Renal Medullary Heat Clearance in the Dog

By Knut Aukland, M.D.

ABSTRACT

Renal medullary heat clearance was investigated in anesthetized dogs to evaluate countercurrent exchange of heat. Sudden changes in the temperature of renal arterial blood were induced by infusion of 3 to 7 ml/min of saline at room temperature. The resulting changes in medullary temperature, measured with fine thermocouples, started with increasing delay from cortex towards the papilla. Average rate constant for heat uptake in the inner medulla was 0.61 min⁻¹. In the outer medulla, rate constants from 0.6 to 5.0 min⁻¹ were observed, with the higher values in the subcortical zone. Inner medullary clearance rose during diuresis, but was practically uninfluenced by lowering perfusion pressure to 35 mm Hg. Calculated heat conduction (diffusion) from cortex into medulla was close to observed clearances, which are thus mainly determined by heat conduction. Clearance due to flow in vasa recta and loops of Henle was small, presumably due to efficient countercurrent heat exchange, whereas urine flow in collecting ducts is not subject to this effect. Formulas for countercurrent exchange not taking into account length diffusion (parallel to the vasa recta) are not valid for medullary heat exchange. The present heat clearance technique cannot be used for estimating medullary blood flow.

ADDITIONAL KEY WORDS

kidney renal medulla vasa recta heat conduction countercurrent exchange local blood flow anesthetized dogs

It is generally accepted that the medullary vasa recta function as a passive countercurrent exchange system, retarding the uptake of diffusible substances into the renal medulla and their removal from it. The efficiency of a countercurrent exchanger is dependent on the physical characteristics of the tubes (length, effective surface area), the flow rate within them, and the diffusibility of the test substance. When an inert diffusible substance is added at a constant rate at the hairpin bend or along the vessels, a steady state concentration gradient from base to apex will be established. According to formulas developed by several investigators, the gradient will be inversely proportional to flow, where $1 < n < 2$, and proportional to the diffusivity of the test substance through the tube wall ($1$-$3$). Accordingly, at a given flow, the clearance of a substance (defined as the amount removed per unit time divided by its concentration) should be inversely proportional to its diffusion coefficient. These formulations, made for steady state clearance, are assumed to hold also for clearance measured from the rate of uptake or removal of the test substance.

In previous experiments in dogs it has been found that hydrogen gas is cleared from the inner medulla with a rate constant of removal of only 0.05 to 0.10 min⁻¹ at low urine flow (4). The present experiments were undertaken to furnish comparable data for clearance of heat, which has an estimated diffusivity 20 to 30 times that of hydrogen gas. Heat clearance would, therefore, be expected to be much lower than hydrogen clearance, provided that heat and hydrogen both are removed mainly by vasa recta flow.

In order to investigate the latter assumption, a study was made of the dependency of medullary heat clearance on urine flow and renal perfusion pressure. In addition, a theoretical
estimation was made of the contribution of heat conduction (diffusion) to heat clearance.

**Methods**

The experiments were performed in mongrel dogs weighing 15 to 25 kg. Anesthesia was induced by Nembutal i.v., 25 mg/kg, and maintained by subsequent doses of 3 to 6 mg/kg. Sodium para-aminohippurate (PAH) in 0.9% saline was given by constant intravenous infusion to maintain a steady arterial plasma concentration of 1 to 2 mg/100 ml. In five experiments urine flow was increased gradually by additional infusion of 0.45% saline or 10% mannitol. PAH in urine and plasma was measured by the method of Smith et al. (5).

A polyethylene catheter was introduced into the femoral artery for pressure recording by means of a Statham pressure transducer and Sanborn amplifier and recorder.

The left kidney was exposed retroperitoneally through a flank incision. A 1.1-mm thick injection cannula mounted on a polyethylene catheter was inserted into the renal artery for infusion of saline. The ureter was cannulated with a polyethylene catheter. In one experiment total renal blood flow was recorded with a Nycotron electromagnetic flowmeter, the probe being placed on the renal artery.

**TEMPERATURE MEASUREMENTS**

Thermocouples were made from 40 gauge (B&S) teflon-insulated constantan and copper wire (Thermo Electric Co., Inc., Saddle Brook, New Jersey). The small dimension of the wires (diameter 0.08 mm) was chosen to minimize heat conduction along the leads. The soldering point was made as small as possible and insulated by a thin layer of varnish. When tested in vitro, the response time was less than 1 sec for 90% deflection. Thermocouples for measuring local temperature in the kidney were introduced and anchored in place in the following way: a 4 to 5-mm thick slice of a rubber stopper was fixed to the constantan wire by stitching the wire three times through the stopper; the distance from the junction was adjusted to half the transverse diameter of the kidney, usually 15 to 20 mm. The copper wire was then stitched through the kidney by means of a round, slightly blunted mending needle, and a rubber stopper fixed to the wire close to the kidney surface, as shown schematically in Figure 7. Two or three thermocouples were placed in the medulla in each experiment.

After each experiment the kidney was removed. The thermocouples were dissected out and their position recorded. In general, no macroscopic bleeding was observed at the thermojunction or along the wire tracks. The kidney was weighed.

A reference thermocouple mounted at the tip of a heart catheter was introduced into the abdominal aorta through the femoral artery. The voltage difference between the renal and the aortic thermocouple was recorded by means of a Keithly Instruments 150 Microvolt-Ammeter and a Honeywell recorder. In some experiments two sets of instruments permitted simultaneous measurements from two sites in the kidney. The instruments were calibrated to give full-scale deflection at 30 μV, corresponding to a temperature difference of 0.75°C.

**EXPERIMENTAL PROCEDURE**

Saline (0.9%) at room temperature (20 to 25°C) was injected into the renal artery catheter at a rate of 3 to 7 ml/min, either by hand or by a finger pump. When the intrarenal temperature became stable at a lower level, the infusion was stopped and the return of intrarenal temperature was recorded. Urine was sampled in 10-min periods for determination of PAH; arterial blood samples were taken in the middle of the clearance periods for PAH and hematocrit determination. Urine flow was also measured frequently between clearance periods.

**Results**

A representative recording showing temperature changes in the inner medulla of dog 9 is shown in the upper part of Figure 1. When the infusion of saline into the renal artery was started, medullary temperature remained stable for about 30 sec and then began to fall. After 5 to 6 min of infusion, the temperature leveled off at a lower value \((T_i)\), usually 0.25 to 0.5°C below control temperature \((T_0)\). The approach to the new level was generally well described by an exponential curve, as shown in the lower part of Figure 1, where \((T - T_i)/(T_0 - T_i)\) has been plotted on a logarithmic scale against time. When the infusion was stopped, the temperature rose again towards control level \((T_0)\) along a curve which closely mirrored the temperature fall during infusion. The exponential rise is evident from plotting \((T_0 - T)/(T_0 - T_i)\) on the logarithmic scale.

**INTERPRETATION**

The temperature changes in the inner medulla obtained in this way reflect changes in medullary heat content per gram of tissue cor-
responding to the temperature change multiplied by the thermal capacity of the tissue. The changes in heat content could be due to variations in heat production (metabolism), variations in medullary heat clearance, or to the introduced change in renal arterial blood temperature. The fact that no consistent difference was observed between heat removal and heat uptake curves (Fig. 1) strongly suggests that changes in heat production and heat clearance are of minor importance, since it is unlikely that the same changes in heat production and heat clearance would be initiated by starting the infusion of cold saline into the renal artery as by stopping the infusion. The observed temperature changes are, therefore, assumed to indicate changes in medullary heat content due to the sudden change in renal arterial blood temperature, and the rate of change in local temperature accordingly measures local heat clearance. It should be noted that this statement is independent of the considerable intrarenal temperature gradients existing at the start of saline infusion (6) since these gradients will be reestablished at a lower temperature level when a new steady state is reached.

The temperature curves shown in Figure 1 are characterized (1) by the initial delay and (2) by the slope of the exponential part of the curve.

(1) It may be difficult to assess the very first apparent change in temperature following the beginning or end of the saline infusion. The delay has therefore been measured on the semilogarithmic plotting as the distance from start (stop) infusion to the intercept of the linear slope at $T_1$ ($T_0$), as shown in the lower part of Figure 1.

(2) The curves are further characterized by the rate constant, $k$, of the exponential part: $T - T_1 = (T_0 - T_1) e^{-kt}$ for heat removal, and $T_0 - T = (T_0 - T_1) e^{-kt}$ for heat uptake, where $t$ is time measured from the end of the initial delay as defined above. If the time is measured in minutes, the rate constant, $k$, will have the dimension min$^{-1}$, and is readily obtained from the half-time $(t/2)$ according to the formula $k = 0.693/(t/2)$. Disregarding the delay and assuming an ideal

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**FIGURE 1**

Upper part: Original temperature recording in dog 9, 10 mm from corticomedullary border. Temperature scale on ordinate placed arbitrarily. Rising temperature downwards. Lower part: Semilogarithmic plot of the curves. Initial delay defined on heat uptake curve at right.

* Circulation Research, Vol. XX, February 1967
square wave temperature change in the renal arterial blood, the rate constant corresponds to clearance (milliliter per minute) per milliliter of tissue, and will for brevity be referred to as local heat clearance, whether the rate constant refers to heat removal or heat uptake. Since a more reliable square wave temperature change is obtained in the renal artery when the infusion is stopped, the heat uptake curves have been used rather than heat removal curves. Owing to recirculation, an ideal square wave is obviously not obtained. It was found, however, that measurement of medullary temperature against a reference thermocouple in ice water gave curves in good agreement with those obtained with aortic reference, but the return to the baseline was better with the latter reference. The significance of heat recirculation seems, therefore, to be of minor importance.

Heat clearance at low urine flow and normal arterial pressure

Inner medulla

Results obtained from 11 probes in the inner medulla in 9 dogs at normal perfusion pressure (mean aortic pressure 110 to 170 mm Hg) and urine flow of 0.1 to 2.0 ml/min, are summarized in Table 1, which also shows effective renal blood flow \[\text{ERBF} = \frac{\text{PAH clearance}}{(1 - \text{Hct})}\] per gram kidney weight. The localization of each probe is given as its distance from the corticomedullary border, measured from the convexity of the kidney towards the tip of the papilla ("axial distance," \(L_1\)), and also as its shortest distance from the cortex in any direction ("shortest distance," \(L_2\)), as shown in Figure 7, right. In spite of considerable individual variations in the course of 1 to 3 hours, and also inter-individual variations, the clearances are distributed fairly evenly about the mean of 0.61 min\(^{-1}\). There is only a slight trend towards lower values in the deepest part of the medulla, whereas the initial delay is clearly shorter for the most superficial probes, as is also evident from Figure 7. Neither slope nor initial delay showed any correlation with effective renal blood flow.

Outer medulla

Heat clearance curves recorded from the outer medulla were less uniform than those recorded in the inner zone. At 2 to 5 mm from the cortex (inner half of outer medulla), a short initial delay was still observed. When plotted on semilogarithmic paper, the curves sometimes showed a tendency to upward concavity, which gave a lower rate constant in the last part of the curve. When this was the case the rate constant was arbitrarily calculated from the average slope down to 50% of full deflection \((T_0 - T_1)\). Observations at normal arterial pressure and urine flow of less than 2 ml/min are given in Table 2, and average clearances and initial delay are shown in Figure 7.

### TABLE 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Probe</th>
<th>Position of probe (mm from cortex)</th>
<th>No. of observ.</th>
<th>Clearance (min(^{-1})) mean</th>
<th>Delay (sec)</th>
<th>ERBF (ml/min · g)</th>
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*Definition for these distances given in text.

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TABLE 2

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<th>Position of probe (mm from cortex)</th>
<th>No. of observ.</th>
<th>Clearance (min⁻¹) mean</th>
<th>Clearance (min⁻¹) range</th>
<th>Delay (sec)</th>
<th>ERBF (ml/min · g)</th>
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In the most superficial part of the outer medulla, no or very short delay was observed and the initial rate constants increased sharply towards the corticomedullary border (Table 1, Fig. 7). Several probes located at the corticomedullary border itself gave clearances from 4 to 7 min⁻¹. These values, which could just as well represent cortical as outer medullary clearance, are not included in the data presented here.

Effect of Diuresis

Medullary heat clearance was studied with 6 probes in 4 dogs at varying urine flow produced by intravenous infusion of 0.45% sodium chloride or 5 to 10% mannitol. Figure 2 shows that inner medullary heat clearance rose considerably with increasing urine flow and that the increase was the same during hypotonic diuresis (dots) as during hypertonic diuresis (crosses). The values presented were observed partly on rising and partly on falling urine flow. Zero flow was obtained by occluding the ureteral catheter. Exactly the same relationship was observed in one more experiment with mannitol diuresis.

Outer medullary heat clearance also increased when urine flow was increased slowly with intravenous infusion of 10% mannitol, as shown in Figure 3. In dog 4 where the
probe was located close to the border to the inner medulla, the control clearance and the increase with increasing urine flow was close to that observed in the inner medulla. (The slopes of the broken lines in Figures 2 and 3, derived theoretically as explained later, are the same in all curves.) In dog 10 where the probe (C) was located closer to the cortico-medullary border, control clearances were about twice as high, but the absolute increase in heat clearance with rising urine flow was rather smaller than in the inner medulla. Clearances obtained from probe B in the same experiment showed even less increase with rising urine flow.

ERBF varied at most 20% in the diuresis experiments, and not in parallel with urine flow or medullary heat clearance.

Influence of Arterial Perfusion Pressure

In 3 experiments renal perfusion pressure was varied by partial occlusion of the abdominal aorta with a Blalock clamp placed on the cardiac side of the renal arteries. In dog 6, inner medullary clearance was measured simultaneously with two thermocouples at 9 and 11 mm from the corticomedullary border (shortest distance). Both probes gave clearances which fell by less than 15% when mean aortic pressure was reduced from 170 to 30 to 40 mm Hg, as shown in Figure 4.

where the order of measurements is indicated by arrows. No change in initial delay was observed.

Outer medullary heat clearance observed in 2 dogs at varying aortic pressure. Probe positions B and A shown in Table 2. Total renal blood flow (RBF) measured in dog 11 with electromagnetic flowmeter after completion of heat clearance measurements.

Discussion

Contrary to expectation, inner medullary heat clearance is about 10 times higher than clearance of hydrogen gas at low urine flow (4), and is also much higher than ethanol clearance (7). The formulas developed for countercurrent systems, stating the clearances as being inversely proportional to the diffusion coefficient (1-3), do not, therefore, fit the heat-hydrogen relationship. Since the formulas have been developed without taking into account length diffusion (parallel to the vasa recta), the unexpected heat-hydrogen relationship might suggest that heat conduction plays an important role, and that medul-
lary heat clearance is not determined by blood flow in the vasa recta.

This assumption is supported by the almost unchanged inner medullary heat clearance when perfusion pressure was reduced. Although total renal blood flow shows marked autoregulation, the blood flow invariably falls sharply when arterial pressure is reduced below 70 to 80 mm Hg. It seems very unlikely, therefore, that medullary blood flow should remain constant when pressure is reduced to 30 to 40 mm Hg, suggesting that clearance is not determined by blood flow. Since glomerular filtration is also stopped or greatly reduced at an arterial pressure of 30 to 40 mm Hg, it also follows that the clearing effect of urine flow in the loops of Henle must be small, thus leaving heat conduction as the main mechanism for inner medullary heat clearance.

Outer medullary heat clearance was more influenced by reduction of arterial pressure in one of two experiments (Fig. 5) suggesting a greater contribution of blood flow in the outer than in the inner medulla.

The contribution of heat conduction can be estimated from the thermal conductivity and the geometry of the tissue. Compared to the relatively slow temperature changes in the inner medulla, the changes occurring on the corticomedullary border may be considered as a square wave (observed rate constants 4 to 7 min⁻¹). Furthermore, the renal medulla may be considered as a cylinder surrounded by cortex, except for the relatively small segment occupied by the papilla and sinus, as shown schematically in Figure 7 (right). This model is very compatible with the increasing temperature from the corticomedullary border towards central parts of the medulla observed under steady state conditions (6).

The radius of the cylinder measured on the excised kidney was close to 10 mm in all cases, except in the extraordinarily large kidney of dog 6 where a radius of 11 to 12 mm was observed. Although the heat conductivity coefficient for the renal medulla has not been measured, other tissues, except fat, have a heat conductivity coefficient (K) of about 1.2 • 10⁻³ cal cm⁻¹ sec⁻¹ °C⁻¹ (8). The thermometric conductivity coefficient, κ (dimension cm² sec⁻¹), corresponding to Fick's diffusion coefficient, is obtained by dividing the heat conductivity coefficient by the product of density (g cm⁻³) and thermal capacity (cal g⁻¹ °C⁻¹). Again no data are available specifically for the renal medulla, but since the density is slightly higher than 1.0 g cm⁻³ and the thermal capacity slightly less than 1.0 cal g⁻¹ °C⁻¹, the product will be close to unity, and a thermal conductivity coefficient of 1.2 • 10⁻³ cm² sec⁻¹ is therefore used. The temperature changes occurring at various depths from the surface of a cylinder with a radius 10 mm with initial temperature T₀ and thermal conductivity coefficient of 1.2 • 10⁻³ cm² sec⁻¹, when suddenly exposed to a surface temperature of T₁, have been replotted from a diagram given by Carslaw and Jaeger (9). As is evident from Figure 6, the clearance curves have the same shape as those observed in the renal medulla. The initial delay increases markedly towards the center. The rate constant is constant in the inner half of the cylinder, 0.41 min⁻¹, compared to an average of 0.61 min⁻¹ observed in the inner medulla (Table 1). In the outer half of the cylinder, the initial rate constant rises sharply towards the surface. (As for the observed clearance curves, the clearance has been estimated from

![Temperature changes in cylinder with initial even temperature, T₀, exposed to a constant surface temperature T₁ at zero time, indicated by arrows. Thermometric diffusion coefficient, κ = 1.2 • 10⁻³ cm² sec⁻¹. Rate constants indicated under each curve.](http://circres.ahajournals.org/content/journals/10.1161/01.cir.20.2.200/F7)

*Figure 6*
the first 50% of desaturation.) A comparison between observed and calculated values is also given in Figure 7, showing fairly good agreement.

The use of a cylinder model for the medulla is only an approximation and due to the curvature in the long axis of the kidney there must also be an element of spherical diffusion. Similar calculations have therefore also been made for a sphere with a radius 10 mm, giving rate constants and delay times as shown in Figure 7 (0.69 min⁻¹ in inner half). Most experimental rate constants for the inner medulla fall within the limits provided by these two models. The penetration of the medulla by calyces and big vessels, as indicated to the left in the schematic kidney section in Figure 7, might contribute to higher clearances and especially to shorter delay than calculated.

These theoretical calculations thus leave very little to be accounted for by flow in the vasa recta and the loops of Henle in the inner medulla at low urine flow. Heat conduction alone also covers the clearances observed in the outer medulla, but a significant contribution of flow clearance cannot be ruled out because a perfect square wave temperature change at the corticomedullary border cannot be obtained experimentally.

The rise in heat clearance with increasing urine flow is probably due to a direct washout effect by flow in the collecting ducts, as previously described for hydrogen gas (4). A possible contribution of a concomitant increase in blood flow cannot be entirely excluded, but the following estimation suggests that blood flow is of minor importance: A urine flow of 100 µl/min • 100 g kidney corresponds to 330 µl/min • 100 g medulla, if the medulla accounts for 30% of total kidney weight (10). Considering the medulla as a perfect mixing chamber, i.e. urine enters the medulla with arterial temperature and leaves at the tip of the papilla with a temperature equal to average medullary temperature, the washout rate due to urine flow will be 0.33 min⁻¹. In Figure 2 this has been illustrated by the broken line where the diffusion plus blood flow clearance at zero urine flow has been set at 0.52 and at 100 µl/min • 100 g at 0.52 + 0.33 min⁻¹. The observed data are well represented by this line, leaving little or nothing
to be accounted for by a possible concomitant increase in medullary blood flow. For comparison, Figure 2 also includes previous observations on hydrogen clearance (4). The even stronger influence of urine flow on hydrogen clearance in the lower flow range is explained as follows: Hydrogen clearance in the inner medulla is only 10 to 20% of heat clearance, but is of the same magnitude in the outer medulla. At the time of inner medullary washout, when the rate constant is determined, the outer medulla is therefore almost completely cleared of hydrogen. The remaining mixing volume for urine flow is accordingly only the inner medulla, resulting in a steeper rise in clearance with increasing urine flow. The rise in hydrogen clearance at low urine flow (Fig. 2) thus corresponds to a mixing volume of only about 10% of the kidney.

The absolute increase in outer medullary heat clearance with diuresis is rather less than the rise in the much lower inner medullary clearance (Fig. 3), whereas a proportionate increase would have been expected if the increase in clearance was due to a concomitant rise in medullary blood flow.

Sadler and Tuttle (11) reported rate constants for heat uptake in the inner medulla of 0.53 to 0.61 min⁻¹; this is in good agreement with the present results. However, their conclusion that local blood flow is 53 to 61 ml/min • 100 g is unwarranted if heat uptake is mainly determined by heat conduction, as suggested by the present results. It seems likely that also heat appearance time (12) is dominated by heat conduction, and therefore is of questionable value for medullary flow measurement.

In accordance with the present results, lower clearances have been obtained with a method designed to measure only convective heat clearance. Perl and Hirsch (13) reported 0 to 50 ml/min • 100 ml "in the medulla,” and Schieve et al. (14) reported an average of 24 ml/min • 100 g in the inner medulla. However, except for the lower figure given by Perl and Hirsch (13), these values are still higher than expected from the present study.

Conclusions

The introduction of a square wave temperature change in the renal artery produces a very rapid temperature change in the region of the arcuate arteries on the corticomedullary border. From here heat is transported to or from the inner medulla mainly by conduction (diffusion); heat exchange is thus diffusion-limited. With greater reduction of large vessel blood flow than produced in the present experiments (aortic pressures below 30 mm Hg), some point must eventually be reached where inner medullary heat clearance also falls, and thus becomes flow-limited, but still not determined by local flow. Although outer medullary clearance may be more flow-dependent, the present type of heat clearance is not suited as an indicator for local medullary blood flow. The convective clearance due to flow in the vasa recta and the loops of Henle is small because of efficient countercurrent heat exchange. Urine flow in the collecting ducts is not subject to countercurrent exchange and is therefore responsible for measurable heat clearance during diuresis. Formulas developed for countercurrent exchange without taking into account length diffusion are not valid for medullary heat exchange. It can be calculated that the error is small for hydrogen gas and negligible for most other substances with lower diffusivity.

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References

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