Autoregulation of renal blood flow in dogs at normal body temperature and at 27°C

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(Received 1 November 1974)

Summary
1. Dogs cooled to 27°C were compared with control dogs maintained at 38°C. The mean arterial blood pressure, renal blood flow and glomerular filtration rate were lower in the hypothermic animals.

2. The relation between mean arterial blood pressure and renal blood flow was investigated. Autoregulation of renal blood flow occurred in the kidneys of normothermic and hypothermic animals. Thus the reduction in renal blood flow during hypothermia is not due simply to the fall in mean arterial blood pressure.

3. Similarities between recordings of renal blood flow obtained at 38°C and 27°C suggest that its autoregulation occurs by the same mechanism at the two temperatures.

4. Autoregulation of renal blood flow occurred in hypothermic kidneys in the presence of a cold-induced vasoconstriction. The observed responses to cold and to alterations in mean arterial blood pressure may take place in different areas of the renal vasculature.

Key words: autoregulation of blood flow, hypothermia, kidney.

Introduction
Hypothemia causes changes in many physiological functions, such as cardiac output, blood pressure, tissue metabolism and urine formation. Nevertheless homeotherms with a lowered body temperature are able to regulate many of these functions and can survive in the hypothermic state for long periods. It is therefore interesting to investigate how the body’s homeostatic functions are modified by hypothermia, and to study the changed relations between the organs of the body. Furthermore, since hypothermia is often encountered clinically, since it is induced during a wide variety of surgery and since low temperatures are increasingly used for organ storage, there is a need for a greater understanding of the body’s adaptation to lowered temperatures.

When body temperature is reduced, renal blood flow in the dog is reported to decrease by 38% at 27°C (Kanter, 1963), 70% at 25°C (Blatteis & Horvath, 1958) and 57% at 25°C (Boylan & Hong, 1966). Glomerular filtration rate also has been found to fall by 49% at 27°C (Kanter, 1963), 54% at 27°C (Page, 1955), 55% at 25°C (Boylan & Hong, 1966) and 65% at 25°C (Blatteis & Horvath, 1958). Similar changes in renal blood flow and glomerular filtration rate have been observed in man (review, Blair, 1964) and in the rat (Johns, 1968).

At normal body temperature, autoregulation of renal blood flow occurs so that the kidney tends to maintain a constant blood flow despite changes in mean arterial blood pressure over the pressure range of about 80–180 mmHg. At normal temperatures autoregulation of renal blood flow probably depends upon changes in the tone of the vascular smooth muscle in response to alterations in arterial pressure (Waugh & Shanks, 1960; Thurau, 1964). There is evidence, however, to show that hypothemia induces

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renal vasoconstriction and it is not known whether this vasoconstriction interferes with the autoregulatory responses of the renal vasculature.

The work described in this report was undertaken to determine what autoregulation of renal blood flow occurs when the body temperature of the dog is reduced to 27°C, and at the same time to assess how much the fall in mean arterial blood pressure contributes to the reduction in renal blood flow.

Materials and methods

Renal function in hypothermia

Ten male and female mongrel dogs, weighing from 6.4 to 25 kg, were used. Anaesthesia was induced by intravenous sodium pentobarbitone (Nembutal, Abbott Laboratories Ltd) in doses sufficient to suppress corneal reflexes and to just suppress shivering. An endotracheal tube was inserted. Deep body temperature was measured with an oesophageal thermometer probe (Light Laboratories electrical thermometer). A nylon cannula (1 mm outside diameter; Portland Plastics) was advanced via a superficial branch of the femoral artery, into the aorta approximately to the level of the left renal artery. A polyethylene cannula (1.45 mm outside diameter) was inserted into the inferior vena cava via a branch of the femoral vein and manipulated, through a midline abdominal incision, into the left renal vein (side branches of the renal vein were ligated). Arterial and venous pressures (at the left kidney) were measured with Bell and Howell model L221 pressure transducers, and recorded on a Devices M8 recorder. A lead II ECG was also recorded, and used to trigger a Devices Neilson instantaneous ratemeter to show the heart rate.

The ureters were separately cannulated with polyethylene tubing (1 mm outside diameter), so that the two kidneys were studied independently: very similar clearance results were obtained from the two kidneys.

Sodium chloride solution (150 mmol/l) containing p-aminohippurate (5.2 mmol/l) and creatinine (10.6 mmol/l), was infused at a rate of 15 ml min⁻¹kg⁻¹ via a cephalic vein cannula. Urine was collected at 30 min intervals for clearance determinations; blood samples were withdrawn from the arterial and renal venous cannulae, and plasma concentrations of p-aminohippurate and creatinine were determined as the average of measurements taken at the beginning and end of each clearance period. p-Aminohippurate and creatinine were assayed with a Technicon Autoanalyser by standard procedures. The renal arteriovenous concentration gradient for p-aminohippurate (Eₐᵥₚₐₜ) was determined, and renal blood flow was calculated with the correction due to Wolf (1941).

Hypothermia was induced in experimental animals by surface cooling for 2 h with crushed ice. Since preliminary observations indicated that the variables recorded can alter with time, it was considered inappropriate to compare measurements obtained before and after cooling the same animals. Instead, two separate groups of animals were compared: an experimental group, cooled to 27°C, and a control group maintained for an equal period of time at 38°C; both groups of animals received exactly parallel treatment (apart from cooling) so that the conditions of the two groups were comparable. Furthermore, it was found necessary to allow a 3 h equilibration period between the preparation of the animals and the remainder of the experiment.

Autoregulation of renal blood flow

This was assessed in twelve dogs of either sex, weighing from 9 to 21 kg. An endotracheal tube, arterial, renal venous and cephalic venous cannulae were placed as described above. Sodium chloride solution (150 mmol/l) was infused at a rate of 15 ml min⁻¹kg⁻¹, and left renal venous pressure and mean arterial blood flow were measured. To vary the renal perfusion pressure, the systemic pressure was reflexly elevated by carotid artery occlusion, and then graded constrictions were applied to the abdominal aorta by a tape placed proximal to the left renal artery. Carotid artery occlusion did not alter the ability of the kidney to autoregulate, but did slightly reduce the plateau renal blood flow.

Left renal blood flow was measured with a Biotronex BL 1000 electromagnetic flow transducer placed around the renal artery, together with a Biotronex BL 620 flowmeter, and was recorded on a Devices M8 recorder. The zero-flow flowmeter-deflection was determined by briefly occluding the renal artery with a pneumatic occluder; this determination was made after every individual flow measurement, since it sometimes varied when the mean arterial blood pressure was altered. The left
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renal artery and a large volume of blood were taken from every animal for calibration of the flowmeter and transducer in vitro. Calibrations were performed at 38°C and 27°C. In other experiments we have good agreement between simultaneous flowmeter and clearance determinations of renal blood flow in normothermic and hypothermic animals (B. J. Chapman, W. R. Whitley & K. A. Munday, unpublished observations).

These experiments followed the time-course previously described, except that in five experimental animals determinations of renal blood flow and mean arterial blood pressure were also made at the end of the equilibration period (i.e. before cooling the animals).

Results

Effects of hypothermia on renal and cardiovascular function

Five dogs (mean body weight 15·0 kg) cooled to an average of 27·4 ±0·2°C were compared with five similar animals (mean body weight 15·6 kg) maintained at 38·1 ±0·5°C. Mean arterial blood pressure was 126 ± 6·8 mmHg in the normothermic group and significantly reduced to 93 ± 6·6 in hypothermic animals (P < 0·001). Heart rate was reduced by 61% from 169 ± 15·0 beats/min to 66 ± 6·4 (P < 0·001). Small, statistically insignificant differences in renal venous pressure and in arterial packed cell volume were observed. Renal function measurements were markedly different between the two groups: the p-aminohippurate clearance was 65% less (110 ± 10 ml/min at 38°C, 39 ± 7 at 27°C; P < 0·001) and the glomerular filtration rate 60% less in the hypothermic group (45 ± 1·4 ml/min at 38°C, 18 ± 2·6 at 27°C; P < 0·001). EPAH was only slightly less in the hypothermic group but this difference was statistically insignificant. Renal blood flow was calculated from the p-aminohippurate clearance, EPAH and the arterial packed cell volume and was found to be 55% less in the hypothermic group (260 ± 26 ml/min at 38°C, 117 ± 22 at 27°C; P < 0·01).

Thus a 55% difference in renal blood flow between the two groups of animals was associated with a 26% difference in mean arterial blood pressure. The relationship between mean arterial blood pressure and renal blood flow was investigated further.

Autoregulation of renal blood flow

Fig. 1(a) shows nine graphs of renal blood flow plotted against mean arterial blood pressure, one example taken from each animal studied at normal body temperature (mean temperature 37·6°C). Fig. 1(b) shows eight such graphs, one from each hypothermic animal (mean temperature 27·1°C). In many of the animals more than one set of measurements were taken at one temperature. Fig. 1(c) summarizes all of the data obtained; for each dog, all flow measurements at one temperature were grouped
according to the mean arterial blood pressure (in 20 mmHg increments of arterial pressure), and the average flow for each pressure step was calculated; these values (one set for each dog) were then taken together and the mean flow (±SEM) was calculated for each 20 mmHg increment in mean arterial blood pressure.

Mean arterial blood pressure before occlusion of the carotid arteries was 110 mmHg (SEM = 3·1, n = 12) at normal body temperature and 92 mmHg (SEM = 5·2, n = 8) when body temperature was lowered; the highest measured values after carotid occlusion were 146 mmHg (SEM = 11·1, n = 9) at normal temperatures, and 131 mmHg (SEM = 12·0, n = 8) in the hypothermic animals.

In normothermic animals (see Fig. 1a and Fig. 1c) at mean arterial blood pressures between 40 and 80 mmHg, the changes in renal blood flow were proportional to changes in the arterial pressure. The intercepts on the blood pressure axis at zero renal blood flow (i.e. the critical closing pressures for the renal vasculature) were in the range 15–44 mmHg. When the mean arterial blood pressure was above 80 mmHg, further increases in pressure did not cause proportional increases in renal blood flow, i.e. autoregulation of the flow occurred. Qualitatively similar results were obtained with hypothermic animals (see Fig. 1). The intercepts on the mean arterial blood pressure axis at which renal blood flow fell to zero, were in the range 30–50 mmHg, the mean critical closing pressure was 29·3 mmHg (SEM = 3·8, n = 7) in the normothermic animals and 38·6 mmHg (SEM = 2·6, n = 7) in hypothermic animals. The difference between these mean values is thus quite large, although it was not statistically significant (P > 0·05, Student's t-test or Wilcoxon rank-sum test). The intermediate part of the graph; it can be seen that autoregulation of renal blood flow was somewhat transiently reduced below the final (autoregulated) steady value; this can be seen in some of the recordings shown in Fig. 2(a) and also in Fig. 3. In the normothermic animals the initial passive phase of the response lasted 2–8 s and the ensuing autoregulatory phase was complete after 30 s.

Marked rhythmic variations in renal blood flow were observed in many of the recordings at both 37°C and 27°C, during the early stages of the autoregulatory responses; this can be seen in some of the recordings of Fig. 2(a) and also in Fig. 3. In one of the recordings shown in Fig. 3 the rhythmic variations
Fig. 2. (a) Changes in renal blood flow immediately after the release of renal artery occlusion in an 11 kg dog at 26-4°C body temperature. Mean arterial blood pressure is shown with each recording; renal blood flow was recorded by electromagnetic flowmeter. When mean arterial pressure was 80 mmHg or above, renal blood flow transiently rose to a peak value and then was reduced within 40 s to a lower stable value. (b) The peak (○) and the stable (●) renal blood flow values from the recordings in (a). The peak blood flow values were proportional to mean arterial pressure, showing that autoregulation did not occur immediately. The stable values are shown as the lower line; these flows were not dependent on mean arterial blood pressure (at pressures over 80 mmHg), indicating that autoregulation took place within 40 s.
FIG. 3. Changes in renal blood flow (in a 21 kg dog at body temperature of 27°C) immediately after the release of partial renal artery occlusion, marked rhythmic oscillations in blood flow being shown during the initial stages of the response. Changes of mean arterial pressure recorded from the lower aorta are also shown. Renal blood flow was recorded by an electromagnetic flowmeter.

Discussion

In the first group of dogs studied mean renal blood flow was 55% less, mean glomerular filtration rate 60% less, and mean arterial pressure 26% lower in animals at 27°C; similar differences, though not as marked, were observed in the second experiment. It is well known that renal blood flow and glomerular filtration rate are less in hypothermic animals (at 25-27°C) than in normothermic animals. There are several factors which could contribute to these changes in renal blood flow and glomerular filtration rate during hypothermia, including: (a) renal vasoconstriction (Blatteis & Horvath, 1958; Boylan & Hong, 1966), which may occur as a direct response to cold (Winton, 1952; Levy, 1959; Chapman, 1970; Withey, Chapman & Munday, 1974), or in response to reduced metabolism (Blair, 1964) or to vasoconstrictor chemicals in the blood (Evonuk, 1966); (b) increase in blood viscosity, due partly to the temperature-dependence of viscosity (Winton, 1952; Merrill, 1969) and also to the haemoconcentration that occurs in hypothermia (Page, 1955; Kanter, 1968); (c) capillary obstruction associated with the thrombocytopenia that develops in hypothermia (Hansson, 1965; Kennedy & Feola, 1970); (d) as a consequence of the falls in cardiac output and mean arterial blood pressure (Blatteis & Horvath, 1958).

We have shown that autoregulation of renal blood flow occurs in dogs with body temperatures of 27°C. The lowest mean arterial pressure at which autoregulation occurred was 80 mmHg. This value was the same at 38°C and 27°C. Since the mean arterial pressure generally remains above 80 mmHg in normothermic and hypothermic animals, the reduction which occurs during hypothermia neither causes nor contributes to the reduction in renal blood flow.

It is widely held that renal blood flow is not dependent on mean arterial pressure at body temperature of 25–27°C, although there is not a great amount of supporting evidence available in the literature (review, Blair, 1964). Blatteis & Horvarth (1959) found little correlation between renal blood flow and mean arterial pressure during cooling, although both were reduced. Moyer, Morris & DeBakey (1957) found that noradrenaline caused a rise in mean arterial pressure without a significant alteration in renal blood flow or in glomerular filtration rate in dogs cooled to 26°C; but this evidence may be difficult to interpret since noradrenaline normally causes renal vasoconstriction as well as a systemic pressor response. Harth, Lutz & Kreienberg (1960) briefly stated that autoregulation of renal blood flow occurs in isolated dog kidneys at 18–21°C and above.

Many workers have studied the effects of alterations of mean arterial pressure on renal haemodynamics at even lower body temperatures. Winton (1952), Harth et al. (1960) and Rassat, Philippe, Mikaeloff & Sassard (1969) found that autoregulation of renal blood flow did not occur at temperatures of 3–12°C. Waugh & Shanks (1960) found a partial or imperfect autoregulatory response in canine kidneys cooled to 3–12°C, and showed that this response is due to alterations in renal interstitial pressure, that the response develops very slowly, taking up to 3 min, and that the response does not involve alterations in the tone of the vascular smooth muscle. At normal body temperatures the autoregulatory response occurs more rapidly, taking 5–30 s; the response is due to alterations in the tone of the preglomerular vascular smooth muscle, and does not involve changes in the capillary or interstitial pressures (Waugh & Shanks, 1960; Thurau, 1964).

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to sudden alterations in mean arterial pressure at 27°C shows two phases: an initial passive phase lasting 5–10 s, followed by an active autoregulatory phase which develops rapidly and is complete after 30–40 s. At 38°C, the initial passive phase lasts 5 s and the active autoregulatory phase takes 20–30 s. The time-course of the response at normal body temperature has been well described by Semple & DeWardener (1959), Waugh & Shanks (1960), Thurau (1964) and Basar, Tischner & Weiss (1968), who have shown that the initial phase is a passive response of renal blood flow to the alteration in mean arterial pressure, and that the autoregulatory phase is due to alteration in the smooth muscle tone in the preglomerular blood vessels. Since the responses of renal blood flow follow very similar time-courses at 27°C and 38°C, it is probable that the same mechanisms are involved and that autoregulation of blood flow at 27°C is produced by the contraction of the preglomerular vascular smooth muscle. The tendency of the renal blood flow to overcompensate transiently for an alteration in mean arterial pressure reducing flow below the normal value (as shown in Fig. 2a and Fig. 3), and also the rhythmic oscillations of the renal blood flow that often occur during the autoregulatory phase of the response, support the conclusion that renal blood flow autoregulation at 27°C is due to vascular smooth muscle contraction; these types of response have also been well described in normothermic kidneys by Semple & DeWardener (1959), Waugh & Shanks (1960), Thurau (1964) and Basar et al. (1968).

Since the fall in mean arterial blood pressure does not contribute to the reduction in renal blood flow, this reduction must be due partly to the increase in blood viscosity during hypothermia (Merrill, 1969) together with a marked increase in renal vascular resistance to flow (Withey et al., 1974). Obstruction of peritubular capillaries should cause a reduction in renal blood flow without a fall in glomerular filtration rate. Since both are reduced by similar proportions during hypothermia, any obstruction must occur mostly in the glomerular capillaries. However, in either case autoregulation of renal blood flow would occur normally in the unobstructed portions of the renal vasculature.

As indicated above, there is probably greater evidence to support the concept of renal vasoconstriction during hypothermia. If only partial vasoconstriction occurs in a large proportion of the renal blood vessels, then both pre- and post-glomerular vessels must be involved, to account for the observed changes in renal blood flow and glomerular filtration rate. However, we have shown that during hypothermia there is a marked reduction in blood flow to about 50% of the kidney (Withey et al., 1974), which can account for the observed reductions in renal blood flow and glomerular filtration rate; this should also permit autoregulation to occur normally in the unaffected regions of the renal vasculature.

Waugh & Shanks (1960), DeWardener & Miles (1952) and Waugh (1964) have shown that intense vasoconstriction within the normothermic kidney impairs or prevents autoregulation of renal blood flow. Kil, Kjerksus & Loyning (1969), however, have shown that when renal blood flow is reduced by about 50% by vasoconstrictor chemicals, autoregulation still occurs; the critical closing pressure of the renal vasculature may be elevated by the vasoconstrictor chemicals, but they did not observe changes in the lowest pressure at which renal blood flow autoregulation can occur. Similar observations have been made in hypothermic kidneys in the present study: reductions of 40–60% in renal blood flow do not impair autoregulation and no change is observed in the lowest mean arterial blood pressure at which autoregulation can occur. It is not possible to state with certainty whether the critical closing pressure of the renal vasculature is altered by hypothermia. An increase in the critical closing pressure generally indicates an increase in vascular smooth muscle tone (Burton, 1965), whereas an unchanged critical closing pressure may suggest that some regions of the renal vasculature were not involved in the increased resistance to blood flow. Merrill, Chon Shon Cheng & Pelletier (1969) showed that the yield stress of blood is not changed by reducing the temperature to 27°C, hence viscosity changes should not affect the closing pressure of the hypothermic renal blood vessels.

Kil et al. (1969) point out the apparent paradox of a renal vasoconstriction (which reduces the plateau renal blood flow) that does not alter the lowest mean arterial blood pressure at which autoregulation can occur. To reconcile these observations they proposed that the renal vasculature has two smooth muscle elements in series: one element sensitive to alterations in mean arterial blood pressure and responsible for autoregulation of renal blood flow, and the second independent element responsive to other vasoconstrictor agents. The present findings are consistent
with such a hypothesis although there are alternative explanations such as the one we have described above.

Acknowledgments

We are grateful to Mrs S. Heron for her help in the analysis of the many blood and urine samples taken during the course of these experiments. W.R.W. acknowledges with thanks the receipt of an MRC Research Studentship.

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