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AUTOREGULATION AND NON-HOMEOSTATIC BEHAVIOUR OF RENAL BLOOD FLOW IN CONSCIOUS DOGS

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SUMMARY

1. Spontaneously occurring haemodynamic variations within 4 h affecting renal blood flow (RBF) were compared with externally induced short changes of renal artery pressure (RAP) in conscious resting dogs.

2. In all animals in which RAP was servo-controlled ($n = 6$), perfect autoregulation of RBF was observed.

3. In all 4 h recordings of spontaneous renal blood flow ($n = 9$), certain combinations of blood pressure and blood flow occurred remarkably frequently as indicated by three-dimensional frequency distributions.

4. Cluster analysis demonstrated significant differences between these areas of accumulation ($P < 0{\cdot}001$). The average number of 'set points' per 4 h session was $3{\cdot}1 \pm 0{\cdot}3$.

5. The shift from one set point to another is probably mediated by multiple control systems impinging on renal haemodynamics as suggested by $1/f$ fluctuations.

6. In seven dogs, an additional renal venous catheter allowed measurements of the arterial–venous (A–V) oxygen partial pressure (P_{O_2}) difference as an indicator of the renal metabolic demand. An inverse relationship between A–V P_{O_2} difference and RBF ($Y = X(-0{\cdot}034) + 40{\cdot}9$, $r = -0{\cdot}9$, $P < 0{\cdot}001$) was found, indicating that the metabolic demands vary little (if at all) between the different set points.

7. The presented data suggest a modified view of renal homeostasis. There exist distinct combinations between RBF and RAP, which are very stable. Autoregulation merely buffers the fluctuations around these set points.

INTRODUCTION

Carl Ludwig postulated in 1861 that renal blood flow (RBF) is uncoupled from the systemic circulation (Ludwig, 1861). However, it took a further ninety years before Shipley and Study quantitatively described renal autoregulation by pressure–flow relationships (Shipley & Study, 1951). Autoregulation constitutes a fundamental principle of renal function: the kidney seems to control its blood supply actively by

intrinsic mechanisms, which make RBF largely independent of mean arterial pressure (MAP). The purpose of autoregulation may be to maintain a uniform renal 'milieu interieur' for the excretory and endocrine functions of the kidney.

Hitherto, in a number of studies undertaken to examine renal autoregulation, renal artery pressure (RAP) changes were induced externally by several means (Gross, Kirchheim & Ruffmann, 1981; Kastner, Hall & Guyton, 1984; Rosivall, Youngblood & Navar, 1986; Iversen, Sekse & Ofstad, 1987; Woods, Mizelle & Hall, 1987; Roman, Cowley, Garcia-Estan & Lombard, 1988; Persson, Ehmke, Nafz & Kirchheim, 1990*b*; Young, Lin & Leduff, 1990). It was shown, that RBF remains constant down to a blood pressure of 60–70 mmHg dependent upon the experimental conditions (Kastner *et al.* 1984; Woods *et al.* 1987; Persson *et al.* 1990*b*; Young *et al.* 1990). Thus, the kidney seems to strive to homeostasis in blood flow, in which interrelated systems can reach an equilibrium. In these studies, however, the question of the long-term stability of basal RBF was not addressed.

We have employed the servo-control of RAP in previous studies, and although the protocols were short (45 min to 1 h), we occasionally noticed that in some dogs the resting level of RBF shifted rather suddenly without any apparent reason (Ehmke, Persson, Seyfarth & Kirchheim, 1990; Persson *et al.* 1990*b*). Autoregulation seemed to prevail, however, at the new level. This would imply a certain amount of innate variability in the renal haemodynamic settings, compatible with the view that healthy physiological systems can reveal an almost unpredictable behaviour. Such a 'I don't know state' (Freeman & Skarda, 1987) within which new activity patterns can be generated might fulfil the task of 'active desynchronization', thus avoiding strictly periodic or homeostatic behaviour.

The present study was undertaken to examine the haemodynamic behaviour of the kidney, which as will be shown, has an efficient autoregulation but also exhibits considerable innate variability. Stable states between certain RBF and MAP values were found as a result of this interplay between autoregulation and spontaneous variability. Tests were also carried out in order to determine whether renal metabolic demands changed in association with spontaneously occurring changes in the blood pressure–blood flow relationship of the kidney in conscious dogs at rest.

METHODS

Conscious foxhounds of either sex were used for these experiments. Foxhounds were chosen for their tame and docile temperament. The dogs had free access to water and received a standard dog diet (Alma H5003, Kempten FRG; Na^+, 4 g kg^{-1}). The experimental kidneys weighed on average 81 ± 4 g (range, 62–105 g), the untouched contralateral right kidneys had a mean weight of 83 ± 3 g (range, 70–104 g). Following initial surgical preparation the dogs were allowed a recovery period of 2 weeks. They were trained to rest in a recumbent position for a recording time of 4 h in order to eliminate artifacts due to physical motion. The recording sessions commenced between 07.45 and 12.30 h. The dogs were fed 15–22 h before the experiments.

Surgical procedures

Anaesthesia was induced by sodium pentobarbitone (20 mg kg^{-1} I.V.) and maintained with halothane and N_2O. The implantation surgery has been described previously (Persson *et al.* 1991). Briefly, an electromagnetic flowmeter (Zepeda Instruments, Seattle, USA) or an ultrasound transit time flowprobe (Transonic Systems Inc., New York) was positioned around the renal artery close to its junction with the aorta. A polyurethane catheter was placed into the abdominal aorta. These implants were required for all protocols.

The implants necessary for protocols 2 and 3 (see below) required a renal artery length of at least 2·5 cm. In addition to the implants for protocol 1, a reinforced inflatable vascular occluding cuff was placed around the renal artery downstream of the flowprobe. A polyurethane renal artery catheter was placed with its tip located downstream of the occluder in order to allow the servo-controlling of RAP. The renal artery catheter and the constricting cuff were connected to an external electropneumatic pressure control system, which allowed us to reduce RAP and keep it constant at a pre-set level (control precision of $< \pm 1$ mmHg) (Gross *et al.* 1981). A silastic catheter was implanted into the left renal vein after ligation of the spermatic or ovarian vein.

As reported previously (Ehmke *et al.* 1990; Persson *et al.* 1991), the left renal pelvis was catheterized retrogradely from a small incision made into the ureter close to the renal pelvis in four dogs. A narrow diameter was chosen for the ureter catheter (outer diameter: 0·9 mm) in order to guarantee free urine flow to the bladder when the catheter was plugged and no sampling was done. The pelvic end of the catheter had holes in the wall to allow complete urine collection. Urine was collected into a fraction sampler. The suction used for complete collection of urine (-40 cmH_2O) was determined prior to the experiments by measuring urine flow rate at various suction pressures. Urine flow rate became independent of suction (i.e. was complete) above a pressure of -20 cmH_2O. The joint anatomical and ureteral catheter dead space was on average 1·2 ml (Ehmke *et al.* 1990). No surgery was performed on the right kidney.

An increase in blood pressure via reflex sympathetic activation was achieved by bilateral common carotid occlusion (occlusive cuffs were implanted around the common carotid arteries). In one dog, leakage of an occluder prevented carotid occlusion. The occluders were inflated with a pressure of 1 bar (10^5 Pa). All catheters, cables and cuff leads were fed s.c. to the dog's neck where they were brought out through the skin. All catheters were filled with a heparin solution (Braun, Melsungen, FRG).

Measurements and blood sampling

Blood pressure was measured in the abdominal aorta and renal artery (Statham pressure transducers: P23Db and Gould pressure processors). An analog recorder (Gould 2600) was used to record the directly measured variables: mean and pulsatile aortic pressures, RAP, heart rate (HR), RBF. HR was recorded instantaneously with a rate-meter (Gould pressure processor). The flowprobes (transit-time or electromagnetic) were precalibrated. The signals were passed through a 7·5 Hz (Zepeda) or a 10 Hz (Transonic) filter. Zero flow for the electromagnetic flowmeter was determined 10 min prior to the experiments by a short maximal inflation of the renal artery cuff. In order to exclude the possibility of electrical artifacts by zero flow drift of the electromagnetic flowmeters, we also measured RBF by an independent method via urine creatinine clearance and extraction in the four dogs with ureter catheters. Creatinine (3 g) was given orally 1·5 h before the recording. RBF was determined according to the equation:

$$\mathrm{RBF} = (1-\mathrm{HCT})^{-1} \times C_U \times U_V \times (C_{pa} - C_{pv})^{-1},$$

where HCT represents haematocrit, C_U is urine creatinine concentration, U_V is urine volume, C_{pa} is arterial plasma creatinine concentration and C_{pv} is renal venous creatinine concentration. The resulting estimated RBF correlated significantly with the electromagnetic RBF measurements ($r = 0{\cdot}7$–$0{\cdot}9$, $P < 0{\cdot}01$–$0{\cdot}001$).

Sample analysis

All blood samples taken during the experiments were collected in tubes containing 3·8% ethylenediaminetetraacetate (EDTA). Creatinine concentrations in urine and in plasma were determined by an automatic creatinine analyser (Beckman, Munich, FRG). Sodium and potassium concentrations were measured by an automatic analyser using ion-selective electrodes (Nova Biomedical, Darmstadt, FRG). P_{O_2} was measured polarographically (Gas Check 939, AVL, FRG).

Experimental protocols

The data were stored on-line (IBM PC-AT) after analog-to-digital conversion. Three protocols were performed. The first protocol addressed the spontaneous occurrence of different haemodynamic set points and was also used for the time series analysis. In order to prevent aliasing,

a sampling rate of 10 Hz was chosen. The second protocol quantified the overall metabolic demands of the kidney by measuring renal oxygen extraction. The last protocol confirmed an intact autoregulatory behaviour in response to externally induced pressure variations.

Protocol 1 ($n = 9$): *spontaneous behaviour of MAP and RBF*. The dogs rested on their right sides for a 4 h recording period. The filtered MAP and RBF signals were sampled at 10 Hz. These values were then averaged by a moving average with a large window size (40 values). No blood samples were taken, and we refrained from manipulating RAP.

Protocol 2 ($n = 7$): *renal oxygen extraction*. In the dogs with renal arterial and renal venous catheters, we investigated if metabolic demands change during RBF variability. Arterial–venous P_{O_2} difference was measured along with RBF. Eighteen renal arterial and renal venous blood samples were taken. RBF and MAP were measured as in protocol 1 (except that the mean values were sampled at 0·1 Hz).

Protocol 3 ($n = 6$): *autoregulatory behaviour*. The dogs with renal and carotid vascular occluders were examined for autoregulation within the physiological blood pressure range. RBF was determined during control conditions, after servo-controlling RAP at 80 mmHg and during an increase of MAP by carotid occlusion. Although carotid occlusion will modestly increase renal nerve activity (Gross & Kirchheim, 1980), it has been shown previously that this will not affect autoregulation of RBF above 100 mmHg in our dogs (Persson *et al.* 1990*b*).

Before commencing each 5 min measuring period, 3 min were allowed for stabilization. The data over this 5 min period was sampled as in protocol 2.

Data handling and statistics

The 10 Hz signals in protocol 1 were averaged by an unweighted moving average with a window size of forty values. Three-dimensional frequency distributions were then composed for the data pairs of each experiment (PC-AT 486). The occurrence was plotted against RBF and MAP. The grids for the surface and contour plots were calculated according to the inverse distance method (Davis, 1985):

$$Z = \left(\sum_{i=1}^{n} Z_i/(d_i)^2\right)\left(\sum_{i=1}^{n} 1/(d_i)^2\right)^{-1},$$

where Z_i is the neighbouring point, d is the distance, and n is the number of Z elements.

A cluster analysis using the K-means method (Hartigan, 1975) was performed to determine non-randomly distributed accumulation of data. The MAP–RBF data pairs were then attributed to a specific cluster. The X–Y co-ordinates of these clusters were determined and tested for significance.

A modification of a previously used fast Fourier analysis was performed for the data in protocol 1 (Persson, Ehmke, Köhler & Kirchheim, 1990*a*). The data pool (144000 values) was reduced to 1024 values by block averaging. A cosine tapering of the first and last 10% of each 1024th value segment was performed to alleviate leakage in the spectral analysis which is associated with a finite data series. A baseline correction was achieved by subtracting mean arterial pressure from each pressure value. Each spectral estimate was normalized by dividing it by the total power, thus the resulting values are without dimension.

To test whether MAP and RBF behave according to a $1/f$ process, the resulting log power of MAP was plotted against the log frequency scale. The linear regression was determined to indicate β. A process is referred to as $1/f$ when β is between 0·5 and 1·5 (Marsh, Osborn & Cowley, 1990). The fractal dimension D was calculated according to the equation $D = E + (3-\beta)/2$. The number of variables E was in this case 1.

Student's t test for paired data (protocol 3) and unpaired data (protocol 1) was applied. Differences were considered significant at a P value below 0·05. Data are presented as means ± the standard error of the means.

RESULTS

Protocol 1

As shown in Figs 1, 2 and 3, the distribution of RBF and MAP pairs was not random. Clear peaks in the frequency distributions indicate accumulation in distinct areas. The top three panels of Fig. 1 show an original 4 h recording. Naturally

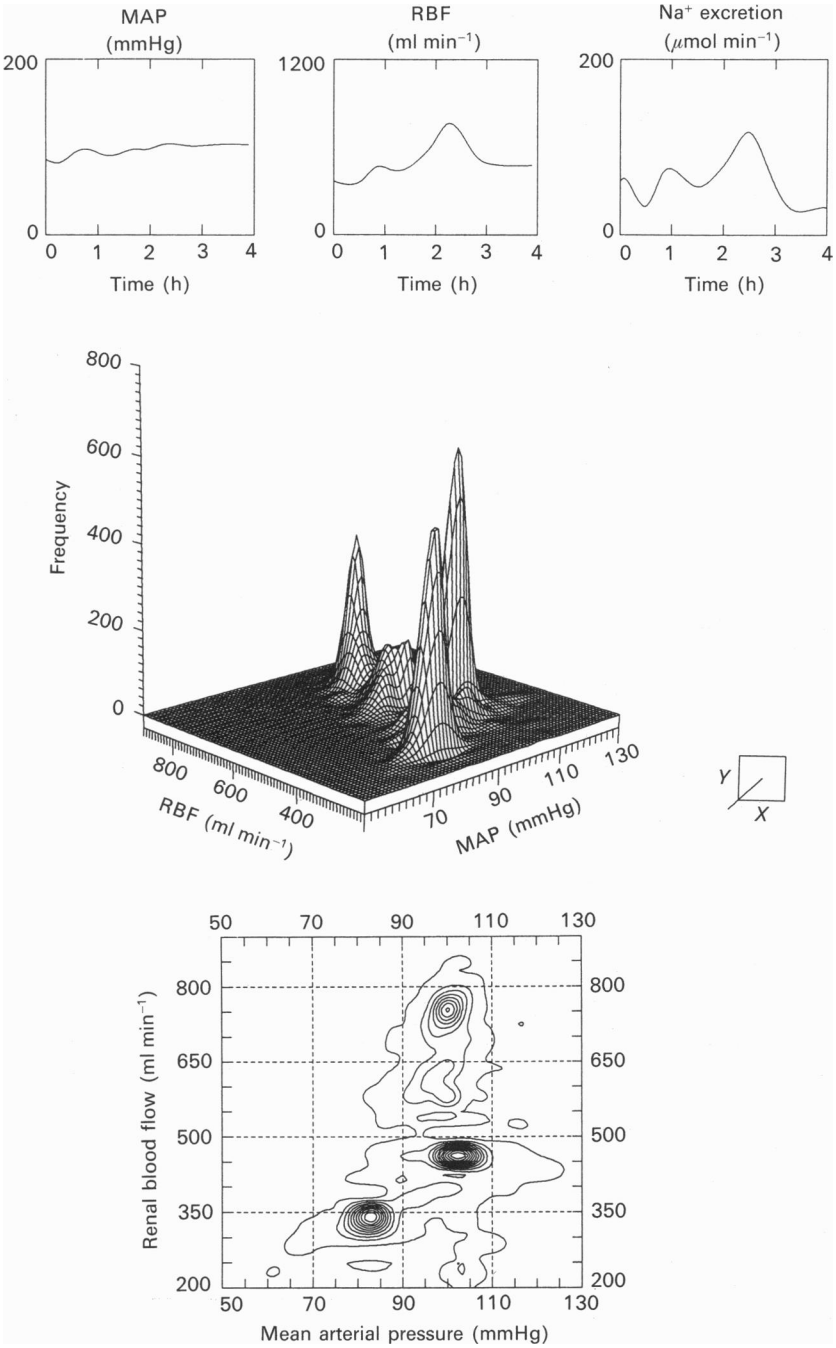

Fig. 1. A characteristic example of a 4 h recording. Top: mean arterial pressure (MAP), renal blood flow (RBF) and sodium excretion *vs.* time. Sodium excretion revealed a similar pattern to RBF. Middle: three-dimensional frequency distribution of RBF *vs.* MAP. Bottom: contour plot of this recording. Note that the highest peak in the middle consists of two time periods, one around the first hour, the second between hours 3 and 4.

occurring fluctuations in RBF are apparent. These fluctuations occurred in a very slow frequency domain (top panels of Fig. 1, top panels of Fig. 4).

Spontaneous very low frequency variations (20 min) have been previously located in the blood pressure signal of our dogs (Persson *et al.* 1990*a*). This is also apparent

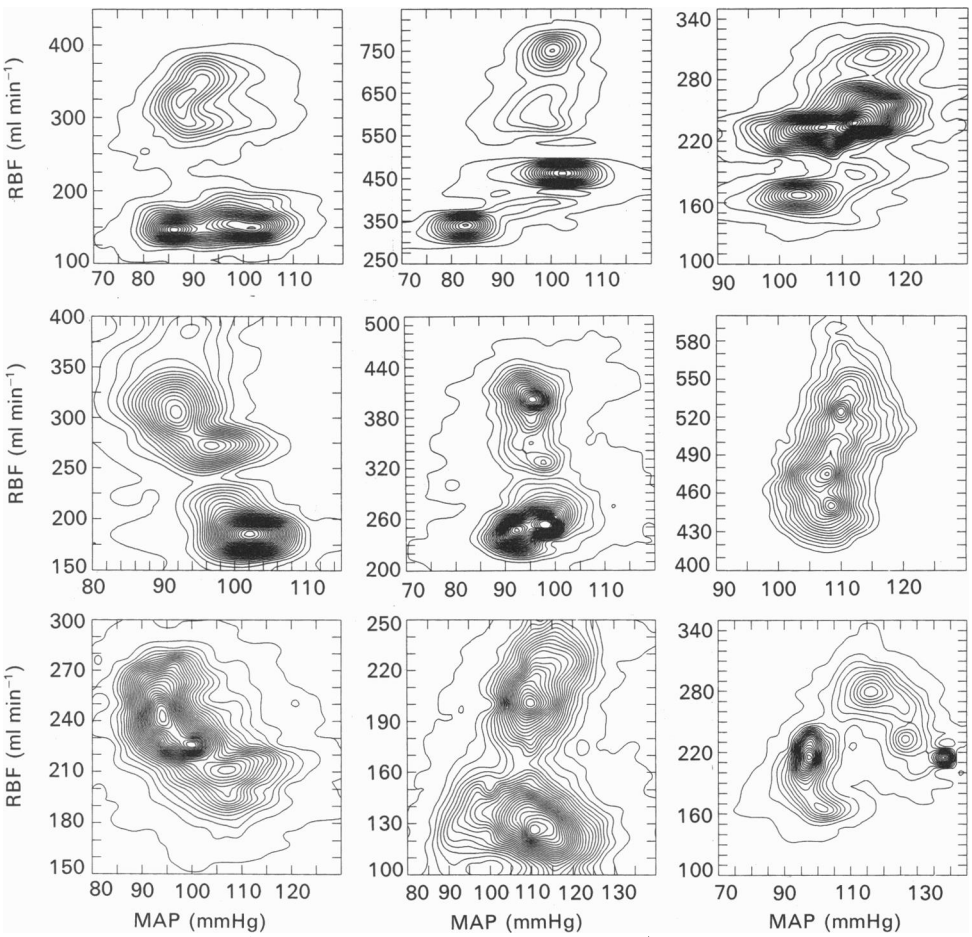

Fig. 2. Contour plots of the recordings of all nine dogs. Each plot is derived from 144000 data pairs. Cluster analysis revealed on average 3·1 ± 0·3 significantly different haemodynamic set points within each session.

in the MAP power spectrum shown in the top left panel of Fig. 4. However, as shown in that study these variations are effectively buffered by baroreceptor reflexes, so they only reach a strong power when baroreceptors are denervated (Persson *et al.* 1990*a*).

As can be expected by the RBF and MAP traces as a function of time (top panels of Fig. 1), the fast Fourier analysis showed high power in the lowest frequency range, especially for RBF (Fig. 4). The log power of the spectra was inversely related to the log frequency. Both MAP and RBF were $1/f$ processes, the regression for MAP (β)

was 0·99±0·11, and for RBF the regression was 1·18±0·27. The correlation coefficients were on average 0·6±0·05 (MAP) and 0·6±0·03 (RBF). The fractal dimension was 3·0±0·05 for MAP and 3·1±0·05 for RBF.

The extent of synchronization between MAP and RBF determines how distinct and significant the resulting peaks in the three-dimensional histograms will be. On

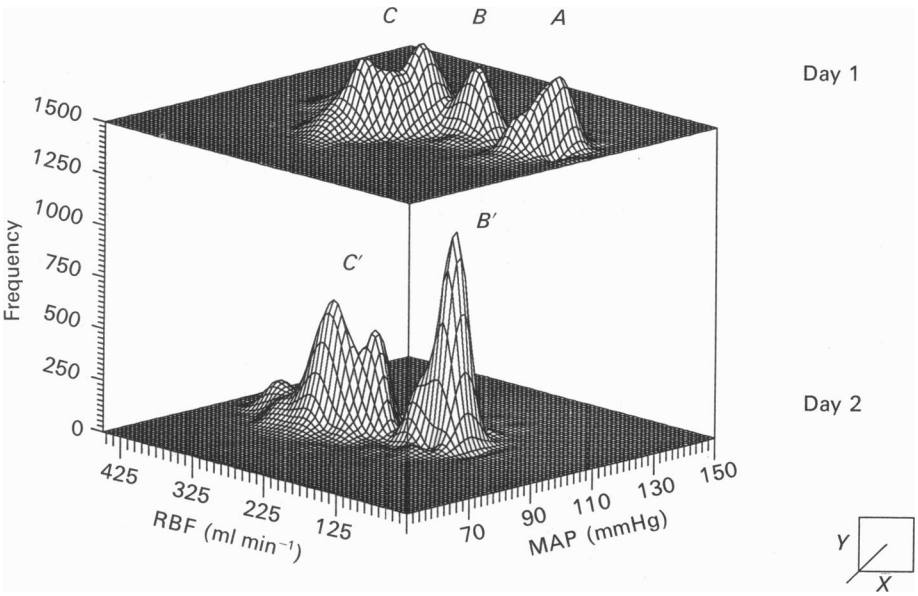

Fig. 3. Recording of a dog on two subsequent days. On day 1, accumulation was found in the areas *A*, *B*, *C*. Note that on day 2 *A′* did not appear, but accumulation was found within *B′* (102 mmHg, 187 ml min^{-1}) and the twin peaks indicated by *C′* (97 mmHg, 264 ml min^{-1}, and 89 mmHg, 313 ml min^{-1}). The corresponding co-ordinates for the region of *B* were 105 mmHg, 197 ml min^{-1}, and for *C*, 97 mmHg, 260 ml min^{-1}, and 87 mmHg, 277 ml min^{-1} respectively. The small differences between days 1 and 2 were partly within the measuring precision; however, they were significantly different in the MAP or RBF direction.

average 3·1±0·3 peaks were found in the 4 h recordings. In all cases these peaks were highly significant ($P < 0·001$) in at least one direction (MAP or RBF). More than 75% of all cluster tests revealed significance for both *X* and *Y* co-ordinates.

The contour plots as seen in the bottom panel of Fig. 1 and in Fig. 2 provide the same information as the surface plots (Figs 1 and 3). The viewer is basically looking from the top down onto the surface. Each contour line represents the 'altitude' in thirty value increments. Generally, very few value pairs formed a bridge between the areas of high density. The exception is the dog depicted on the middle right panel of Fig. 2. Here the cluster analysis located two significant clusters; however, they together share a rather diffuse base indicating more random distribution.

We refer to autoregulation as a variance of MAP in the absence of concomitant changes in RBF. Accordingly, a single long stretched peak around a certain distinct RBF value in the horizontal pressure axis would be expected in the surface diagrams of the 4 h recordings shown in Fig. 2. The patterns in Fig. 2, however, do not

regularly support this suggestion. The high density in certain areas suggests that there are specific set points in renal haemodynamics. The first four plots of Fig. 2 for example show very steep peaks with close contours in part, parallel to the MAP axis. This indicates little RBF variability, hence, autoregulation does exist within these

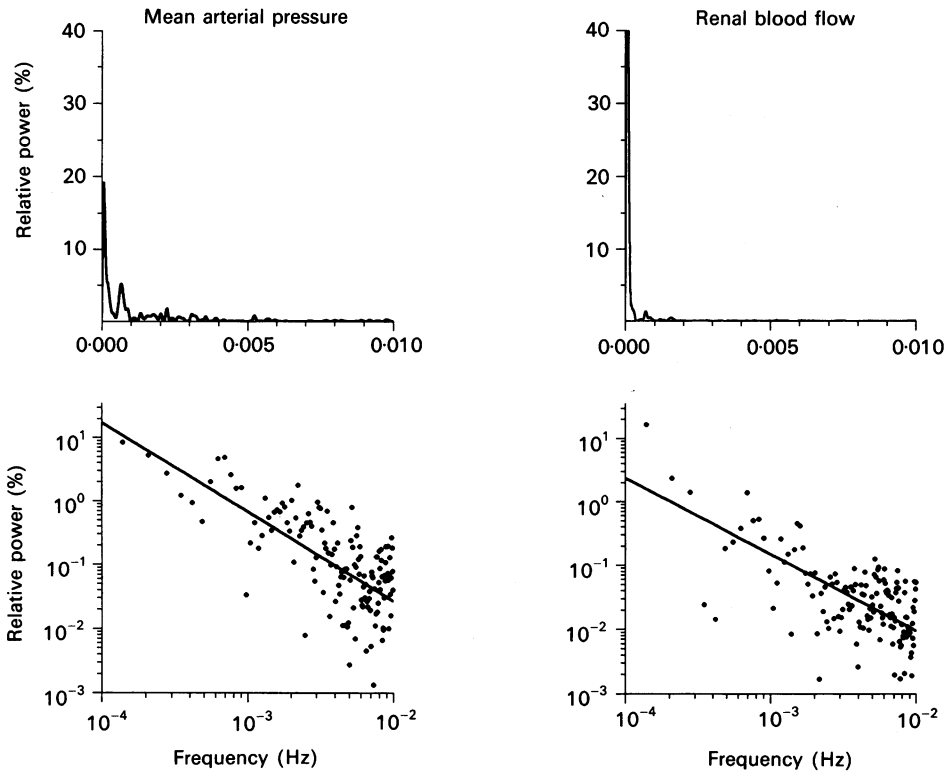

Fig. 4. Power spectra for MAP and RBF of a representative recording. The upper panels show that the power spectral density is very high within the low frequency range. This is more pronounced for RBF. The bottom panels show the corresponding log–log plots, which indicate a $1/f$ process.

set points, which conform with the potent autoregulatory behaviour found in protocol 3.

As seen in Fig. 1, the pattern of sodium excretion resembles the pattern of RBF. In four dogs where urine was sampled, the correlation between RBF and sodium excretion ranged between $r = 0{\cdot}7$ ($P < 0{\cdot}01$) and $r = 0{\cdot}9$ ($P < 0{\cdot}001$).

Protocol 2

In the seven dogs used in this protocol P_{O_2} was determined in the renal arterial and in the renal venous plasma. This was done in order to investigate if the metabolic demand of the kidney varies between the set points. The samples obtained during the 4 h recording periods of each dog were ranked according to the magnitude of RBF. These pairs were then averaged (Fig. 5). Hence, each data point represents the mean of seven dogs. The arterial–renal venous P_{O_2} difference reveals a close inverse

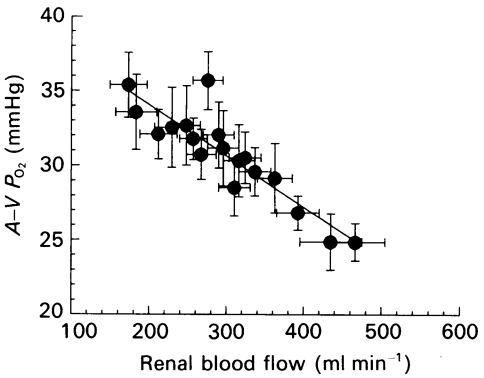

Fig. 5. The arterial–renal venous P_{O_2} difference was taken as an indicator for renal metabolic demands. A close correlation to RBF was found ($Y = X(-0{\cdot}034) + 40{\cdot}9$, $r = -0{\cdot}9$, $P < 0{\cdot}001$). Hence, oxygen extraction varies little between the set points.

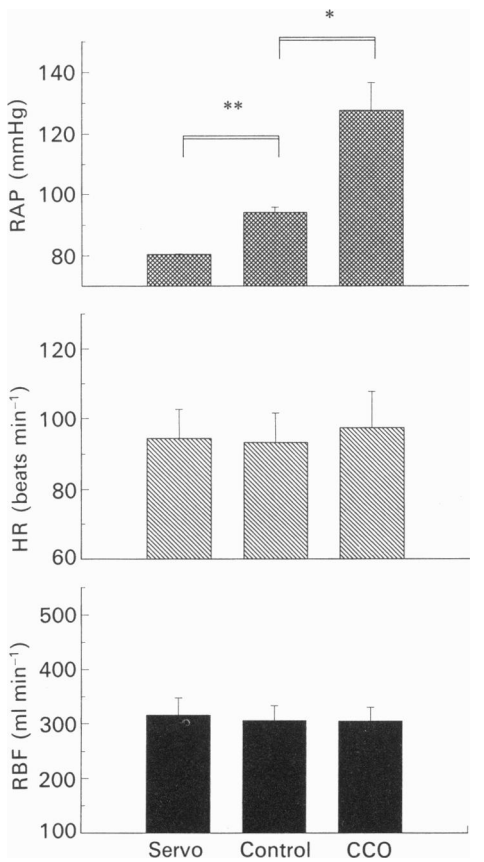

Fig. 6. An intact autoregulatory behaviour to external manipulation of RAP is demonstrated ($n = 6$). RBF was determined during control conditions, during servo-control of RAP at 80 mmHg (Servo), and during an increase in blood pressure via common carotid occlusion (CCO). RBF remained constant despite these changes in RAP. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$. HR, heart rate.

correlation to RBF ($Y = -0{\cdot}034X + 40{\cdot}9$, $r = 0{\cdot}9$, $P < 0{\cdot}001$). With increasing RBF the P_{O_2} difference decreases. Thus, the metabolic demand does not differ to the same degree as RBF.

Protocol 3

As mentioned above there were, on average, 3·1 set points of RBF during the 4 h recordings. If an intact autoregulation is found within these set points, RBF should be well autoregulated within short protocols. In order to demonstrate an intact autoregulatory behaviour, RBF was determined during control conditions, during a reduction of RAP to 80 mmHg, and during an increase in blood pressure due to common carotid occlusion (CCO, Fig. 6). This was measured in the six dogs in which CCO and the servo-control of RAP was possible (these implants require a renal artery length of $> 2{\cdot}5$ cm). The entire protocol had a duration of roughly 25 min. As depicted in Fig. 6, the large changes of RAP had only negligible effects on RBF, i.e. there was an intact autoregulatory response.

DISCUSSION

Spontaneous renal haemodynamic behaviour

Renal autoregulation can be seen as a classic example of homeostasis. Fluctuations resulting from external stimuli are compensated for and the system stabilizes at a steady state as if unperturbed. Provided that only the principle of autoregulation determines the spontaneous behaviour of renal haemodynamics, RBF should not change during MAP fluctuations. This implies that our three-dimensional plots should reveal a single long stretched peak at a certain blood flow value. As seen in Figs 1, 2 and 3, this is only partly so. Distinct accumulation around several RBF and MAP combinations were found suggesting a change of set points. Between these set points remarkably little accumulation was found. The spontaneous haemodynamic variability, which shifts the renal haemodynamic set point may result from the interaction of several intrinsic feedback systems and, thus, does not necessarily require external perturbation. This would conform with the theories arising in the field of non-linear dynamics (Goldberg, 1991), which suggest that even slight changes in haemodynamics can have hardly predictable effects. The interplay between the potent autoregulatory mechanisms and spontaneous variability may explain the non-consistent patterns of the MAP–RBF relationship seen in the recordings of Fig. 2 and supports the concept of an active desynchronization, which averts strictly periodic or homeostatic behaviour.

The hardly predictable behaviour reflecting multiple processes with overlapping time scales commonly shows a $1/f$ relationship. In a $1/f$ spectrum the power of a rhythmic component is inversely related to its frequency. Hence such curves are scale invariant, i.e. there is no characteristic time scale for the underlying dynamic process. The implication of scale invariance is that no single control system determines the haemodynamic regulation. As seen in Fig. 4 such a $1/f$ behaviour was derived for MAP and RBF. However, to attribute definitively the spontaneous renal haemodynamic behaviour to a non-linear dynamic model is not possible: The 4 h recordings are not sufficient to generate enough spontaneous changes in RBF or

MAP to allow adequate analysis. Unfortunately, continuous recordings over longer periods than 4 h would also include several different external perturbations such as physical motion, arousal and different sleep phases.

Much attention was paid in this study to avoiding as many external influences as possible when recording RBF and MAP since several physiological processes can induce changes in RBF. The conscious dogs were studied at rest in a recumbent position in order to prevent large variations in renal sympathetic nerve activity due to postural changes. Experimentally induced alterations in sympathetic nerve activity can influence renal haemodynamics by modifying the lower limit of autoregulation or affecting basal RBF (DiBona, 1982; Persson *et al.* 1990*b*). Feeding also affects renal haemodynamic control by both protein (Murray & Brown, 1990) and sodium intake (Osborn & Kinstetter, 1987; Keil, Lehnfeld, Reinhardt, Mohnhaupt & Kaczmarczyk, 1989). Therefore we did not feed the dogs on the morning before the experiments. Also the experiments were performed at different times of the day. In four dogs we attempted to block the change of set points by converting enzyme inhibition (2 g Ramipril, Hoechst, FRG), blockade of endothelium-derived relaxing factor (500 mg N^G-nitro-L-arginine, Sigma, FRG) and also by an autonomic blockade using hexamethonium (5 mg kg^{-1} bolus injection, then 5 mg^{-1} kg^{-1} h^{-1}, authors' unpublished observations). Although the MAP range decreased, the same change of set points was seen as reported above. Thus, these systems alone do indeed not seem to generate this behaviour *per se*.

Autoregulatory behaviour

As shown in Fig. 6 externally induced acute changes of RAP within the range of the spontaneous blood pressure variability exerted a typical autoregulatory response, which is consistent with the great number of studies performed to investigate renal autoregulation (Kastner *et al.* 1984; Rosivall *et al.* 1986; Iversen *et al.* 1987; Woods *et al.* 1987; Roman *et al.* 1988; Persson *et al.* 1990*b*; Young *et al.* 1990). Since, on average, less than one change of set point occurs per hour it is very likely, that the more rapid changes of RAP in protocol 3 were induced within one and the same set point. Hence, one can interpret autoregulation as the stabilizing mechanism forming the basis for renal haemodynamic set points: externally induced acute changes of MAP are effectively buffered by autoregulation; however, autoregulation is spontaneously overridden by intrinsic mechanisms which induce the change of set point. Thus, there appears to be a pronounced interplay among the homeostatic and non-homeostatic mechanisms controlling renal haemodynamics.

These findings are in general compatible with a recent investigation (Marsh *et al.* 1990) employing spectral analysis of RBF and MAP. In their study, very slow oscillations of MAP (in the range of hours) were not compensated for by autoregulation. Higher frequent blood pressure changes were efficiently buffered ($-6{\cdot}5 \pm 0{\cdot}5$ dB). It appears as if the renal vasculature behaves as a gap filter. Rapid variations (e.g. pulsatile pressure) cannot be buffered; similarly very low frequent fluctuations also pass this filter (Marsh *et al.* 1990). Between the upper and lower cut-off point of this filter we have autoregulation which maintains a constant flow rate. This would also apply for the present study; however, the spontaneous changes in RBF occurred on average about three times per hour. This would be below the cut-

off point in the study of Marsh *et al.* This discrepancy might be explained by the difference in protocols. The recordings of the study of Marsh *et al.* were over 2–3 days. The variability of MAP over this time span is largely dependent on circadian and ultradian rhythms as well as to physical motion, grooming and food intake and may interfere with the endogenous changes.

Renal function within different set points

The arterial–venous P_{O_2} difference was take as an indicator for the renal metabolic requirements. As blood sampling will obscure the discrete measurements of RBF and MAP and flushing could possibly evoke artifacts, the measurements of P_{O_2} were made in a separate protocol. The close negative correlation between A–V P_{O_2} difference and RBF (Fig. 5) indicates that with increasing RBF the oxygen extraction decreases. Thus, the oxygen uptake may vary little between the different set points.

The bulk of the metabolic requirements of the kidney is determined by sodium reabsorption (Deetjen & Kramer, 1961). The similar pattern of RBF and sodium excretion (see Results, Fig. 1, top panels) can be explained by the oxygen uptake. Provided the changes of RBF also change renal sodium loading, we obtain parallel changes of sodium excretion and RBF owing to the fact that sodium reabsorption does not keep pace with the sodium loading. It must be kept in mind, however, that for the longer-term control of sodium balance this observation may only be of minor importance.

In summary, the measurements of P_{O_2} suggest that changes in renal set point do not evoke the same expected change in the overall metabolic demands of the kidney. Hence, baseline sodium excretion varies dependent on the prevailing set-point.

Conclusion

The present data suggest a modified view of renal homeostasis. Non-homeostatic fluctuations are probably due to the interplay of several control mechanisms which impinge upon renal haemodynamics. Autoregulation, in analogy to baroreceptor control of blood pressure, merely buffers the fluctuations around these set points. As a result several metastable set points in renal haemodynamics are formed. Renal metabolic demand varies little (if at all) during the spontaneous variability.

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