perfusion pressures. Therefore, those vessels provide a relatively low resistance pathway for perfusion. Pressure in glomerular capillaries may equal that of the perfusion line at low rates of perfusion, but P_{GC} never rises above about 0·5 kPa, even when the perfusion pressure is increased to the (presumably) unphysiological level of 3 kPa. Because of the relative constancy of P_{GC}, the ratio P_{GC}/P_{PERF} falls steeply towards zero as the perfusion pressure (P_{PERF}) is increased. It is likely, therefore, that glomerular capillaries pose the main resistance to flow through the renal vasculature, at least out of the vessels in which measurements have been made so far. Pressure in the LPEVs did not exceed about

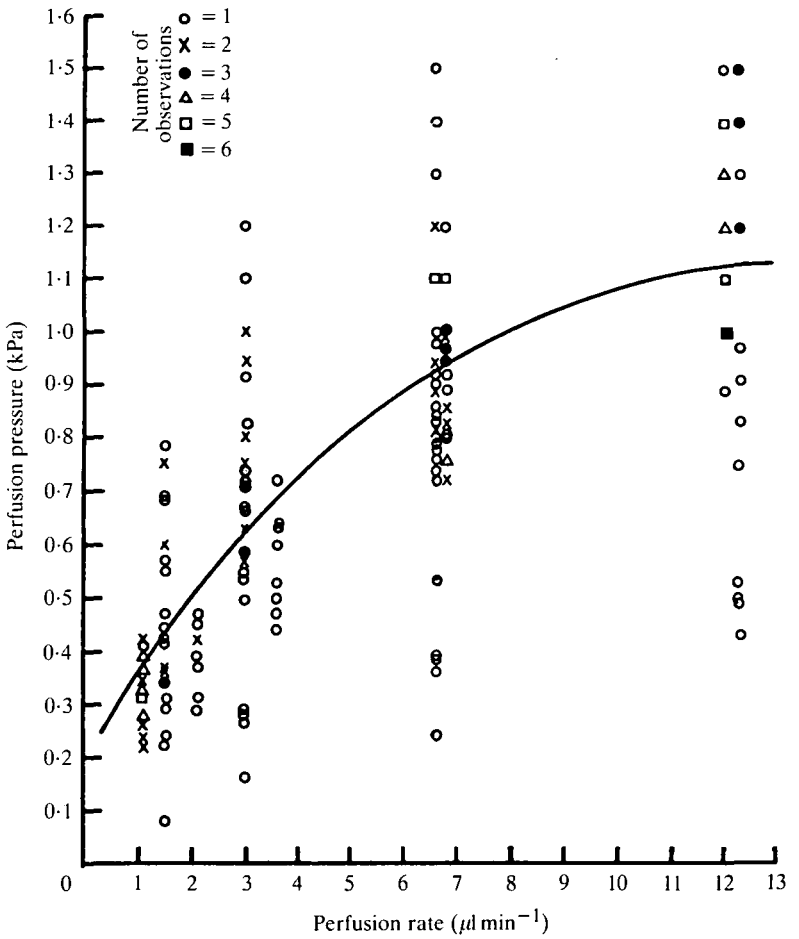

Fig. 2. The relationship between the rate of perfusion and the pressure generated in the perfusion line. The parabolic line was fitted to the data points by a least-squares approximation. The symbols represent the number of observations made at each x, y intersect.

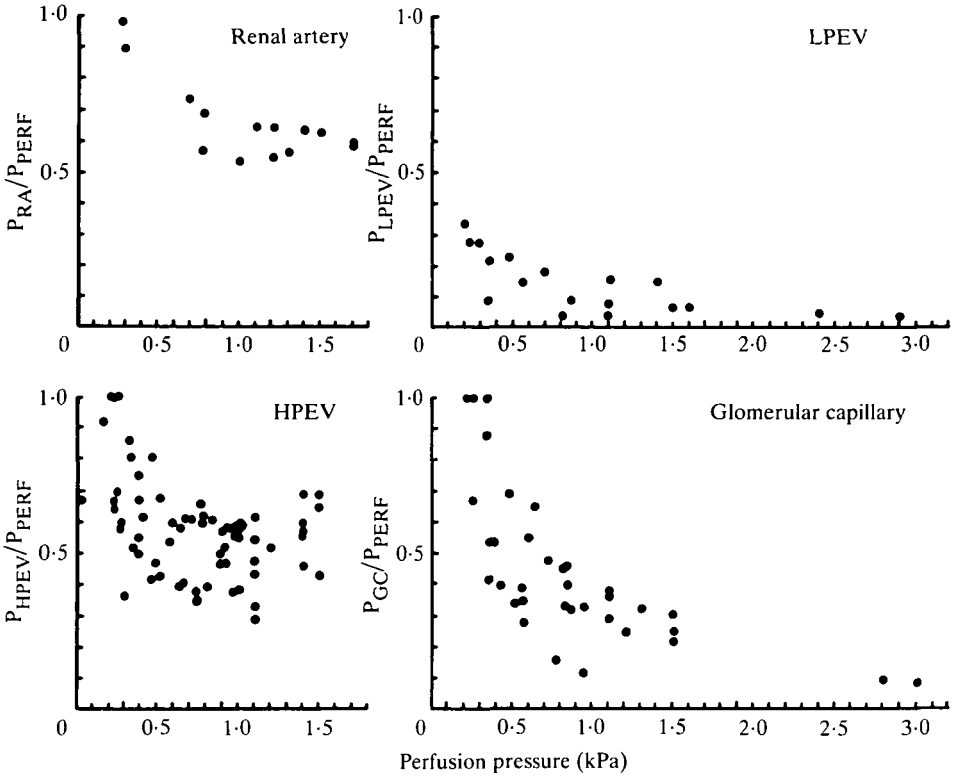

Fig. 3. The relationship between perfusion pressure and the ratio of the pressure in individual vessels of the perfused renal vasculature relative to the perfusion pressure. P_{PERF}, perfusion pressure; P_{RA}, pressure in renal artery; P_{LPEV}, pressure in low pressure efferent vessel; P_{HPEV}, pressure in high pressure efferent vessel; P_{GC}, pressure in glomerular capillaries.

40% of the perfusion pressure. This finding, plus the fact that pressure in the LPEVs (P_{LPEV}) never exceeds P_{GC}, supports the view that those vessels are efferent to the glomerular capillaries (Riegel, 1986*b*).

Effects of resistance changes on glomerular capillary function

The pressure pattern seen most commonly, and in all perfused glomerular capillaries, is illustrated in Fig. 4. At *A*, perfusion rate was increased from 2·6 to 4·7 μl min^{-1}. Initially there was no change in flow resistance (R, = P_{PERF}/perfusion rate) which was about 0·3. However, during a period of about 12 min between *A* and *B*, flow resistance fell to a value of about 0·25. The P_{GC} rose from 0·33 to 0·42 kPa when the perfusion rate was increased (*A*) and then fell to 0·33 kPa by the time the perfusion rate was lowered (*B*). The perfusion pressure also fell by about 0·3 kPa, so that the resistance of the entire perfused renal corpuscle fell. The decline in both perfusion resistance and P_{GC} suggests that the main resistance change was the fall in the capillary resistance. The most likely cause of this fall was the expansion of the glomerular capillary surface area. This conclusion is supported by the fact that

during the period of falling P_{GC} (between *A* and *B*), SGFR rose from 24 to 50 nl min^{-1}. This phenomenon of an increasing SGFR despite a steady or falling P_{GC} was a consistent observation in the four glomerular capillaries in which it was possible to measure P_{GC} and SGFR simultaneously (see also Fig. 7).

In some preparations changes of perfusion rate provoked short-term changes in P_{GC}, suggesting that resistance changes may be brought about by rapid dilatation or contraction of blood vessels. In the upper oscillograph trace of Fig. 5, a reduction in perfusion pressure resulted in a transient fall in P_{GC} which fell gradually thereafter. An increase of perfusion pressure provoked only a transient rise in P_{GC} (Fig. 5, lower trace). These short-term changes were not observed sufficiently consistently to ascertain the conditions of flow or pressure that bring them about, so their significance is difficult to assess.

Observation of glomeruli both during perfusion (Riegel, 1978) and during normal blood flow shows that the capillary tuft is fully capable of contraction and expansion, and that this can occur instantaneously or gradually. Under the conditions of the present experiments it was not possible simultaneously to observe the perfused renal corpuscles and measure their SGFR. Efforts to do this sequentially were unsuccessful.

Measurements of single glomerulus filtration rate

Fig. 6 and Table 1 summarize the data obtained from perfusions of the glomeruli in which reliable measurements of SGFR were made. Fig. 6 shows the relationship between P_{GC} and SGFR in four renal corpuscles in which it was possible to measure the two parameters simultaneously. It is clear from the data that P_{GC} and SGFR vary independently (see Fig. 7).

Although there is considerable scatter, the data of Table 1 reveal two results of possible significance. First, average SGFR and perfusion pressures in these studies were comparable to average SGFR and segmental artery pressures of renal corpuscles through which blood was flowing (Riegel, 1986*b*). Second, the proportion of

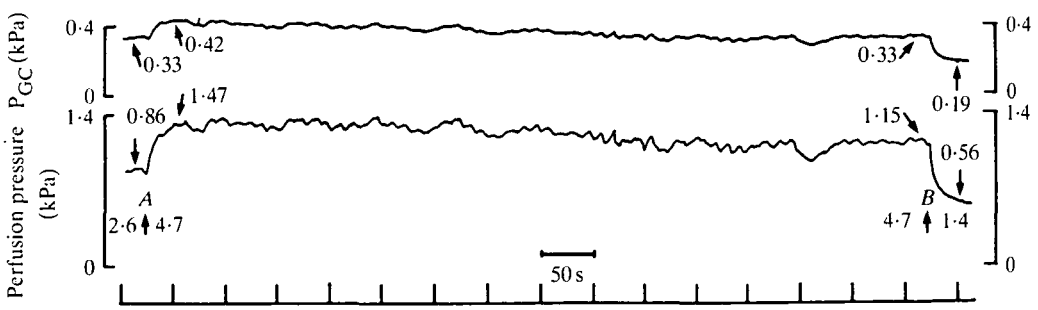

Fig. 4. Oscillograph trace of the perfusion pressure and pressure in the glomerular capillaries (P_{GC}) during a period after the perfusion rate was increased (*A*) and then, after about 12 min, decreased (*B*). The values of perfusion rate (in $\mu l\ min^{-1}$), perfusion pressure (P_{PERF}) and P_{GC} are indicated for the periods immediately before and immediately after *A* and *B*. The single glomerulus filtration rate (SGFR) at *A* was 24 nl min^{-1} and at *B* was 50 nl min^{-1}.

fluid perfusing renal corpuscles which forms the primary urine (the single glomerulus filtration fraction, SGFF) is, on average, quite small. The SGFF does not appear to bear a simple relationship to either perfusion pressure or perfusion rate. In some perfusions, SGFF was directly proportional to both perfusion pressure and perfusion rate. However, in others the SGFF rose during a time when the perfusion

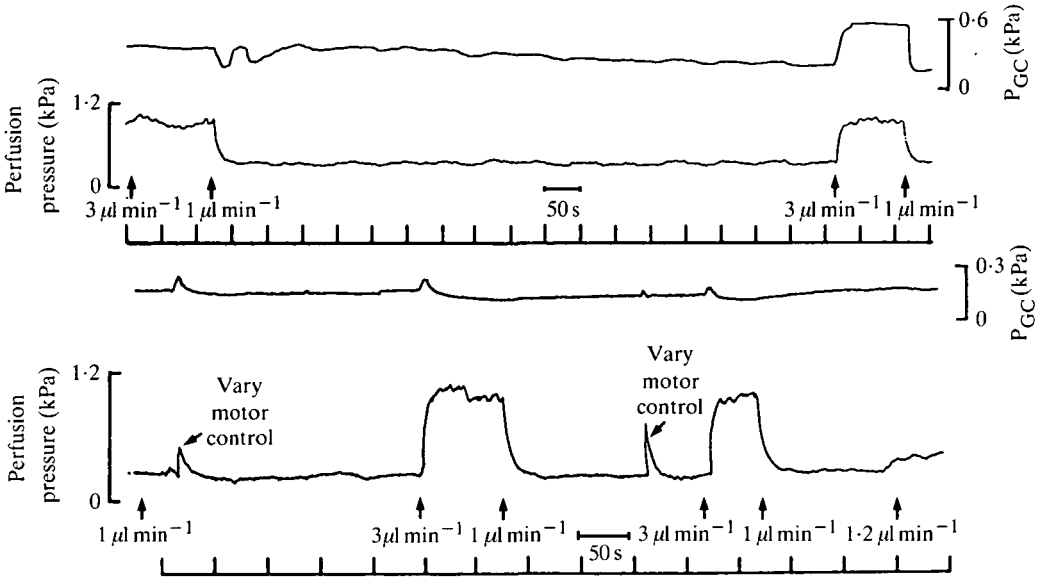

Fig. 5. Upper trace: short-term changes in the pressure in the glomerular capillaries (P_{GC}) in response to decreases in the perfusion pressure. Lower trace: short-term changes in P_{GC} in response to increases in the perfusion pressure. Perfusion rates are marked.

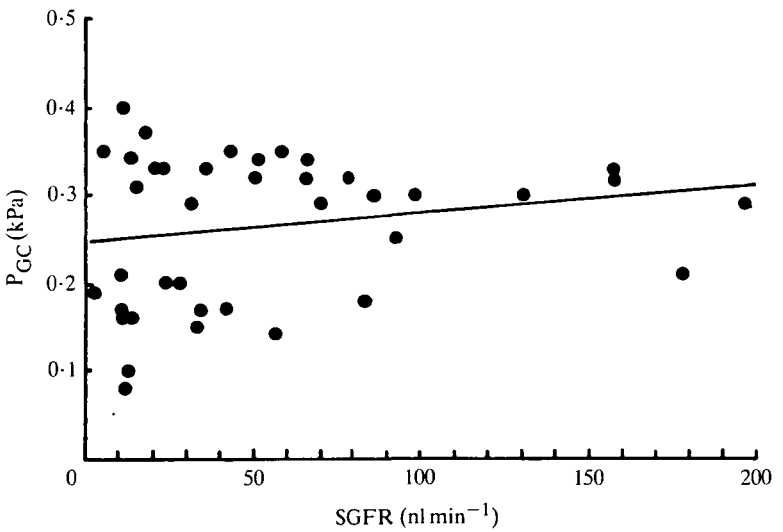

Fig. 6. The relationship between pressure in the glomerular capillaries (P_{GC}) and single glomerulus filtration rate (SGFR). $r = 0{\cdot}203$; $P > 0{\cdot}05$.

Table 1. *Summary of data derived from the perfusion of glomeruli with Ringer whose colloid osmotic pressure was 1·6 kPa*

	Perfusion pressure (kPa)	Perfusion rate (μl min^{-1})	SGFR (nl min^{-1})	SGFF	COP (kPa)
Average	0·98	2·80	28·1	0·015	0·54
S.D.	0·56	2·49	35·3	0·023	0·11
Range	0·22–3·0	0·4–12	1·6–196	0·0006–0·16	0·35–0·68
N	102	102	102	102	9

Single glomerulus filtration fraction (SGFF) was calculated by dividing single glomerulus filtration rate (SGFR) by the perfusion rate.
COP, colloid osmotic presssure.

rate fell (e.g. Fig. 7). Whether or not SGFF is directly related to the area of capillary surface exposed to fluid perfusing the glomerular capillary is also problematical. As was illustrated in Fig. 4, during a period when the SGFR doubled and there were other indications that the capillary surface area increased, the SGFF did not change appreciably.

As shown in the last column of Table 1, colloid enters the glomerular fluid of perfused renal corpuscles; in this respect, perfused capillaries differ from normal glomeruli (Riegel, 1986*b*). However, colloid never attains a concentration in the urine which would favour osmotic flow from capillary lumen to urinary space. The pressure difference across the capillary wall (ΔP)* is determined by the glomerular capillary hydrostatic pressure (P_{GC}) minus the COP of the perfusion fluid (π_{PF}) minus the hydrostatic pressure of the urinary space (P_{US}) plus the COP of the glomerular fluid (π_{US}):

$$\Delta P = P_{GC} - \pi_{PF} - P_{US} + \pi_{US}.$$

Using maximum values for P_{GC} (0·42 kPa, Fig. 6), π_{PF} (1·6 kPa, Table 1), P_{US} (0·05 kPa, Riegel, 1986*b*) and π_{US} (0·68 kPa, Table 1), $\Delta P = -0{\cdot}55$.

Why it is that colloid enters the urine produced by perfused renal corpuscles is unknown, but it may be due to low molecular weight polymers. The batch of Ficoll 70 used consisted of a mixture of polymers whose average relative molecular mass was 68 000. However, according to the technical data received with the Ficoll 70, about 30 % of the sample consisted of polymers which have relative molecular mass less than one-half of the average. Therefore, it is possible that the COP of urine of perfused renal corpuscles is due to filtered low molecular weight polymers of Ficoll 70.

Occasionally glomerular capillaries were damaged by attempts to penetrate them with pressure-sensing micropipettes. Damage was indicated by a rapid rise in SGFR which would not diminish when the perfusion rate was lowered. Analysis of the COP

* It is difficult to know what to call this term, since ΔP is usually used to represent differences of hydrostatic pressure. ΔP will therefore be used until such time as the nature of the force responsible for net movement of fluid across the hagfish glomerular capillaries is identified.

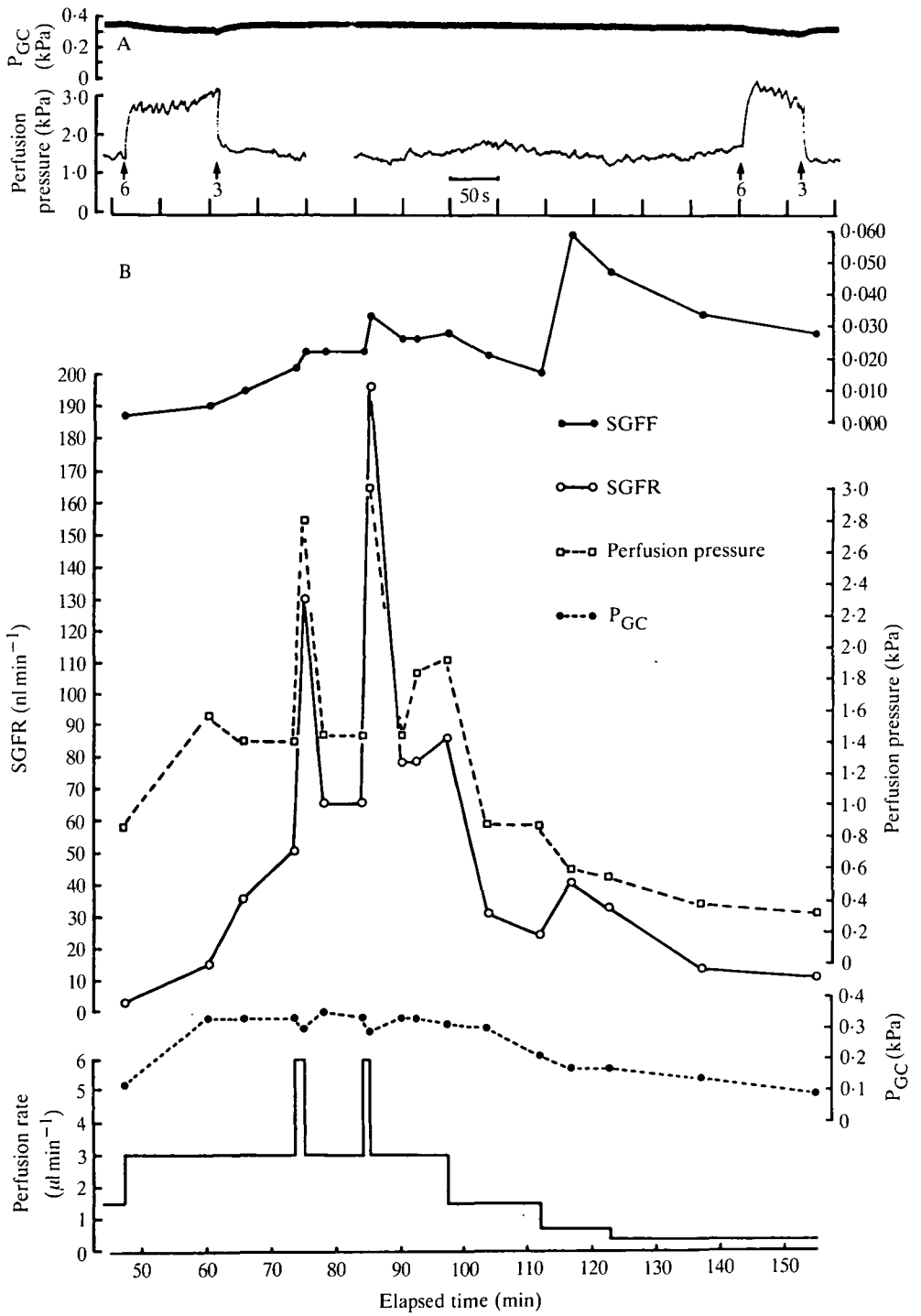

Fig. 7. (A) Pressure changes in a perfused glomerular capillary (P_{GC}) in response to changes in the perfusion rate. Numbers below the vertical arrows indicate the perfusion (in μl min^{-1}). The oscillograph trace covers the approximate period between minutes 73 and 85 shown in B. (B) Changes in the single glomerulus filtration fraction (SGFF), single glomerulus filtration rate (SGFR) and P_{GC} of an isolated, perfused renal corpuscle.

of samples of glomerular fluid from such preparations yielded values at least double those shown in Table 1. Furthermore, the COP of glomerular fluid produced by perfused renal corpuscles in which the glomerular capillaries were undisturbed did not differ from the COP of glomerular fluid produced by renal corpuscles in which the glomerular capillaries had been punctured but there was no indication of damage.

Fig. 7 illustrates an experiment which summarizes all of the factors known to bear significantly on hagfish glomerular function. An isolated renal corpuscle was perfused at known rates whilst the SGFR and pressures in the perfusion line and a glomerular capillary were measured simultaneously. Characteristically, pressure in the glomerular capillary rose to a steady value (approx. 0·3 kPa) as the perfusion rate was increased. This value of P_{GC} was maintained whilst the perfusion rate was kept constant at $3\,\mu l\,min^{-1}$. At about minute 74 of perfusion, the perfusion rate was doubled briefly. This caused the SGFR to increase from about 50 to $130\,nl\,min^{-1}$. Simultaneously, there was a slight fall in P_{GC} (see oscillograph trace in upper part of Fig. 7.). At about minute 84 of perfusion, the perfusion rate was again doubled briefly to $6\,\mu l\,min^{-1}$ with very similar results to those described earlier. After about 97 min, the perfusion rate was lowered. The P_{GC} remained relatively steady for some minutes afterwards, whilst the SGFR fell.

Values of SGFF are plotted in the upper part of Fig. 7. Of particular interest is the observation that SGFF rose steeply after minute 112 of perfusion. Since the perfusion rate was lowered at that time, the rise in filtration fraction must indicate that glomerular capillary flow constituted a greater proportion of the total renal corpuscular flow. Consequently, it is likely that glomerular capillary flow is maintained by an active mechanism which responds to changes of flow rate. The highest value of SGFF measured in a perfused glomerulus was 0·16. This value was measured under conditions virtually identical to those shown in the latter stages of the perfusion shown in Fig. 7, namely a diminished rate of perfusion during which P_{GC} remained relatively steady.

DISCUSSION

Perfused renal corpuscles of the hagfish appear to function in a normal manner, but there are differences from the function of intact renal corpuscles. First, colloid enters the glomerular fluid. Second, the presence of colloid in the perfusion fluid seems to lower the pressure measured in some parts of the renal vasculature. This was especially noticeable in renal arteries and the HPEVs. Pressures measured in those vessels were never more than about 70% of the perfusion pressure. In intact renal corpuscles, the pressure measured in those vessels can be almost equal to the perfusion pressure (i.e. pressure in the segmental artery supplying the renal corpuscle, Riegel, 1986*b*). The reduction of pressure in blood vessels perfused with colloidal solutions is a well-known effect. It results from an increase of flow through the perfused blood vessels, probably brought about by a direct effect of COP on the vasomotor tone of the blood vessel wall (Riegel, 1978). It is unlikely that either of the differences between perfused and intact renal corpuscles mentioned above represents

a departure from normal of a magnitude sufficient to vitiate the main conclusions of the following discussion.

It seems paradoxical that SGFR of hagfish varies directly with supply pressures (Stolte & Eisenbach, 1973; Riegel, 1978), yet SGFR is independent of pressure in the glomerular capillaries. A possible resolution of this paradox is to consider that P_{GC} is an effect of other factors operating in glomerular capillaries, and that it is these factors which are determinants of glomerular filtration. As was shown in Fig. 2, perfusion rate varies directly with perfusion pressure. Consequently, it may be assumed that changes of SGFR reflect changes in one or more of three factors: (1) the rate of perfusion of the glomerular capillaries, (2) changes in the area of the glomerular capillaries that is perfused or (3) the rate at which fluid crosses the walls of the glomerular capillaries. However, pressure in the glomerular capillaries (P_{GC}) clearly is not directly involved in glomerular filtration.

There do not seem to be studies of the glomeruli of other vertebrates which are comparable to those of the hagfish. Single glomeruli of mammals have been isolated and perfused (e.g. Savin & Terreros, 1981; Osgood *et al.* 1983), but these studies have not provided data which allow an unequivocal assessment of the influence of flow and pressure in the perfused capillaries on the SGFR. However, the very extensive studies of single glomeruli of laboratory rats (reviewed recently by Arendshorst & Gottschalk, 1985) reveal some interesting similarities with hagfish glomeruli. The relationship between SGFR (called single nephron glomerular filtration rate: SNGFR) and P_{GC} is similar; P_{GC} varies little despite a wide variation (about threefold) in SNGFR. However, there is a marked correlation between SGFR and glomerular plasma flow, especially in glomeruli in which the filtration coefficient, K_f, is high. (K_f is the product of the area of the glomerular capillaries and the rate of fluid movement across the glomerular capillaries.) Since K_f is increased by increased flow through the glomerular capillaries, it must be assumed that increased flow increases one or the other (or both) of the parameters constituting the term. However, in laboratory rats of all kinds there is a marked inverse relationship between K_f and the effective filtration pressure. Since P_{GC} constitutes the largest component of the effective filtration pressure, it is puzzling that it should have such a pronounced inverse effect on the filtration coefficient. Therefore, it seems possible that in the laboratory rat, as in the hagfish, filtration by single glomeruli does not bear a simple relationship to arterial pressure. Perhaps in the rat some proportion of P_{GC} is an effect of changes in other parameters and not the main cause of glomerular filtration.

This conclusion should not be misunderstood. It does not indicate that the writer believes that arterial pressure is unimportant to the process of glomerular filtration. In all vertebrates, except, apparently, the hagfish, there appears to be an effective filtration pressure in the glomerular capillaries generated by the arterial pulse. However, there are similarities between the filtration process in vertebrate glomeruli and in invertebrate organs, for example some Malpighian tubules (Farquharson, 1974; Maddrell & Gardiner, 1974; Dalton & Windmill, 1981) in which scant possibility exists that filtration is underlain by externally applied hydrostatic

pressure. Furthermore, in some vertebrates, such as the 'Munich-Wistar' rat and the squirrel monkey (Arendshorst & Gottschalk, 1985), an amphibian, *Amphiuma means* (Persson, 1981) and the river lamprey, *Lampetra fluviatilis* (McVicar & Rankin, 1985), effective filtration pressure disappears at some point within the glomerular capillaries. Does this imply the cessation of the process of glomerular filtration at that point? If so, the hagfish stands as an example, unique only amongst vertebrates, of an animal that has somehow overcome the limitations of the relationship first described by Starling.

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