

# Renin Response to Stimulation of Cardiopulmonary Mechanoreceptors in Man

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**ABSTRACT** Plasma renin activity (renin) and hemodynamic response to venous pooling of blood in legs were studied in 24 healthy volunteers and four patients who after bilateral nephrectomy received a functioning renal transplant. Blood pressure cuffs were placed around subjects' thighs and inflated at a pressure 5 mm Hg below the individuals' diastolic pressures. 30 min after thigh cuff inflation, renin significantly increased in all volunteers (mean = 125%). Inflation of cuffs induced a decrease of right atrial pressure, cardiopulmonary blood volume, and cardiac output, but there were no changes in the intra-arterial systolic and diastolic pressure or in the pressure amplitude. After cuffs were deflated, renin and hemodynamic parameters returned toward normal.

In nine volunteers in whom thigh cuff inflation initially elicited renin increases, subsequent intravenous propranolol (0.25 mg/kg) abolished the response to repeated cuff inflation. The renin increase to thigh cuff inflation was absent or suppressed in four patients with a recently transplanted denervated kidney.

It is concluded that thigh cuff inflation elicited a reflex-mediated renin increase, and that the reflex stemmed from stimulation of cardiopulmonary mechanoreceptors.

## INTRODUCTION

There is a large body of evidence about the existence and physiologic role of cardiopulmonary mechanoreceptors (1, 2). Stimulation of these receptors causes a general withdrawal of the sympathetic outflow, but the effect on renal sympathetic tone is most pronounced (3-5). It has been shown that cardiopulmonary receptors mediate renin release in animals (6-9).

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Whereas it is known that in human beings, cardiopulmonary receptors respond to physiologic stimulation (10, 11), the role of these receptors in the regulation of the renin release remains questionable. In one report on stimulation of low pressure receptors in humans, plasma renin increased (12), whereas in another report (13) such an increase was not observed. Both studies investigated small groups and used low degrees of lower body negative pressure as a means of decreasing right atrial pressure without effecting changes in arterial pressure.

We decided to investigate the relationship of cardiopulmonary mechanoreceptors and the renin release in a large number of subjects using a technique of impeding venous return to the heart, which unlike lower body negative pressure, does not change the intra-abdominal pressure. Our results with leg tourniquet inflation suggest that stimulation of cardiopulmonary mechanoreceptors causes significant changes in plasma renin activity levels.

## METHODS

All studies were initiated at 8 a.m. in ambulatory subjects.

*Volunteers.* Studies were initiated in 27 healthy male volunteers (ages, 18-42) but could be completed only in 24 subjects. Three subjects developed early bradycardia and hypotension necessitating discontinuation of the procedure.

All subjects were resting in recumbency. One set of three interconnected pediatric blood pressure cuffs was wrapped high around each thigh. After 60 min of rest, the cuffs were inflated at a pressure 5 mm Hg below the subject's diastolic blood pressure and the inflation was maintained for 30 min. Plasma renin activity (henceforth called renin) and the hemodynamic measurements were taken after 60 min of rest and after 30 min of cuff inflation. An additional early hemodynamic measurement 5 min after cuff inflation was taken in all subjects. This basic protocol was altered in the following manner. In 11 of 24 subjects, renin and hemodynamic measurements were also taken 30 min after cuff deflation. In 9 of 24 subjects, renin was measured also at 10 and 20 min of cuff inflation to determine the time-course of the renin response. Finally, a pediatric cuff was placed around the ankle and inflated for 10 min in 7 of 24 subjects to obtain "sham" renin values.

9 of 24 subjects were chosen for additional studies with propranolol. After the basic protocol was completed and the thigh cuffs were deflated, they received intravenous propranolol (0.2 mg/kg). A booster dose (0.05 mg/kg) was given 30 min later. 40 min after the initial dose, renin and hemodynamic measurements were repeated, the cuffs inflated again and 30 min later a final set of measurements was taken.

**Patients.** One male and three female patients, who after bilateral nephrectomy, received a functioning renal transplant, were investigated. Details of their histories are given later (Fig. 4). Like control subjects, they rested for 60 min and then thigh cuffs were inflated for 30 min. Renin measurements at rest and after inflation were obtained, but systemic hemodynamic measurements were not done. Blood pressures in these patients were determined by a standard cuff and heart rates from electrocardiographic tracings. One patient was studied twice on different days.

In all four patients, on separate occasions, plasma renin response to isoproterenol infusion was investigated. After 60 min resting in recumbency, 30 ng/kg per min of isoproterenol was infused. Renin was measured at rest and after 20 min of isoproterenol infusion.

Renin was measured by radioimmunoassay of generated angiotensin I (14) after a 60-min incubation period at a pH of 6.0. All samples from any one subject were measured in a single assay run.

Cardiac output was measured by dye dilution (Cardiogreen, Hynson, Westcott and Dunning, Inc., Baltimore, Md.; Gilford densitometer, Gilford Instrument Laboratories Inc., Oberlin, Ohio; Hewlett-Packard 4578 polygraph, Hewlett-Packard Co., Palo Alto, Calif.). Details of the procedure used in our laboratory can be found in earlier publications (15, 16). In short, a 4-F caliber Swan-Ganz catheter (Edwards Laboratories, Inc., Santa Ana, Calif.) was introduced into an antecubital vein and floated to the right atrium. A 2½-inch long catheter of an 18-gauge long dwell needle (Becton, Dickinson & Co., Rutherford, N.J.) was placed in one brachial artery. Statham strain gauges (Statham Instruments, Inc., Oxnard, Calif.) for recording of right atrial (P23BB) and arterial (P23Db) pressure were placed at midaxillary level in the fourth intercostal space.

Duplicate determinations of all hemodynamic measurements were made at each point of observation and the values were averaged.

Serum epinephrine and norepinephrine concentrations were measured before and 7 min after inflation of thigh cuffs in 13 subjects and two renal transplant patients. In our laboratory a modification of the single-isotope radioenzymatic method of Passon and Peuler (17) was used. The lower limit of sensitivity<sup>1</sup> is 10 and 5 ng/liter of serum for norepinephrine and epinephrine, respectively. All measurements were carried out in duplicate and the results averaged.

Forearm blood flow was determined by venous occlusion plethysmography and a mercury in silastic strain gauge (18) in five volunteers.

Procedures were approved by the institutional Committee for Use of Human Subjects for Experimental Purposes (University of Michigan Medical School). All subjects read, understood, and signed a detailed informed consent form. The form emphasized a subject's right to withdraw at any time during the procedure. Paired *t* test (19) was used for testing the significance of differences.

<sup>1</sup> Amount of standard that produces two times the counts of the blank.

## RESULTS

### *Renin response and its hemodynamic determinants.*

Average renin responses in 24 volunteers are given in Table I. Preliminary analysis of the time-course in nine subjects indicated that renin rises became significant after 30 min of cuff inflation. Consequently, in the remainder of the study, renin was measured only 30 min after cuff inflation. A composite illustration of renin values at rest, after sham inflation of the ankle cuff, 30 min after thigh cuff inflation and 30 min after deflation is given in Fig. 1. Mean renin values at rest and after ankle cuff inflation were identical. After 30 min of thigh cuff inflation, renin was above control values. Renin increased in all subjects and the smallest increase substantially exceeded the largest increase observed with the sham cuff inflation. 30 min after deflation, the mean value returned toward normal but was still 48% above the resting value.

Hemodynamic measurements before, during, and after leg congestion are summarized in Table II and their relationship to changes in renin is illustrated in Fig. 2. During cuff inflation there was no change in the systolic or diastolic blood pressure. Right atrial pressure, central blood volume, and cardiac output decreased and a small but significant increase of the heart rate was observed. The calculated peripheral vascular resistance increased. After deflation of the cuff, all hemodynamic parameters returned toward control values.

*Evidence for reflex activation.* As seen in Fig. 2, peripheral venous pooling by thigh cuffs caused a decrease of cardiac output, but the blood pressure did not

TABLE I  
*Plasma Renin Activity before and after Inflation and Deflation of Thigh Cuffs*

	Plasma renin activity		
	Rest	Thigh cuff inflated (30 min)	Thigh cuff deflated (30 min)
	ng/ml/h		
<i>n</i> = 11	2.12±0.66 (0.55–6.83)	4.50±1.22§ (1.18–12.28)	3.03±0.96‡ (0.42–9.76)
<i>n</i> = 13	1.10±0.18 (0.66–1.99)	3.20±0.90 (0.98–8.85)*	—
Total <i>n</i> = 24	1.70±0.41	3.80±0.71§	—

*n*, number of subjects.

Values are means±SE. Range is given in parentheses. The significance levels of differences from rest values (\*) and of differences from values during inflation to values after deflation of thigh cuffs (‡) are indicated: \* *P* < 0.05; ‡ *P* < 0.01; § *P* < 0.001.

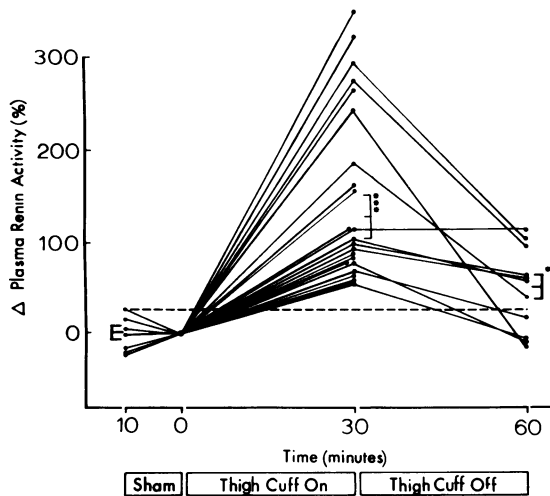


FIGURE 1 Percentage of changes from resting plasma renin values after ankle cuff ("sham") and thigh cuff inflation and subsequent deflation of thigh cuffs. Results with thigh cuff inflation were available in 24 subjects. Results after sham cuff and deflation of thigh cuffs were obtained in 7 and 11 subjects, respectively. The broken line indicates the upper limit of variability observed after ankle cuff inflation. Means and standard errors of changes from resting values are indicated by brackets. Asterisks denote the significance of differences from the resting values: \* $P < 0.05$ ; \*\*\* $P < 0.001$ .

decrease because of a simultaneous increase of the total vascular resistance. This increase in the calculated resistance was confirmed by plethysmographic measurement of forearm blood flow. In five volunteers, resting forearm blood flow was  $3.97 \pm 0.84$  (SE) ml/min per 100 ml of tissue. 6 min after thigh cuff inflation, forearm flow significantly decreased to  $2.94 \pm 0.60$  ( $P < 0.025$ ). This regional decrease of blood flow (26%)

substantially exceeded the reduction of cardiac output (11%). The reflex nature of the increase of forearm and hand vascular resistance after venous pooling of blood by lower body negative pressure has been amply demonstrated by others (20, 21).

Further evidence that thigh cuff inflation elicits an adrenergically-mediated response is shown by the significant rise in serum norepinephrine levels (Fig. 3) during limb congestion. Serum epinephrine increase from a mean of  $61 \pm 9.9$  ng/liter before to  $81.6 \pm 16.8$  ng/liter after inflation was not significant.

*Evidence that renin increase is reflex mediated.* The renin response to thigh cuff inflation in patients who had functioning but denervated transplanted kidneys differed from that observed in normal subjects (Fig. 4). Three of the four patients failed to increase renin after thigh cuff inflation. The fourth patient received the transplant 9 mo before the experiment. His renin response to cuff inflation was in the lowest range observed in healthy subjects (0.65 ng/ml per h). The percentage rise in this patient (10%) is well below the lowest observed in control subjects.

All four transplant cases refused invasive hemodynamic measurements. Their heart rate response to thigh cuff inflation was the same as in healthy subjects (Fig. 4, panel II), indicating that they were exposed to a similar degree of circulatory stress as healthy subjects. Furthermore, plasma norepinephrine response was measured in two patients and was among the highest observed in the study (Fig. 3, broken lines).

To test whether transplanted kidneys were capable of responding to sympathetic stimulation, isoproterenol was infused. As seen in panel III of Fig. 4, all patients had a normal renin response to isoproterenol.

Further evidence that the renin elevation was

TABLE II  
Hemodynamic Characteristics of Subjects at Rest and after Inflation and Deflation of Thigh Cuffs

Time, min	Rest 60	Thigh cuff inflated 5	Thigh cuff inflated 30	Thigh cuff deflated 30
RAP, mm Hg	$-3.94 \pm 0.39$	$-6.53 \pm 0.57$ §	$-6.36 \pm 0.56$ ‡	$-5.20 \pm 0.53$
SBP, mm Hg	$117.65 \pm 2.74$	$116.70 \pm 3.12$	$118.27 \pm 4.58$	$127.80 \pm 4.99$ *
DBP, mm Hg	$63.09 \pm 1.49$	$63.35 \pm 1.49$	$65.14 \pm 1.50$	$67.90 \pm 2.85$
QI, liter/min/m <sup>2</sup>	$2.79 \pm 0.11$	$2.45 \pm 0.10$ §	$2.47 \pm 0.10$ §	$2.74 \pm 0.45$
CBVI, ml/m <sup>2</sup>	$888 \pm 30$	$780 \pm 24$ §	$763 \pm 28$ §	$916.45 \pm 44.95$
TPRI, U/m <sup>2</sup>	$30.41 \pm 2.33$	$34.94 \pm 2.54$ §	$34.43 \pm 3.01$ §	$30.82 \pm 1.78$
HR, beats/min	$60.05 \pm 1.85$	$62.17 \pm 2.05$ §	$64.95 \pm 2.39$ ‡	$63.70 \pm 3.33$
	(n = 21)	(n = 21)	(n = 21)	(n = 10)

Abbreviations: RAP, right atrial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; QI, cardiac index; CBVI, central (cardiopulmonary) blood volume index; TPRI, total peripheral resistance index; HR, heart rate; n, number of subjects. Significance levels of differences from rest (\*) and differences from thigh cuff 5 min to thigh cuff 30-min values (‡) are indicated: \*  $P < 0.05$ ; ‡  $P < 0.01$ ; §  $P < 0.001$ .

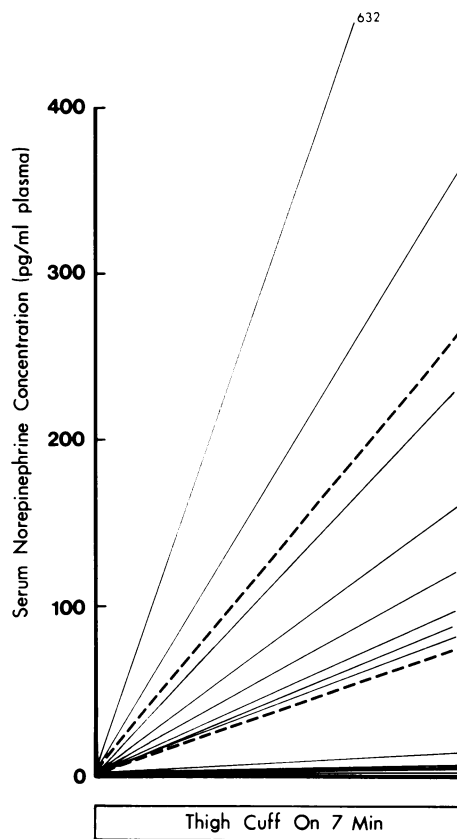
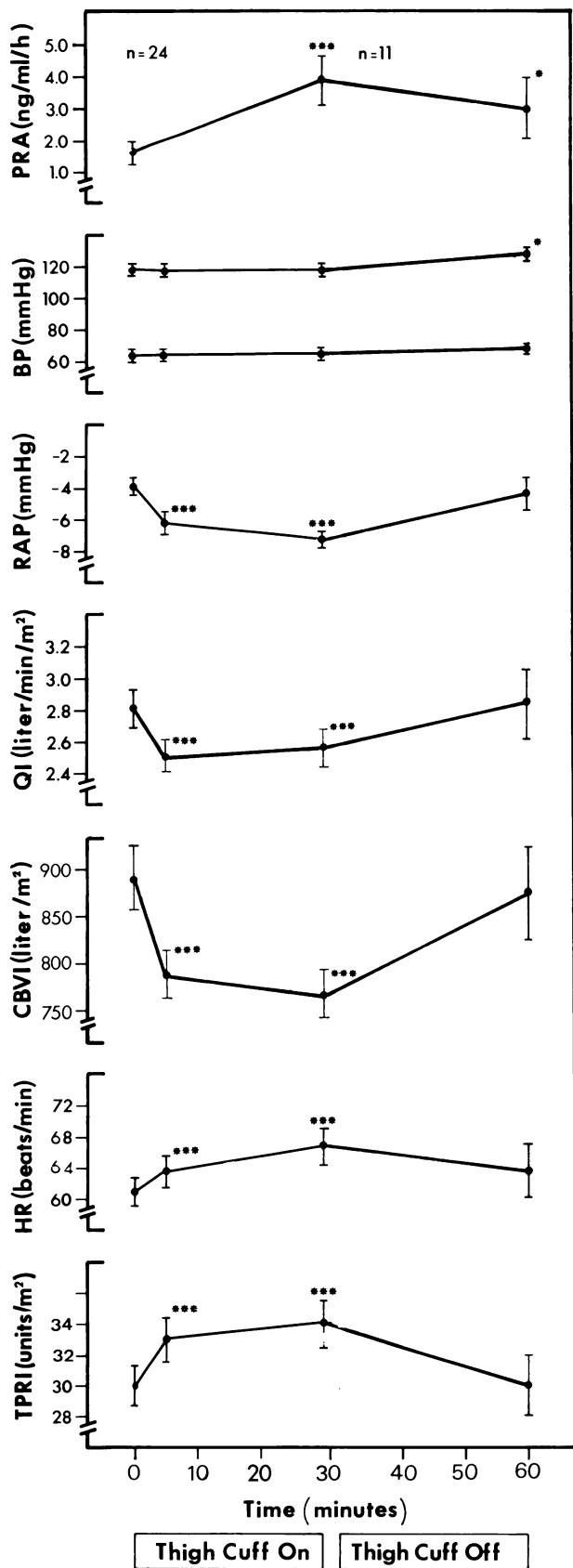


FIGURE 3 Serum norepinephrine responses to thigh cuff inflation in 13 subjects. Changes from resting values are shown. Two subjects, represented by broken lines, are renal transplant cases (open triangle, square [Fig. 4]).

mediated by beta adrenergic stimulation comes from experiments with propranolol, shown in Fig. 5. Nine control subjects initially showed the usual increase of renin. They then received the beta adrenergic blockade. When the thigh cuff was reinflated after blockade, renin failed to increase, in spite of similar hemodynamic changes (Table III).

## DISCUSSION

*Choice of technique.* Thigh cuff inflation caused circulatory responses similar to ones observed with the application of negative pressure to the lower body.

FIGURE 2 Hemodynamic and plasma renin responses to inflation and deflation of thigh cuffs. Note that the number of subjects changes. After cuff deflation, significance of changes from resting values was tested only for the 11 involved subjects. PRA, plasma renin activity; BP, intra-arterial blood pressure; RAP, right atrial pressure; QI, cardiac index; CBVI, cardiopulmonary (central) blood volume index; HR, heart rate; and TPRI, total peripheral resistance index. Symbols as in Fig. 1.

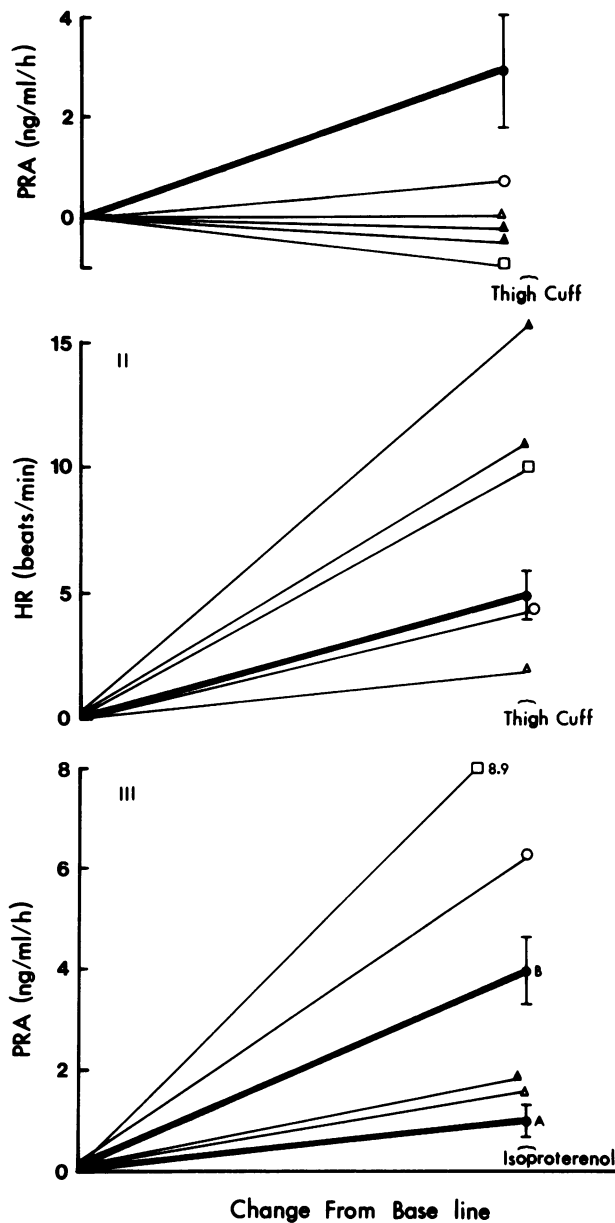


FIGURE 4 Plasma renin (panel I) and heart rate (panel II) responses to thigh cuff inflation and heart rate response to isoproterenol infusion (panel III) in renal transplant patients and healthy subjects in this study. In panel III, normal values obtained in another study from our laboratory are given (40). Thick line, A, in panel III represents normal values on 160 meq sodium intake and line B on 10 meq sodium intake in healthy subjects. All patients had bilateral nephrectomy. All were receiving prednisone (5–20 mg), hydrochlorothiazide (50–100 mg), and azothioprine (50–150 mg). Solid triangle represents responses in a 26-yr-old woman, who received a transplant 3 mo before the procedure. Her serum creatinine was 1.3 mg/100 mg. Circle denotes responses in a 30-yr-old man, who received the transplant 9 mo before the experiment. Serum creatinine was 1.7 mg/100 mg.

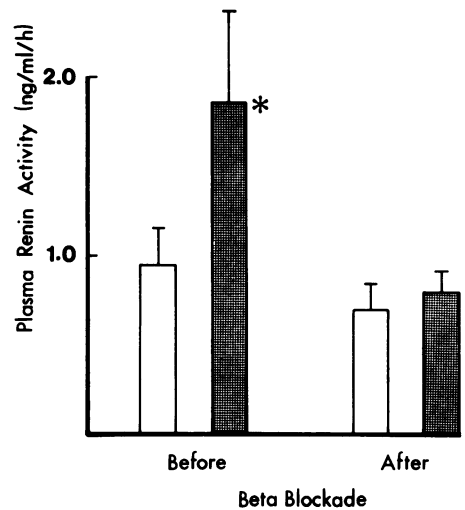


FIGURE 5 Response of plasma renin activity to thigh cuff inflation before and after beta blockade with propranolol in nine subjects. Open columns present mean values before and dotted columns mean values 30 min after thigh cuff inflation. Vertical bars indicate standard errors. Symbols as in Fig. 1.

Peripheral venous pooling with lower body negative pressure results in a decrease of right atrial pressure (11), cardiac output (22), and of forearm blood flow (10, 11, 20, 23).

Compared to this technique, thigh cuff inflation offers some advantages. With lower body suction, the negative pressure is transmitted to the abdominal cavity. Substantial pooling of the blood in the splanchnic area (20, 24) and a decrease of the intra-abdominal pressure manifested as lowering of the diaphragm (25) and reduction of intragastric relaxation pressure (26) have been reported. Circulatory reflexes can be elicited from the richly innervated abdominal cavity (27). It is also conceivable that the negative pressure could be transmitted to the kidneys. These problems are not encountered with thigh cuff inflation.

All of our subjects tolerated the procedure without any visible or reported discomfort. The three individuals with presyncope appeared at ease before hypotension.

*Review of results.* We investigated whether peripheral venous pooling of blood causes renin responses in man. Cuff inflation caused a decrease of the right atrial pressure and a diminution of the cardiopulmonary blood volume. A reflex adjustment of the circulation was elicited; total peripheral vascular resistance increased, forearm blood flow decreased, and an

Represented by an open triangle is a 17-yr-old girl, who had the transplant 7 mo before the procedure and whose serum creatinine was 1.4 mg/100 mg. Represented by a square is a 30-yr-old woman, who received the transplant 7 mo before the procedure and whose serum creatinine was 1.5 mg/100 mg.

TABLE III  
*Hemodynamic Values before and after Beta Receptor Blockade  
 with Intravenous Propranolol*

	Before propranolol		After propranolol (0.25 mg i.v.)	
	Rest	Thigh cuff inflation (30 min)	Rest	Thigh cuff inflation (30 min)
RAP, mm Hg	-2.99±0.65	-5.11±1.03*	-2.62±1.01	-4.75±0.9*
QI, liter/min/m <sup>2</sup>	2.84±0.16	2.44±0.14*	2.26±0.11	1.88±11‡
CBVI, ml/m <sup>2</sup>	868±56	707±46‡	832±24	725±22‡

The significance levels of the differences from rest values are indicated: \*  $P < 0.05$ ;  
 ‡  $P < 0.025$ .

increase of serum norepinephrine was observed. This reflex adjustment was accompanied by an increase of renin. There is good evidence that this renin increase was reflex mediated: (a) renin increase was suppressed in patients with denervated renal transplants, and (b) renin failed to increase in healthy subjects after beta receptor blockade with propranolol. Because the right atrial pressure decreased and there were no changes in arterial pressure, the reflex likely originated in the area of cardiopulmonary mechanoreceptors.

The statement, that in our study, renin increased as a result of stimulation of cardiopulmonary mechanoreceptors requires further discussion. Angell-James and Daly (28) have shown that changes in mean blood pressure and pulse pressure are important determinants of arterial baroreceptor activation. Both these parameters were unchanged with cuff inflation in this study. In addition, the velocity of pressure changes may also influence arterial baroreceptor responses (29, 30). This complement of baroreceptor stimulation cannot be assessed from our results. However, Zoller et al. (11), using small degrees of lower body negative pressure, caused comparable changes in central venous pressure as in our study, and failed to observe changes in arterial  $dp/dt$ . Therefore, it is reasonable to assume that in our study the contribution of arterial baroreceptor activation to the renin response was small or absent.

Evidence that cardiopulmonary receptors participate in the control of renin release in animals comes from several sources. In their study of dogs after cardiac autotransplantation which severed most afferent pathways from cardiac receptors, Thames et al. (6) noted subnormal renin responsiveness to hemorrhage. Mancina et al. (7), by cooling the vagus nerves in dogs, demonstrated tonic inhibition of renin emanating from receptors in the cardiopulmonary region. Inflation of balloons in the right (8) and left (31) atrium of dogs causes a decrease of the renin release. Recently,

Thames (32) demonstrated that stimulation of veratrum-sensitive left ventricular receptors causes suppression of renin release in dogs. It is known that these receptors can also be activated by distention of the ventricle (33).

Whereas animal experiments favor a role of cardiopulmonary receptors in renin regulation, human investigations are scarce and controversial. Studies with water immersion provide indirect evidence for a volume action on cardiac receptors and renin release in man. During head-out water immersion, an increase in the central blood volume and right atrial pressure (34) and a suppression of renin is observed (35). It is likely that the renin suppression stemmed from distention of cardiopulmonary receptors by the expanded cardiopulmonary blood volume during water immersion. A more direct test of the role of cardiopulmonary receptors in man was provided by Fasola and Martz (12). They observed a substantial increase of renin during -20 mm Hg of lower body negative pressure. This degree of lower body negative pressure produces a selective stimulation of cardiopulmonary receptors (11, 36). The only other report on lower body negative pressure and renin response (13) *prima facie* appears to speak against a role of cardiopulmonary receptors in renin regulation in man. Thus, Mark and Abboud (13) applied -10 and -20 mm Hg negative pressure for 10 min and did not find a renin increase in six subjects. At -40 mm Hg, arterial pressure decreased and plasma renin increased. Consequently, they concluded that high pressure baroreceptors play a dominant role in renin regulation. The reason for this conclusion may be in the timing of renin determinations; 10 min of observation in lower body negative pressure is most likely insufficient. Oparil et al. (37), using 80° tilt, observed a small increase of renin after 5 min; the increase was highest after 20 min. Similar results were reported by others (38, 39). In these studies with the strong stimulus of orthostasis, it took considerable time before large renin changes were ob-

served. With a milder stimulus such as  $-20$  mm Hg of negative pressure it may take longer than 10 min for the first change of renin to appear in peripheral blood. In Fasola and Martz's study (12) observations were made after 30 min of  $-20$  mm Hg lower body negative pressure and the renin was increased. Analysis of the time-course in nine patients in our studies demonstrated mild increases after 10 and 20 min, but changes were fully expressed only after 30 min.

**Conclusion.** Our study suggests that the increase of renin observed in man after thigh cuff inflation is reflex mediated and that this reflex originates in cardiopulmonary mechanoreceptors.

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