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Cardiac afferents and the renal response to positive pressure ventilation in the dog

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Abstract. The effects of cardiac denervation on renal function during spontaneous breathing (SB) and controlled mechanical ventilation (CMV) were investigated in six mongrel dogs. Selective and reversible blockade of cardiac afferents was achieved by instillation of procaine 2% into the pericardium. Application of procaine 2% into the pericardium during SB caused a statistically significant depression of urine flow (−55%), of sodium (−64%) and potassium excretion (−42%), and of inulin (−21%) and PAH-clearance (−30%). After institution of CMV with a positive end-expiratory pressure (PEEP) of 10 cm H_2O a further, statistically significant decrease in urine flow (−42%) and sodium excretion (−70%) and of the inulin (−15%) and PAH-clearance (−38%) was observed. Global hemodynamics, mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP) and cardiac index (CI) did not change significantly after installing procaine 2% into the pericardium during SB. After institution of CMV an increase in CVP and MPAP occurred whereas MAP and CI remained unchanged. During the following periods of spontaneous breathing first with blockade of cardiac afferents and later after washing out the procaine with NaCl 0.9% all parameters of renal function approached control levels as measured in the first period of spontaneous breathing without cardiac denervation.

Key words: Cardiac afferents – Denervation of the heart – Controlled mechanical ventilation – Positive airway pressure – Kidney function

Introduction

Positive intrathoracic pressure as induced by positive pressure ventilation is associated with a deterioration of renal excretory function and hemodynamics. This has been demonstrated in healthy [1 – 3] and sick human subjects [4, 5] as well as in animals [6 – 12]. The mechanisms by which this renal response is mediated are still controversial but it is generally assumed that neural reflex mechanisms induced by increases in intrathoracic pressure cause the decrease in renal function.

In 1954, Gauer et al. [6] suggested that shifts of blood away from the intrathoracic vascular bed to the abdomen leads to an activation of atrial stretch receptors followed by a subsequent increase in the release of antidiuretic hormone (ADH) resulting in an antidiuresis. This theory was later refuted by Baratz et al. [8], Tarak et al. [9] and Fewell et al. [10]. They demonstrated in dogs [8, 10] and rats [9], that bilateral cervical vagotomy failed to abolish the renal response to continuous positive pressure ventilation (CPPV). Their conclusion was that the impairment in renal function originated from the simultaneously decreased cardiac output.

Sectioning the vagi, however, does not selectively eliminate afferents of cardiac origin which represent only 10% of all vagal afferents [13]. Furthermore the elimination of other afferents such as arterial baroreceptors and lung stretch receptors can strongly influence the cardiovascular system and provoke interactions between global and renal hemodynamics.

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The purpose of this study was to investigate the significance of cardiac afferents alone in mediating the renal response to positive pressure ventilation using a specific approach to exclude cardiac afferents, namely the application of local anesthetic into the pericardium [13 – 19].

Material and methods

The influence of positive pressure ventilation on renal excretory function and hemodynamics during denervation of cardiac afferents was studied in six mongrel dogs (48.2 + 7.5 kg means ± SD).

The study protocol consisted of five periods (Table 1). The described sequence of breathing and ventilatory modes was chosen to exclude a trend with time in the course of the experiments.

Anesthesia was introduced with a single injection (1.6 ml/kg) of a chloralose/urethrane mixture (40 g urethrane + 4 g chloralose dissolved in 500 ml NaCl 0.6%) followed by endotracheal intubation. Muscle relaxants were not used during the study.

Urine flow was measured using a uretheral catheter inserted into the bladder. The arterial pressure was measured with a catheter placed via the femoral artery with its tip in the descending aorta and the pulmonary artery pressure using a 7F-Swan-Ganz catheter (Edwards Laboratories). The catheters were connected to Statham gauges (P37B, P230P) whose outputs were continuously recorded on a Beckmann 5525C 8-channel polygraph. Heart rate was derived from the ECG using a cardiotachometer.

In the middle of each study period the cardiac output was determined using a thermodilution cardiac output computer (Edwards Laboratories 9250). The mean of three consecutive measurements was recorded.

For the determination of inulin, PAH and osmolal clearances an aliquot of urine was taken from the total collection to establish urinary concentrations; for plasma concentrations blood was obtained at the midpoint of the collection period. The osmolality was determined with a Knaur osmometer by the freezing point depression method. Urinary and plasma concentrations of inulin and para-ammino hippuric acid (PAH) were analyzed using an Eppendorff flame photometer.

Urine collecting periods were reported by equilibration periods of at least 1 h.

The arterial blood gases were measured at the same time (AVL-gas check). Glomerular filtration rate and renal plasma flow were determined using inulin and PAH clearance, respectively. Inulin and PAH were each injected as a bolus of 2 g, followed by an infusion (2 ml/kg/h). The infusate consisted of 20 ml inulin 10%, 10 ml PAH 20% and 50 ml of the chloralose/urethrane solution for maintenance of anesthesia all in 500 ml NaCl 0.6%; the infusion was isotonic with plasma. The mean serum concentrations were, 20% to 30% for inulin, and 1% to 2% for PAH. The body surface area was calculated by the formula of Guyton [22] for dogs over 5 kg: BSA (body surface area) = $0.112 \times BW$ (kg) [2, 3], and all values were expressed per 1.73 m^2 of body surface.

To facilitate the instillation of procaine into the pericardium, a thoracotomy via the xyphoid route was performed and a soft PVC-catheter with multiple perforations at its distal end was sutured into the pericardium. During this procedure, the dogs were mechanically ventilated (CMV). Care was taken not to damage the pleural space and to eliminate any leaks around the catheter. The thorax was closed and all air removed via an intrathoracic catheter. After this period the dogs were allowed to recover for 2 – 3 h. They breathed spontaneously while circulatory variables were measured and urine collected every 20 min, to ensure a constant urine flow.

Each 15 min during this period 10 ml NaCl 0.9% was instilled into the pericardium after removing the previous portion in order to obtain similar transmural pressure gradients during the measuring periods.

If the urine flow was constant for three consecutive measuring periods a two hour period of spontaneous breathing was taken as the control. Pericardial local anesthesia was then induced with 10 ml procaine 2% every 15 min in the same manner as the 0.9% sodium chloride solution instilled during the control period. This seemed to be equivalent to the 3 ml of local anesthetic given by Arndt et al. [19] into the feline pericardial sac.

The block was established within 3 min and was reversed by extensive washing out of the procaine with NaCl 0.9%. The changes were manifest by a decrease in heartrate after instillation of the procaine and an increase after washing-out.

Mechanical ventilation was with a servo ventilator 900B (Siemens Elema, Sweden) with a positive end-expiratory pressure of 10 cm H_2O and an inspiratory O_2-concentration of 21%. Minute volumes of 100 ml/kg were maintained at a rate of 25 to 30 breaths/min.

Statistical evaluation was carried out by a four-step-procedure for each variable. In the first step a so called 'omnibus-test' (analysis of variance: repeated measure design over all 5 time points) was performed. If this test was not significant ($\alpha = 0.05$), the procedure was stopped. No further analysis was made with this measurement. The interpretation of such a result is, that no change of the measurement could be shown over the whole experiment. If the omnibus test was

significant the time trend was tested in the second step of the procedure. This was done by pairwise t-tests comparing the 1st with the 5th period. Since for this step the error of the second kind is of great interest, significance level was chosen to $\alpha = 0.1$. For measurements showing a time trend the following analysis has to be interpreted with caution. In the third step a global test (analysis of variance: repeated measure design) was performed again, but only for the first three (the really interesting) time periods. In case of a significant result ($\alpha = 0.05$) of the global test the last step was done. In the fourth step pairwise t-tests were carried out ($\alpha = 0.05$).

With this stepwise procedure the global significant level of $\alpha = 0.05$ for the last two steps is assured. So further α-adjusting (e.g. Bonferroni) is not necessary.

The main endpoint variable in the experiment was urine flow. For only this variable could the results be interpreted in a confirmatory way. All other variables were treated by an explorative analysis. Formally, we will also describe 'significant results' in the explorative analysis.

Results

The mean values + SEM obtained during each measuring period (SB without cardiac denervation, SB and CMV with cardiac denervation) are shown in Fig. 1 and in Tables 2 and 3.

When arterial pressure ($p = 0.20$) and arterial carbon-dioxide tension ($p = 0.54$) showed no statistically

Table 1. Study protocol

Periods	Remarks	Duration
Spontaneous breathing (SB)	Without denervation of cardiac afferents	2 h
Spontaneous breathing (SB + procaine)	With denervation of cardiac afferents by instillation of procaine 2% into the pericardium	2 h
Controlled mechanical ventilation (CMV + PEEP)		2 h
Spontaneous breathing (SB + procaine)		2 h
Spontaneous breathing (SB)	After reversal of cardiac denervation by washing out the procaine 2% with NaCL 0.9%	2 h

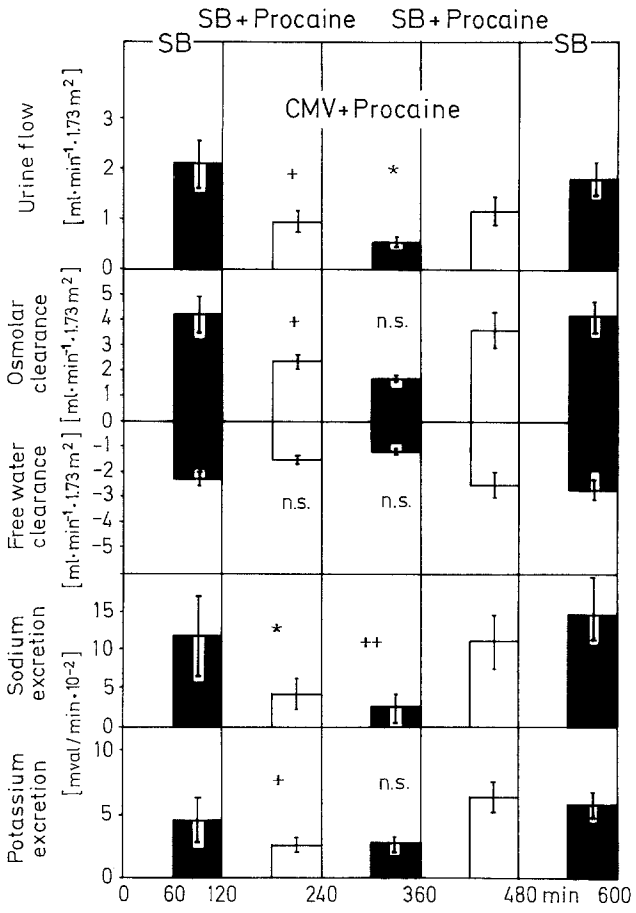

Fig. 1. Excretory renal function during spontaneous breathing and controlled mechanical ventilation in chloralose/urethrane anesthesized dogs ($n = 6$) with and without pericardial local anesthesia with procaine 2%. After the application of procaine into the pericardium a statistically significant decrease in urine flow, sodium and potassium excretion and osmolar clearance could be observed. Institution of controlled mechanical ventilation was accompanied by a further decrease of the above mentioned parameters except potassium excretion. During the following periods fo SB first with and later without cardiac denervation all parameters increased towards or exceeded the control values during the first period with SB. Statistical evaluations were made as described in the text. + $p<0.05$ SB + Procaine vs. spontaneous breathing (t-test for paired observations), ++ $p<0.05$ CMV + Procaine vs. spontaneous breathing + Procaine (t-test for paired observations), * $p<0.05$ SB + Procaine vs. spontaneous breathing (sign-test)

significant changes over the whole experiment (1st step of the analysis).

Only cardiac index ($p = 0.03$) showed a significant time trend (2nd step of the analysis). This trend could not be shown for the first three time points ($p = 0.26$, 3rd step of analysis).

Instillation of procaine 2% into the pericardium during spontaneous breathing was accompanied by statistically significant reductions in urine flow, sodium and potassium excretion, osmolar clearance as

Table 2. Renal and global hemodynamic measurements in chloralose/urethrane anesthetized dogs ($n = 6$) during spontaneous breathing with and without pericardial local anesthesia with procaine 2% and during controlled mechanical ventilation with pericardial local anesthesia

	SB	SB + Procaine 2%	p-values VS. SB	CMV + Procaine 2%	p-values VS. SB + Procaine 2%	SB + Procaine 2%	SB
Inulin-clearance (ml/min × 1.73 m^2)	251.6 ± 29.5	200.7 ± 16.8	0.059[c]	170.1 ± 12.4	0.039[a]	208.3 ± 8.5	251.1 ± 17.4
PAH-clearance (ml/min × 1.73 m^2)	806.7 ± 81.0	563.2 ± 80.5	0.003[a]	404.1 ± 42.3	0.023[b]	638.9 ± 93.5	780 ± 117.5
Heart frequency (Beats/min)	150.8 ± 3.1	126.5 ± 8.7	0.018[a]	119.2 ± 4.4	n.s.	133 ± 6.8	154.3 ± 3.3
Mean arterial pressure (mm Hg)	110.3 ± 6.4	121.7 ± 11.5	n.s.	115.8 ± 10.6	n.s.	114.2 ± 7.5	113.8 ± 5.8
Mean pulmonary artery pressure (mm Hg)	15.7 ± 1.7	18.0 ± 1.9	n.s.	25.5 ± 1.4	0.01[b]	20.5 ± 1.5	16.0 ± 0.8
Mean central venous pressure (cm H_2O)	6.25 ± 0.9	8.3 ± 1.4	n.s.	14.9 ± 1.7	0.003[b]	8.25 ± 1.4	5.75 ± 1.2
Cardiac index (l/min/lm^2)	3.56 ± 0.5	3.63 ± 0.5	n.s.	3.23 ± 0.4	n.s	4.24 ± 0.4	4.21 ± 0.4

[a] $p < 0.05$ SB + Procaine vs. spontaneous breathing (t-test for paired observations)
[b] $p < 0.05$ CMV + Procaine vs. SB + Procaine (t-test for paired observations)
[c] $p < 0.05$ SB + Procaine vs. spontaneous breathing (sign-test)

Table 3. Blood gas measurements in chloralose/urethrane anesthetized dogs ($n = 6$) during spontaneous breathing with and without pericardial local anesthesia and controlled mechanical ventilation with pericardial local anesthesia

	SB	SB + Procaine 2%		CMV + Procaine 2%		SB + Procaine 2%	SB
pO_2 (mm Hg)	87.63 ± 7.74	71.15 ± 4.94	0.016[a]	88.07 ± 6.8	0.033[b]	72.6 ± 6.04	82.67 ± 5.29
pCO_2 (mm Hg)	36.92 ± 1.52	40.53 ± 3.02	n.s.	37.17 ± 1.33	n.s.	38.83 ± 0.247	36.73 ± 0.9
pH	7.31 ± 0.016	7.27 ± 0.028	n.s.	7.24 ± 0.02	n.s.	7.30 ± 0.02	7.33 ± 0.18

[a] $p < 0.05$ SB + Procaine vs. spontaneous breathing
[b] $p < 0.05$ CMV + Procaine vs. SB + Procaine

well as glomerular filtration rate and renal plasma flow. The free water clearance did not change significantly. Global hemodynamics remained unchanged. Only heart rate decreased significantly (Fig. 1, Table 2).

Institution of CMV with PEEP of 10 cm H_2O led to a further depression of excretory function and renal haemodynamics. A statistically significant decrease of the above mentioned parameters could be substantiated (Fig. 1, Table 2).

These differences in renal function were not paralleled by similar changes in systemic hemodynamics. Only mean pulmonary artery and central venous pressure increased significantly after institution of CMV (Table 2).

During the succeeding periods of spontaneous breathing first with and later without cardiac denervation renal excretory function and hemodynamics improved as compared with the preceding CMV period. They reached or exceeded control levels during the first periods of SB with and without cardiac denervation.

Arterial oxygen tension (Table 3) was depressed during spontaneous breathing after instillation of procaine 2% into the pericardium, improved significantly during CMV, decreased again during the second period of SB with cardiac denervation and normalized in the last period of SB without cardiac denervation. Arterial carbon-dioxide tension hardly altered throughout the whole study.

Discussion

The principle findings of this study are (1) selective elimination of cardiac afferents by instillation of 2% procaine into the pericardium is followed by a statistically significant depression of renal hemodynamic and excretory function, that (2) institution of con-

trolled mechanical ventilation during local pericardial anesthesia is accompanied by a further significant decrease in renal excretory function and hemodynamics despite a blockade of cardiac afferents and (3) these changes in renal excretory function and hemodynamics are not paralleled by similar changes in global hemodynamics.

These findings are partly in accord with results of previous investigations that have tried to elucidate the role of cardiac afferents in mediating the renal response to increased positive airway pressure by cooling [24–28] or sectioning [9, 11, 23] the vagi. They failed to demonstrate that bilateral cervical vagotomy abolishes the effects of positive airway pressure on renal function and suggested that other reflex mechanisms such as sinoaortic baroreceptors may be involved or that a direct influence on the kidneys via decreased global hemodynamics does exist.

They, however, did not consider that only some 10% of vagal afferents are of cardiac origin [13, 19] and that cooling or sectioning the vagi eliminates other afferents [30] and may influence global hemodynamics as well as interactions between the different receptors.

This study investigated the selective role of cardiac afferents in mediating the renal response to positive airway pressure. The method chosen for selective and reversible denervation of cardiac afferents has been used by many authors [14–18] and has been fully discussed recently by Arndt et al. [19]. They have shown that instillation of procaine 1% (e.g. approximately 10 mg/kg) into the pericardium of cats blocks myelinated and non-myelinated cardiac afferents reliably and reversibly without affecting afferents coming from other sources and they concluded that pericardial local anesthesia eliminates the heart as a reflexogenic area.

To minimize the side effects of procaine in the pericardium, on muscle function, efferent nerves, and hormone production, only 10 ml procaine 2% (e.g. approximately 4 mg/kg) were instilled. In three dogs, the efficacy of this amount and concentration of procaine was tested in the manner described by Arndt et al. [19].

We found that the amount given blocked afferent nerve impulses completely and selectively in the three dogs and concluded that the results of Arndt et al. [19] in cats could be transferred to our experiments in dogs.

The decreases in urine flow, sodium and potassium excretion as well as inulin and PAH-clearance after application of procaine 2% into the pericardium observed in this study, highlight the importance of arterial and ventricular cardiac receptors in blood volume regulation as described by Gauer et al. [6] and Henry et al. [23] and later confirmed by others [17, 24–26]. However, the observation that during local intrapericardial blockade further depression of renal function occurs after institution of CMV, indicates that alterations in renal function caused by positive pressure ventilation are not solely governed by cardiac afferents.

The alterations of renal function in the dogs with denervated cardiac afferents, however, are quantitatively less pronounced than in dogs with intact hearts [21]. This is probably due to the generally reduced level of renal function during cardiac denervation.

It is important to point out that the clearly marked effects on renal function after denervation of the heart by instillation of procaine 2% into the pericardium were not accompanied by similar changes in global circulatory function during spontaneous breathing or later after institution of positive airway pressure.

Mean arterial pressure and cardiac index did not change significantly during the whole study. Heart rate decreased slightly after instillation of procaine and increased again after washing-out. This was interpreted as the consequence of simultaneously blocking efferent and afferent cardiac fibres [19].

The increase in pulmonary artery and central venous pressures during CMV is a reflection of the changes in mean intrathoracic pressure.

Blood gas analyses (Table 3) showed not significant changes in pH and pCO_2. Arterial oxygen tension fell after instillation of procaine 2% during spontaneous breathing and increased after institution of controlled mechanical ventilation with blockade of cardiac afferents, decreased again in the second period of spontaneous breathing with denervated cardiac afferents and reached control levels in the final period of SB without cardiac denervation. This fall of arterial pO_2 during the periods of SB with cardiac denervation can possibly be explained by a degree of paralysis of respiratory muscles caused by diffusion of local anesthetic through the pericardium.

In conclusion, our results show that cardiac afferents play an important role in the regulation of excretory function and hemodynamics of the kidneys, but a further deterioration of kidney function which is caused by shifts in airway pressure and hence intrathoracic pressure has to be attributed to other physiological mechanisms which cannot be defined from the results of this study.

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