FINAL REPORT

TITLE: ROLE OF ATRIAL RECEPTORS IN THE CONTROL OF SODIUM EXCRETION

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During the period of 1968-69, an attempt was made to determine whether the cardiac receptors produced a redistribution of intrarenal blood flow. The method of choice was a silicone perfusion technique developed by Dr. Sidney S. Sobin, Department of Physiology and elegantly used by Dr. Barger of Harvard University. Barger and his co-workers had presented evidence that the renal nerves are influential in redistributing blood flow from the cortical to the medullary circulation which might account for significant sodium retention. Both the krypton wash-out technique and silicone casting technique were used to demonstrate this redistribution phenomena.

Stimulation of the cardiac receptors by positive and negative pressure breathing failed to elicit a cast pattern similar to that obtained by Barger and co-workers. Further, there were no significant differences in the casted patterns of innervated or contralateral denervated kidneys (Fig. 1). Then several attempts were made to confirm Barger's observations that direct renal nerve stimulation produced the phenomena. We were unable to reproduce the Barger pattern (Fig. 2). After a relatively long period of failure to elicit patterns comparable to those published by Dr. Barger and co-workers, it became evident that the technique of silicone casting differed. Following in-situ renal nerve stimulation, Dr. Barger and colleagues removed the kidneys from the body, interrupted blood flow, cannulated the renal artery and then perfused the silicone casting material. Dr. Sobin's technique used in our studies consisted of cannulating the abdominal aorta and inferior vena cava with polyethylene T tubes without interrupting flow to the kidneys. After a stabilization period, flow was interrupted and silicone casting fluid was perfused instantaneously at physiologic pressures.

A siginficant effort was made, following the recognition of the differences in technique, to evaluate whether these techniques of and by themselves could account for the differences in findings. The technique consisted of perfusing one kidney in-situ (Sobin technique) following the excision of the contralateral kidney for subsequent perfusion outside the body (Barger technique). The silicone perfusion pattern in the excised kidney resembled those presented by Barger and colleagues, and could quite readily be interpreted as demonstrating redistribtuion, while the in situ kidney showed no evidence of a redistributed pattern (Fig. 3). The pattern in the in situ perfused kidney was consistent with all our previous work. It was concluded from these studies that the redistributed pattern of renal blood flow as previously demonstrated by the silicone casting technique was probably artifactual. This work was presented in abstract form at the Federation Proceeding Meetings of 1969 in Chicago. (Abstract is enclosed).

During the period of 1970-71, an extensive effort was made to determine whether the atrial receptors had a pronounced influence on sodium excretion and by what efferent pathways were these receptors affecting renal function. The studies consisted of comparing the response in an innervated to the contralateral chronically denervated kidney to mild positive pressure breathing (PPB) in the saline volume expanded chloralose anesthetized dogs. In the absence of significant changes in arterial pulse pressure or blood gases which exclude any influence of the chemo-receptors and high-pressure baroreceptors, mild positive pressure breathing significantly reduced sodium excretion, urine flow, free-water clearance, and paraminohippuric acid (PAH) clearance. The response in the normal kidney was more rapid and more marked than that in the contra-lateral denervated kidney when positive pressure breathing was induced. Small but insignificant changes in glomerular filtration rate (GFR) as measured by

creatinine clearance were also in evidence. The reduction in GFR could not account for the changes in urine flow and sodium excretion as fractional urine flow and fractional sodium excretion were as significantly depressed as normal sodium excretion and urine flow (Figs. 4 and 5). After twenty minutes of positive pressure breathing, the response in the denervated kidney was identical to that in the innervated kidney suggesting that the procedure of increasing end expiratory airway pressure (ave. 13.5 cm H_2O) caused the release of some humoral agent (natriuretic hormone) which will reduce renal function in addition to the demonstrated change in renal nerve activity. Thus at lease three efferent mechanisms are involved in the atrial "volume" receptor effects on renal function: antidiuretic hormone (ADH), renal nerve activity and possibly natriuretic hormone which results in the maintenance of plasma volume. This work was presented in abstract form at the Federation Proceedings Meetings in 1969 in Chicago. Further, a preliminary report of this work has been published in Research in Experimental Medicine, Vol. 157 (1972). Copies of both the abstract and the article are enclosed. A manuscript is also in preparation.

The specific contribution of the left atrial receptors to the antinatiuretic effect of PPB was also examined. In order to evaluate the contribution, a chronically implantable balloon device was developed (Fig. 6). The device consists of an external silastic tube 1/4 inch in diameter and a size 14 (Fr) Foley urinary retention catheter with a 5 cc retention balloon. Two dacron felt stainless steel sleeves are placed over the silastic tube, one is glued at the end which is to be inserted into the atrial appendage. The other is positioned at the point of rib closure to prevent pinching of the outer tube.
The Foley catheter is inserted into this previously prepared tube. The device is then sutured into the atrial appendage which has been exposed through the fourth intercostal space in the pentobarbitol anesthetized dog. Following recovery of the animal, experiments were carried out in chloralose anesthetized dogs.

The effectiveness of the device in increasing left atrial pressure, heart rate and urine flow was tested and the response compared to the published reports of others. It was found that our results compared favorably. We observed an increase in heart rate, and urine flow with changes in arterial pressure (Figs. 7 and 8).

The contribution of the left atrial receptors to the PPB antinatiuresis was then examined. It was found that if left atrial pressure was increased with balloon obstruction of the mitral orifice during the PPB episodes, urine flow, sodium excretion and PAH clearance increased. When the balloon was deflated and PPB maintained, renal function was again depressed. The magnitude of the reversal in kidney function indicates that the discharge from more than one set of receptors within the thorax capable of affecting renal function is altered by PPB (Fig.9).

Further, efforts were made to identify what these additional receptors might be. Very preliminary evidence was obtained which indicates that receptors in the right atrium are more severely affected by PPB than those in the left atrium. The PPB depression in firing rate from left atrial receptors was 33% of control, while the right atrial receptors had about a 60% in their firing rate. The quantitative difference in the response of these two receptor regions accounts for the inability to completely reverse the renal response to PPB with left atrial balloon inflation. In addition, the senitivity of the atrial receptors was re-examined. It was found that the B type receptors of Paintal decrease their firing with as little as a 1% reduction in total blood volume.

LEGENDS

Figure 1. Effect of negative pressure breathing on the silicone cast pattern of the renal vascular system. *

Figure 2. Effect of renal nerve stimulation on the silicone filling of the renal vascular system. *

Figure 3. Effect of excision on the silicone rubber filling of the renal vascular system. *

Figure 4. Fractional urine flow (UV/C_{creat}) during 15 minutes of positive pressure breathing. At 13 cm H_2O mean tracheal airway pressure. Dark bars are the innervated kidneys and the white are the contralateral denervated kidneys.

Figure 5. Fractional sodium excretion (C_{Na}/C_{cr}) during 15 minutes of positive pressure breathing at 13 cm H_2O mean tracheal airway pressure. Dark bars are the innervated kidneys and the white are the contralateral denervated kidneys.

Figure 6. Balloon device implanted into the left atrium.

Figure 7. Effect of balloon inflation in the left atrium on mean aortic pressure (MAoP), left atrial pressure (LAP) and heart rate.

Figure 8. Effect of balloon inflation on urinary parameters. UV = urine volume, GFR = creatinine clearance, C_{PAH} = clearance of para-aminohippuric acid, C_{H_2O} = free water clearance, and $U_{Na}V$ = sodium excretion.

Figure 9. Effect of balloon inflation during positive pressure breathing (CPB) on urinary parameters.

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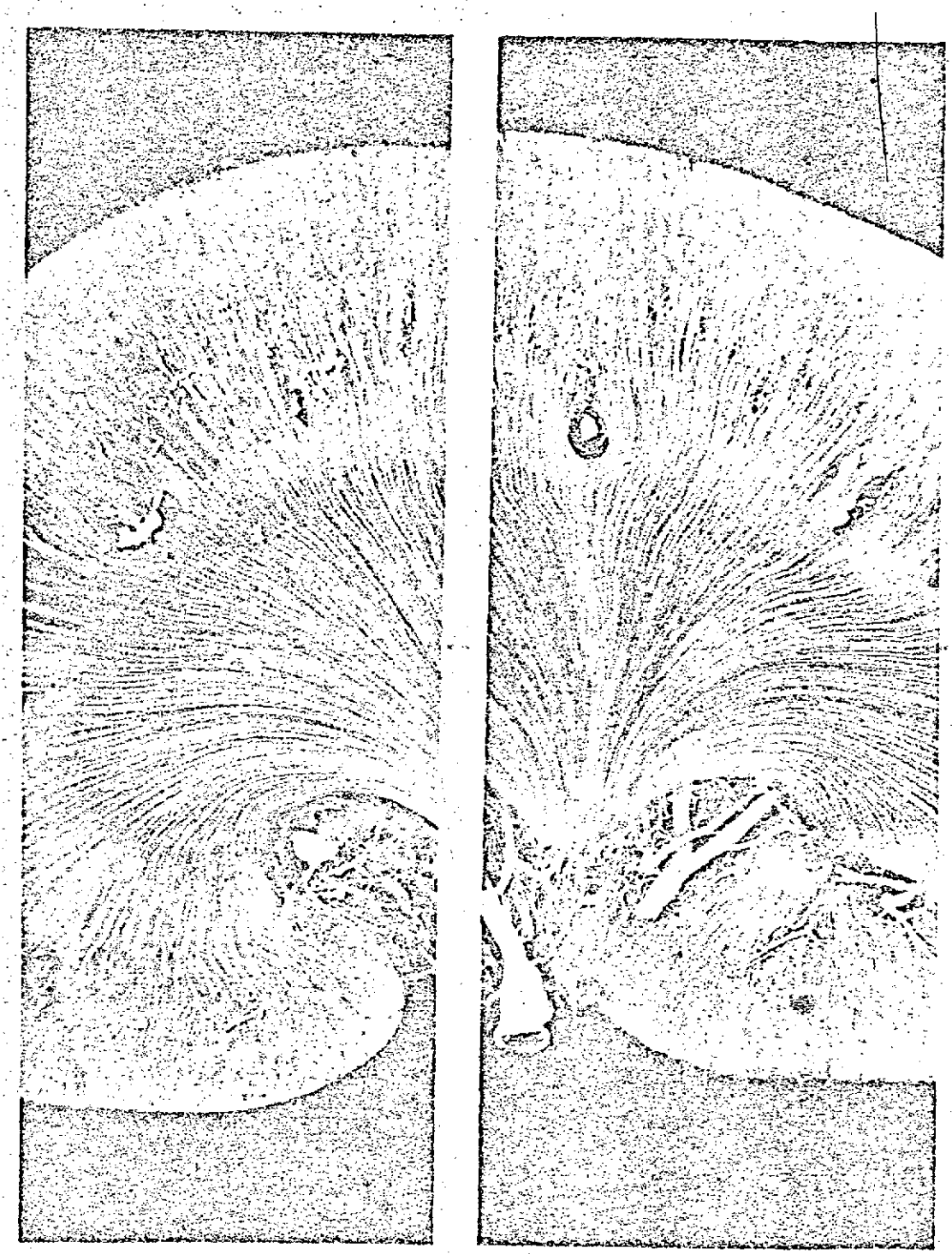
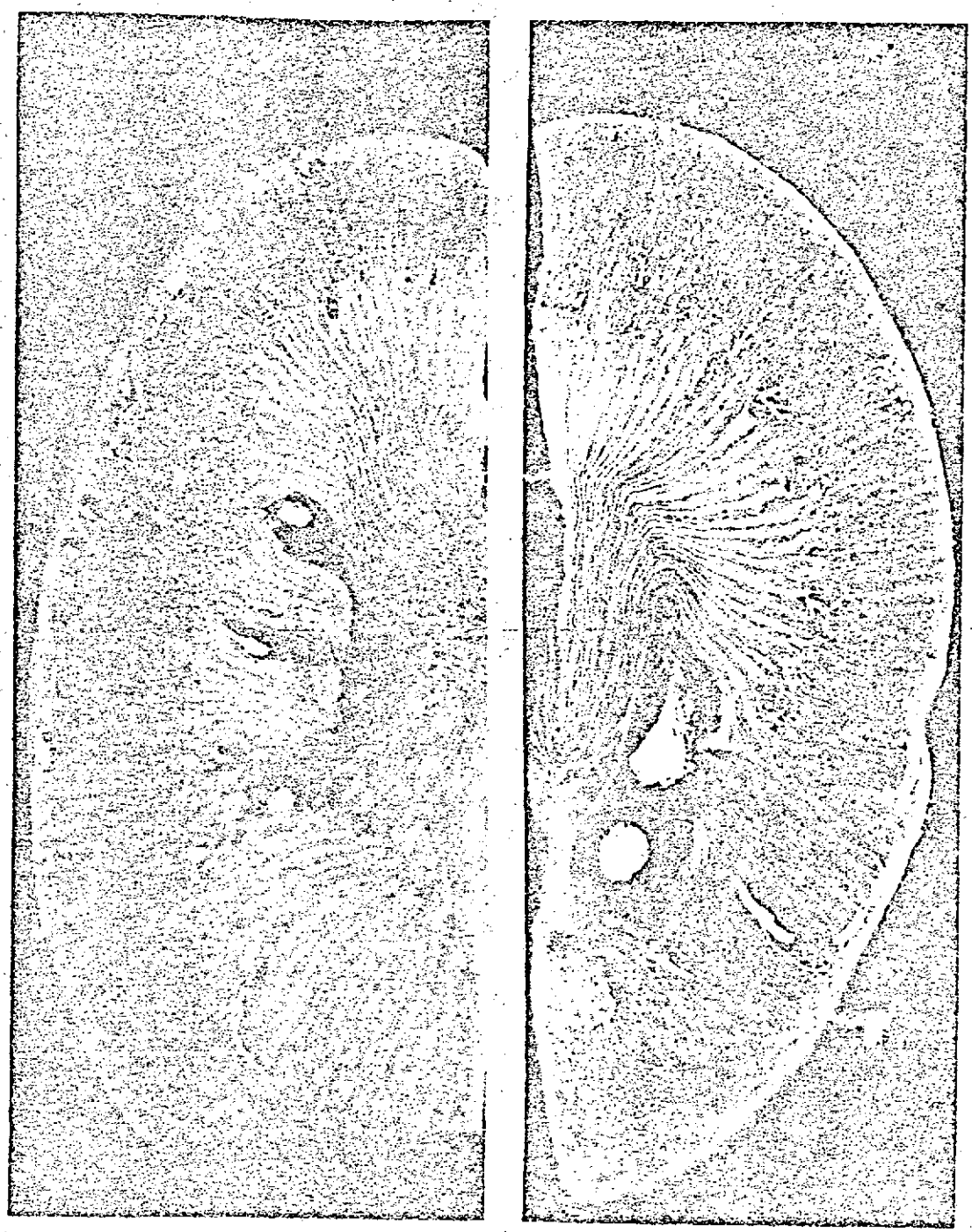
* The light areas are the silicone rubber.



Innervated

Denervated

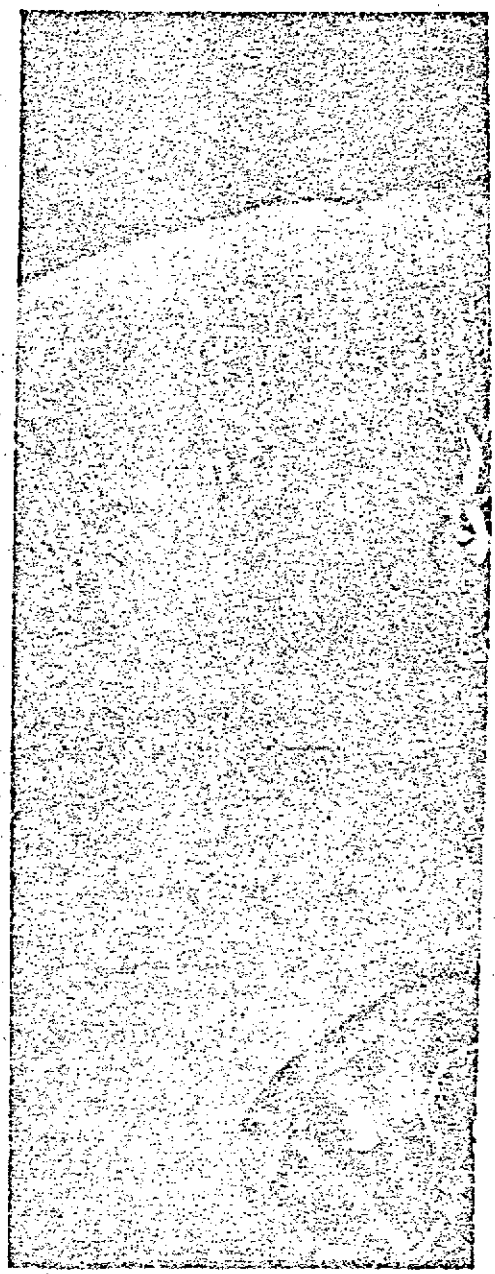
Fig 1



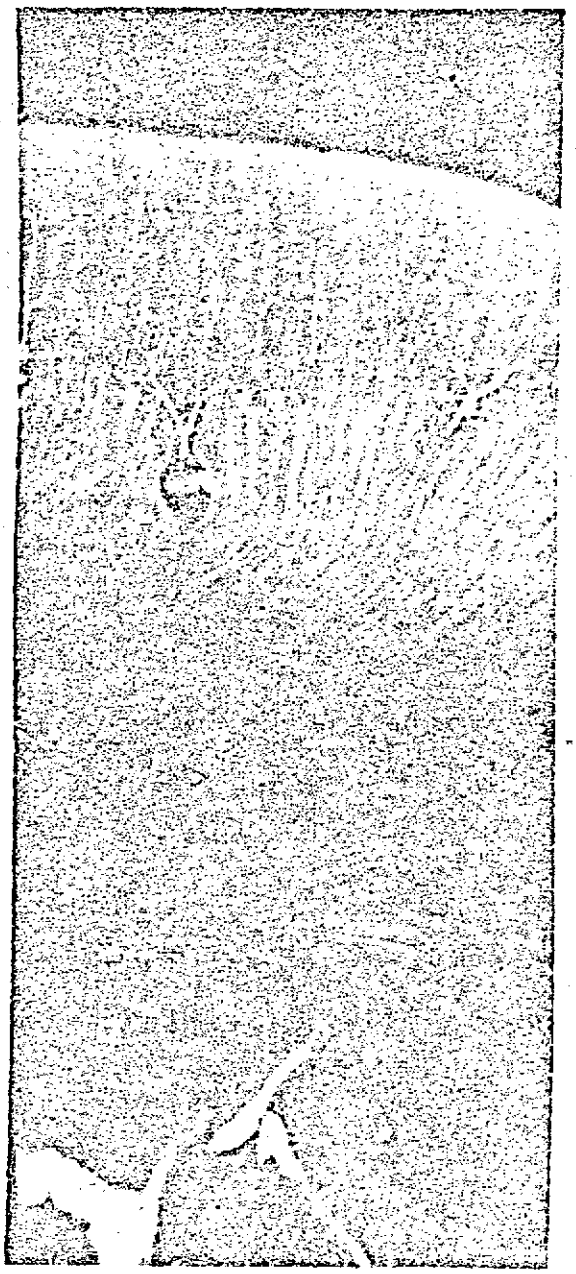
Denervated

Stimulated

Fig 2



Excised



In situ

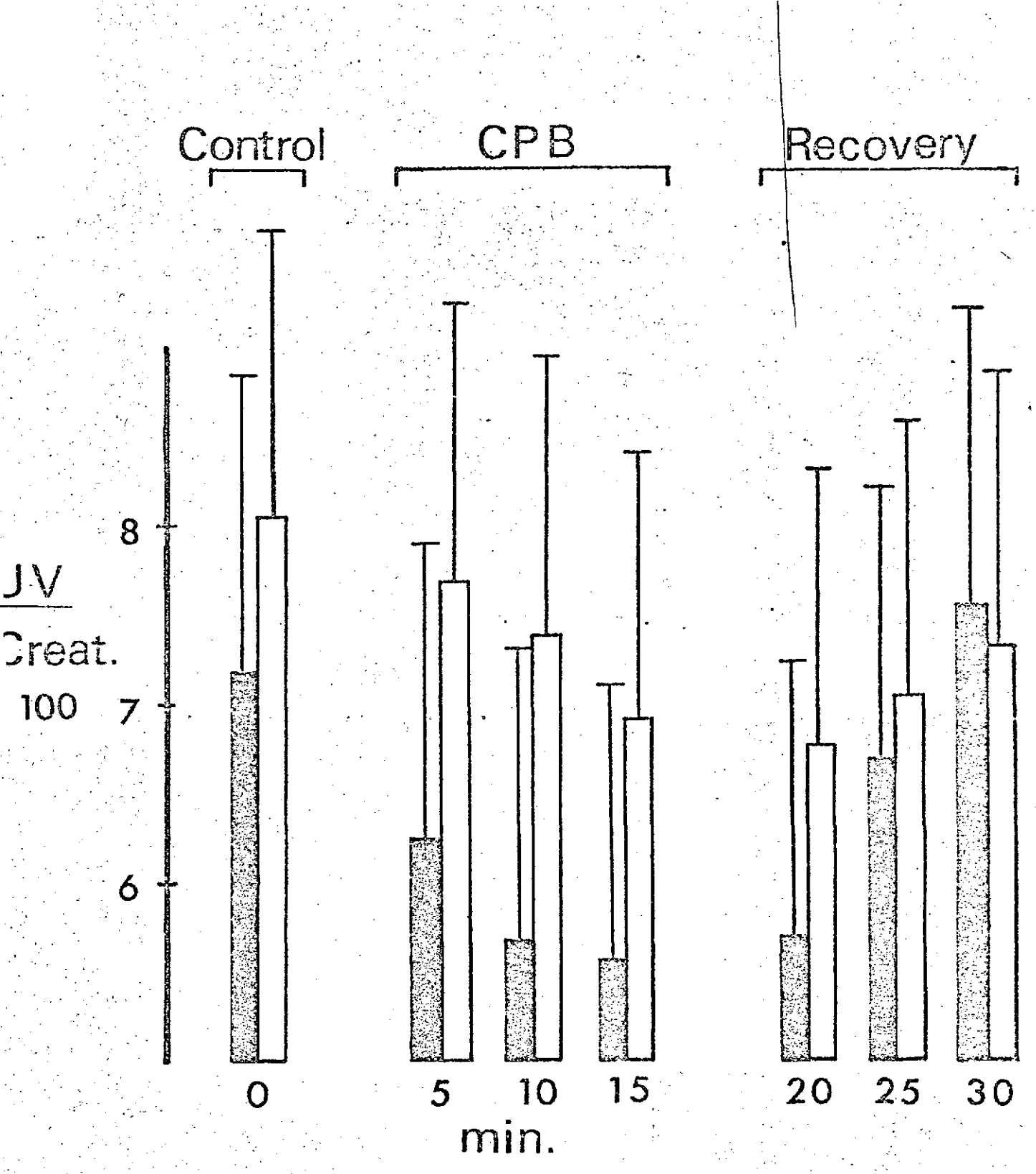
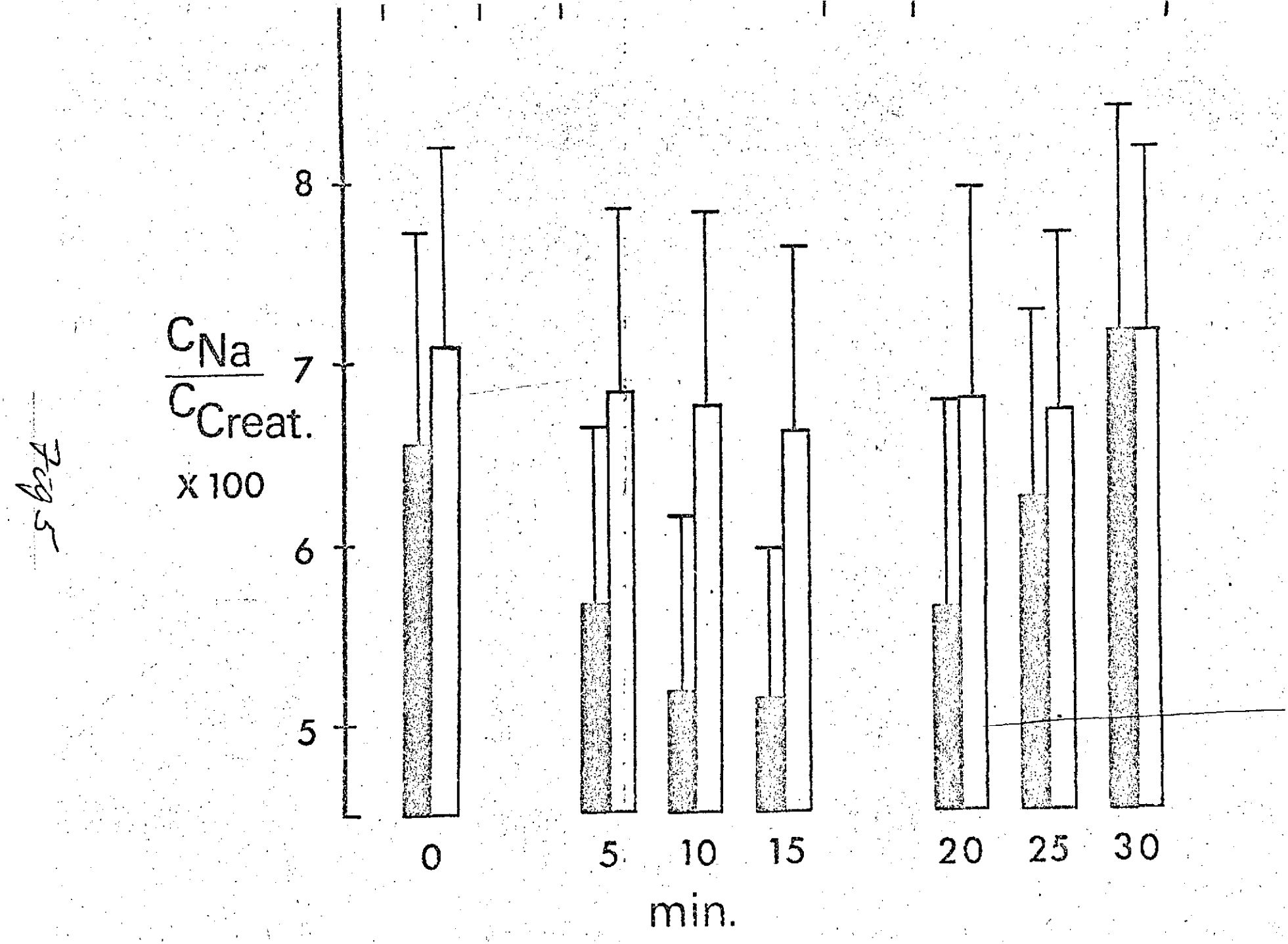
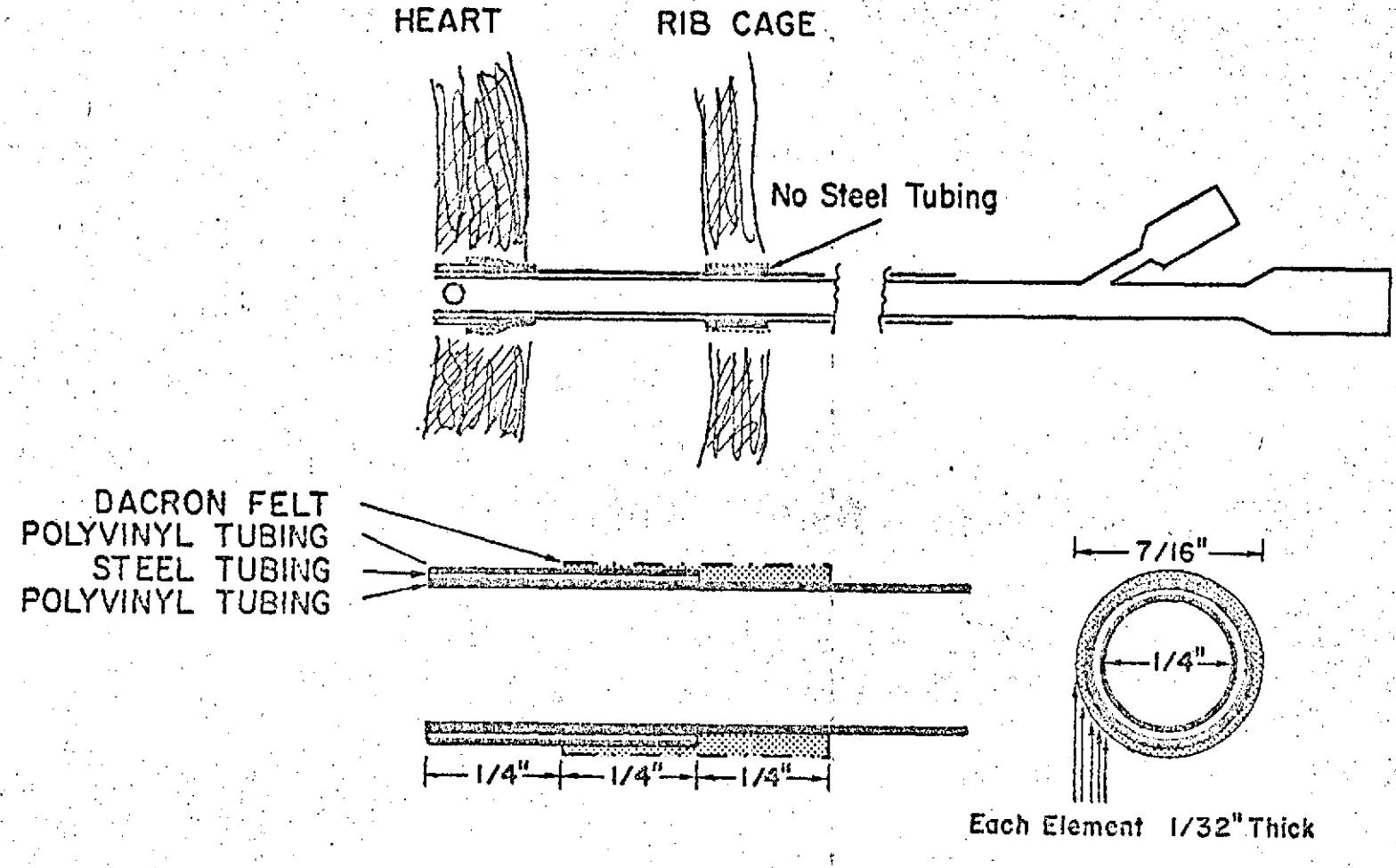
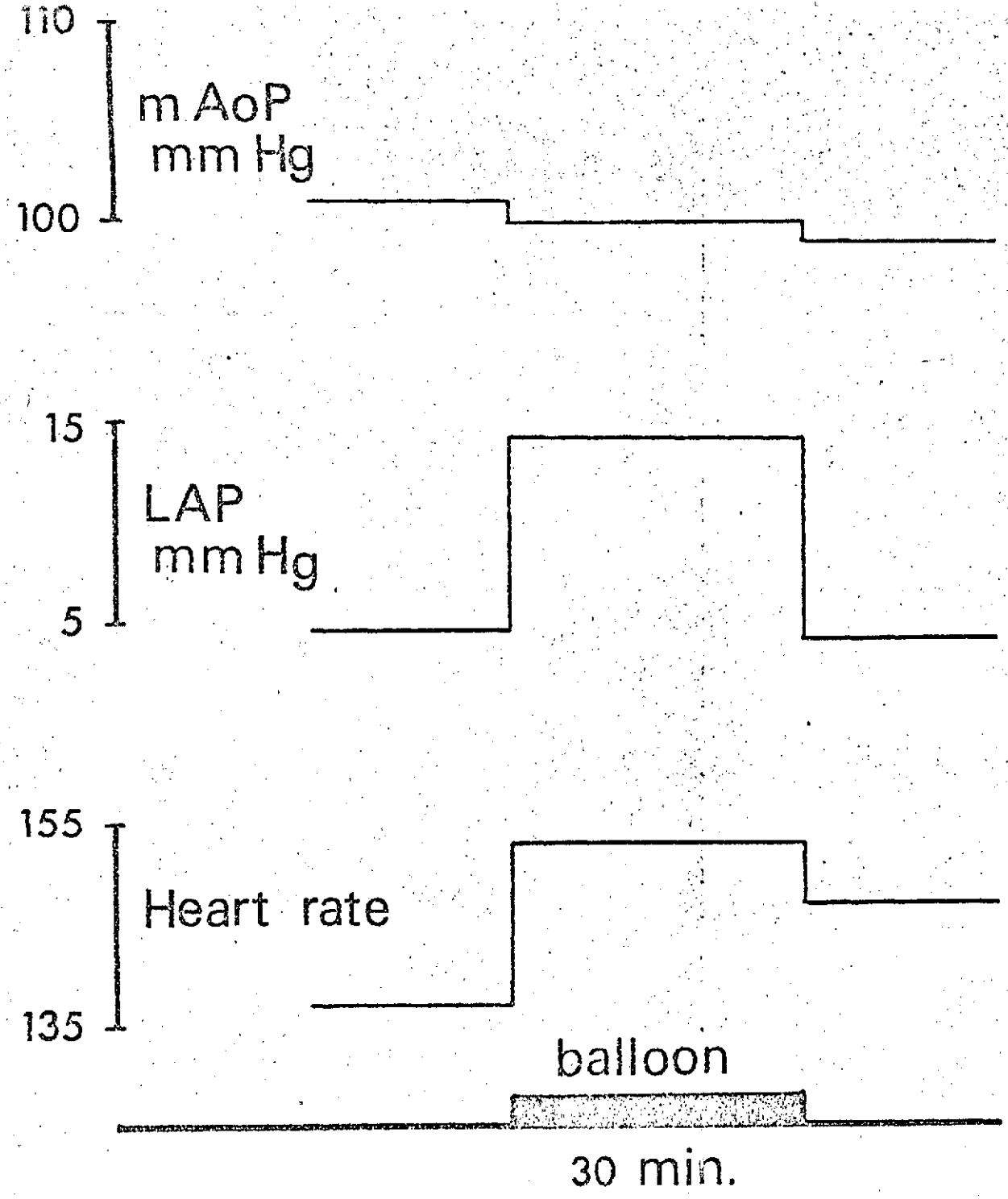


Fig 4


$\frac{C_{Na}}{C_{Creat.}}$ x 100
8
7
6
5
0
5
10
15
20
25
30
min.


HEART
RIB CAGE
No Steel Tubing
DACRON FELT
POLYVINYL TUBING
STEEL TUBING
POLYVINYL TUBING
1/4"
1/4"
1/4"
7/16"
1/4"
Each Element 1/32" Thick


110
m AoP
mm Hg
100
15
LAP
mm Hg
5
155
Heart rate
135
balloon
30 min.

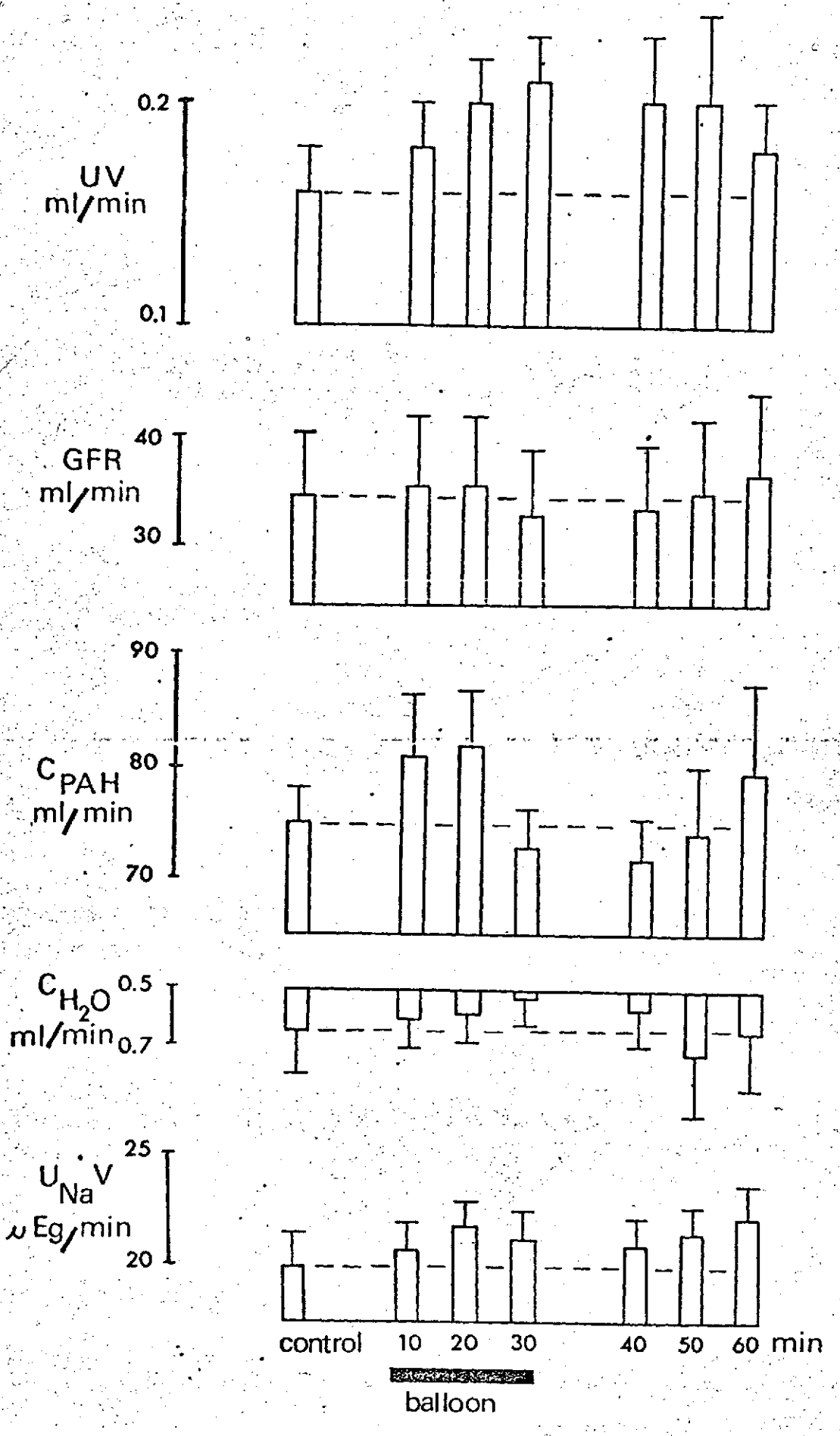
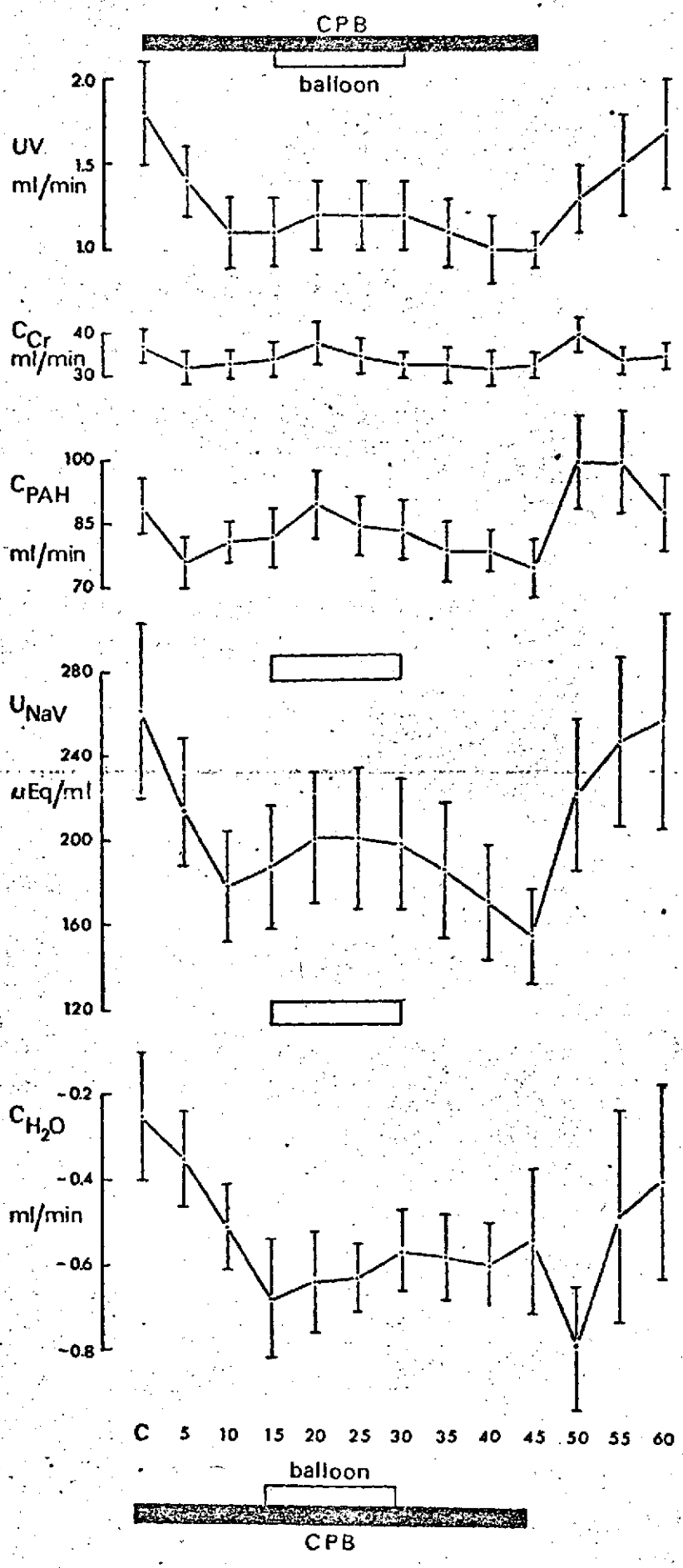

0.2
UV
ml/min
0.1
40
GFR
ml/min
30
90
80
C_{PAH}
ml/min
70
C_{H_2O}
0.5
ml/min
0.7
25
$U_{Na}V$
μEq/min
20
control
10
20
30
40
50
60
min
balloon

Fig 8


CPB
balloon
2.0
UV
1.5
ml/min
1.0
C_{Cr} 40
ml/min 30
100
C_{PAH}
85
ml/min
70
280
U_{NaV}
240
μEq/ml
200
160
120
-0.2
C_{H_2O}
-0.4
ml/min
-0.6
-0.8
C 5 10 15 20 25 30 35 40 45 50 55 60
balloon
CPB

CRITIQUE OF RENAL SILICONE ELASTOMER PERFUSION. L.W.Chapman*, H.M.Tremer, S.S.Sobin. Univ. of So. Calif. School of Med., Dept. of Physiol., Los Angeles, Calif. 90033.

Change in the functional state of the microcirculation within an organ may be demonstrated by intravascular "physiologic" perfusion of silicone elastomers under controlled experimental conditions which include an undisturbed circulation until the moment of perfusion. These techniques were developed in this laboratory (14th Conference, this Society, Fed. Proc. 25:1749, 1966). Others have recently studied the renal microcirculation using silicone materials in which perfusion was carried out in situ after death or ex vivo after removal from the physiological stimulus. Our insistence on circulatory integrity was based solely on physiologic considerations, and experimental proof was obtained by comparing in five dogs the filling pattern of in situ perfused and excised ex vivo perfused pairs of kidneys exposed to the same neurogenic stimulus elicited by bilateral carotid artery clamping. The time between clamping and perfusion was 4 and 10 min. in 2 groups of animals in the ex vivo preparation. The pattern of the in situ perfused kidney was severely diminished and chiefly confined to the cortico-medullary junction when compared with the ex vivo kidney where the cortex and medulla were more densely filled. It is concluded that microvascular filling during silicone elastomer perfusion and a physiological stimulus is markedly altered by removal of the kidney from the stimulus prior to perfusion. Supported by L.A. County Heart Assoc. Grant #218 and N.I.H. Grant #HE-11152.

2305 Physiology

NEURAL EFFECT OF CARDIAC RECEPTORS ON RENAL SALT EXCRETION. L.W.Chapman,* U.Mittmann* and J.P.Meehan, Univ. of So. Calif. Sch. of Med., Los Angeles, California 90033.

The contribution of cardiac receptors on the renal response to isotonic saline expansion of the extracellular space has been studied. Normal and denervated kidneys of seven dogs under chloralose anesthesia (150 mg/kg) were compared to determine a neural involvement which has been denied (Carswell, et al, Q.J.Exp.Physiol. 1970). Following I.V. saline expansion (12 ml/min), inhibition of the cardiac receptors by specific reduction of thoracic blood volume was accomplished by positive pressure breathing (PPB) (5-15 cm H_2O end expir. press.) for 50 min. In addition to PPB the left atrium was distended for 20 min. by a chronically implanted left atrial balloon 15 min. after onset of PPB. Aortic pressure, arterial pH, pO_2, pCO_2, remained unchanged throughout the entire experiment. PPB caused an immediate drop in urine flow, Na & K excretion (20% in 5 min) with a 12% reduction of C-PAH in 5 min by the innervated kidney while no change of these parameters occurred in the denervated kidney at 5 min. Creatinine clearance remained unchanged. Inflation of the balloon interrupted the drop in urine flow and salt excretion suggesting that receptors in the left atrium mediate changes in sodium excretion in the presence of high circulating levels of ADH as indicated by the decreased free water clearance. The immediate response and difference between innervated and denervated kidneys suggest that cardiac receptors affect renal function by neural pathways. Supported by A.F.Contract #53-5137-1736, L.A.Co.Ht.Assn.#218,NIH-#HE11152.

FED PROC 1971

Neuraler Einfluß von Mechanoreceptoren des Herzens auf die renale Salzausscheidung

Neural Influence of Cardiac Mechanoreceptors on the Renal Salt Excretion

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Die Lage von Dehnungsreceptoren im Niederdrucksystem des Kreislaufs, besonders in der dorsalen Wand der Vorhöfe und an der Mündung der großen Venen in die Vorhöfe [6, 7], ließ vermuten, daß sie Information über den Füllungszustand des venösen Systems an das ZNS vermitteln. Gauer u. Henry [2] wiesen nach, daß eine veränderte Dehnung des linken Vorhofs das extracelluläre Flüssigkeitsvolumen über die Sekretion von Adiuretin beeinflußt. Ein funktioneller Zusammenhang von kardialen Dehnungsreceptoren mit der renalen Natriumausscheidung blieb umstritten, zumal es bei pathologisch erhöhtem intrathorakalem Blutvolumen (ITV) in der Herzinsuffizienz zu einer Natriumretention und nicht, wie nach der Receptortheorie zu erwarten, zu einer Natriurese kommt.

In unseren Versuchen sollte geklärt werden, welchen Einfluß eine verminderte Dehnung der kardialen Mechanoreceptoren auf die renale Natriumausscheidung hat, wenn eine Beeinflussung der Nierenfunktion durch veränderten Perfusionsdruck oder arterielle Baro- und Chemoreceptoren ausgeschlossen wird. Der mögliche Einfluß des Nierensympathicus auf die Nierenfunktion sollte durch einen Vergleich von innervierter (IN) und denervierter Niere (DN) untersucht werden.

Methodik. Kontinuierliche Überdruckbeatmung (PPB) gilt als geeignete Methode, um das ITV und damit die Dehnung kardialer Mechanoreceptoren zu vermindern [5]. Die Versuche wurden an 18 gemischtrassigen, weiblichen Hunden, deren linke Niere 1 Woche vor dem Versuch denerviert worden war, in Chloralosenarkose (100—120 mg/kg) durchgeführt. Die Tiere (20,5 kg) wurden 1 Std lang mit gepufferter Na-Bicarbonat-Kochsalzlösung vorhydriert (12 ml/min; pH 7,45; 38°C; 300 mosm/l). Danach wurde die Infusionsgeschwindigkeit dem Harnzeitvolumen (UV) angeglichen. Bei konstantem UV wurden die Hunde intubiert und 15 min lang mit Überdrucken von 20—30 cm H_2O inspiratorisch und 5—15 cm H_2O exspiratorisch beatmet (Harvard Respirator).

Ex wurden die Drucke in der Aorta, Vena iliaca und im rechten und linken Vorhof mit Stathamelementen und der Fluß in einer Arteria femoralis elektromagnetisch gemessen und auf einem Direktschreiber fortlaufend registriert (Brush Instr. Div.) Arterielles pH, pO_2 und pCO_2 wurden mit Radiometer-Elektroden gemessen.

UV, Kreatinin (C_{Kr}) und Paraaminohippursäure-Clearance (C_{PAH}) und Harn-Natrium-Konzentration (Flammenphotometer) wurden in Abständen von 5 min getrennt für IN und DN gemessen (Technicon Autoanalyzer). Unterschiede zwischen der Kontrollperiode und der Beatmungsperiode und zwischen IN und DN wurden mit Varianzanalysen geprüft [8].

Res exp Med 157, 177–179 1972

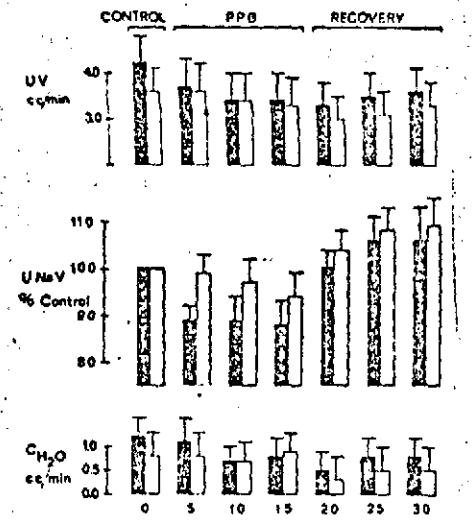

Abb. 1. Harnzeitvolumen (*UV*). Natriumausscheidung (*UNaV*) und Freiwasser-Clearance während 15 min Überdruckbeatmung (*PPB*) mit 9 cm H_2O in innervierten (schwarze Säulen) und denervierten Nieren (weiße Säulen) von 18 Hunden. UV und UNaV sind in den innervierten Nieren bereits nach 5 min PPB signifikant verringert. Eine Verminderung in den denervierten Nieren ist signifikant geringer und zeitlich verzögert

Ergebnisse. Während 15 min PPB (9 cm H_2O mittlerer Trachealdruck) waren arterielles pH, pO_2 und pCO_2 nicht signifikant verändert. Systolischer und diastolischer Aortendruck blieben ebenfalls unverändert, so daß eine Beeinflussung der Nierenfunktion durch arterielle Baro- und Chemorezeptoren unwahrscheinlich war. Die Drucke im rechten und linken Vorhof und in der Vena iliaca stiegen um etwa 2 mm Hg. Die Herzfrequenz stieg von 119 auf 138 Schläge/min an.

Bereits nach 5 min PPB fiel das UV in der IN von 4,2 ± 0,6 ml/min auf 3,7 ± 0,6 ml/min ab, während es in der DN unverändert blieb ($p < 0{,}05$). Nach 15 min PPB war das UV in der IN um 20% und in der DN um 11% vermindert. Der Unterschied zwischen IN und DN war nicht mehr signifikant (Abb. 1).

Ähnlich wie das UV fiel die Natriumausscheidung in der IN bereits nach 5 min PPB um 11% ab, während sie in der DN erst nach 15 min signifikant erniedrigt war. Die Freiwasser-Clearance war in IN und DN nach 10 min PPB erniedrigt und erreichte 5 min nach Beendigung der PPB ein Minimum (42 bzw. 38% des Kontrollwerts).

Die C_{Kr} war in IN und DN während der PPB nicht signifikant verändert. In den ersten 5 min der Beatmungsperiode fiel C_{PAH} in der IN signifikant steiler ab als in der DN. Nach 15 min PPB war der Unterschied nicht mehr signifikant.

Diskussion. Die Impulsfrequenz von Afferenzen der Dehnungsrezeptoren des linken Vorhofs ist der Impulsfrequenz des efferenten kardialen Sympathicus umgekehrt proportional [3]. Der Anstieg der Herzfrequenz in unseren Experimenten mit verminderter Dehnung der Vorhöfe mag auf diesen kardio-kardialen Reflex zurückzuführen sein.

Kürzlich beschrieb Karim [4] eine verminderte Impulsfrequenz des Nierensympathicus bei erhöhter Dehnung des linken Vorhofs. In unseren Versuchen ist bei verminderter Dehnung von Herzvorhöfen und großen intrathorakalen Venen entsprechend mit einer erhöhten Impulsfrequenz des Nierensympathicus zu rechnen. Es kam zu einer raschen Verminderung der Natriumausscheidung in der IN und zu einer signifikant geringeren und zeitlich verzögerten Reaktion in der DN. Die rasche und stärkere Verminderung der C_{PAH} in der IN ist ein Hinweis dafür, daß der renale Sympathicus die Natriumrückresorption durch eine verringerte Nierenrindendurchblutung beeinflußt hat.

Die zeitlich verzögerte Verminderung der Freiwasser-Clearance in IN und DN und der Natriumausscheidung in der DN legt jedoch in Übereinstimmung mit Arbeiten anderer Autoren eine Beteiligung von Adiuretin [5] und anderen hormonalen Faktoren [1] nahe.

In unseren Experimenten mit akuter Verminderung des ITV beschleunigte der Nierensympathicus offenbar die Depression der Nierenfunktion, ohne jedoch für den Reaktionsablauf verantwortlich zu sein.

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