Congestive heart failure in normotensive man *Haemodynamics, renin, and angiotensin II blockade*

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SUMMARY The role of the renin angiotensin system was evaluated in 18 normotensive patients with chronic congestive heart failure and in 5 controls. No correlation was observed between plasma renin activity and cardiac index. There was a significant inverse correlation between renin and pulmonary capillary wedge pressure ($r = -0.61$, $P < 0.01$). Renin values of the patients appeared to be increased when compared with controls with similar left ventricular filling pressure. Specific angiotensin II inhibition by saralasin decreased arterial pressure in 8 out of 14 patients: their renin was significantly higher than that of the remaining 6 patients ($P < 0.01$). The 2 patients with the lowest renin levels responded to saralasin with a blood pressure increase. Left ventricular filling pressure decreased in all but these latter 2 patients with either little change or an increase in stroke volume. Thus, renin levels appear to be increased in normotensive patients with congestive heart failure when related to left ventricular filling pressure. Renin via angiotensin II plays a role in the blood pressure control of many patients with congestive heart failure. In some patients angiotensin II blockade appears to improve cardiac function by unloading the left ventricle.

Renin via angiotensin II plays an important role in blood pressure homeostasis (Sancho *et al.*, 1976; Posternak *et al.*, 1977) and in sustaining blood pressure in various forms of hypertensive diseases (Brunner *et al.*, 1974a; Streeten *et al.*, 1976). Not only does angiotensin regulate the circulation by modifying arteriolar tone, but also renal haemodynamics have been shown to modulate its generation (Davis and Freeman, 1976). Thus, the renin-angiotensin system represents an important link in the chain of mechanisms regulating the circulation.

What role does the renin-angiotensin system play in congestive heart failure? Recent studies in animals have shown that renin secretion is high in the early stages of acute experimental congestive heart failure (Watkins *et al.*, 1976; Morris *et al.*, 1977) and may later return to normal after compensatory salt and water retention (Watkins *et al.*, 1976). These studies suggest that the renin-angiotensin system participates in the genesis of experimentally-induced heart failure. In patients with chronic congestive heart failure, renin levels have been found to be high, normal, or low (Brown *et al.*, 1970; Nicholls *et al.*, 1974). So far as is known there are no clinical studies available relating plasma

renin activity to haemodynamic indices of cardiac function in normotensive patients with congestive heart failure. In addition, the haemodynamic effects of specific inhibition of angiotensin in such patients have not yet been reported.

The present study was designed to determine relations between plasma renin activity and various haemodynamic indices in normotensive patients with congestive heart failure. In addition, the effects of specific angiotensin inhibition by saralasin (Pals *et al.*, 1971) were assessed. Our results suggest that plasma renin activity is related to left ventricular filling pressure and that specific inhibition of the renin-angiotensin system can improve cardiac function in many patients.

Subjects and methods

Fourteen men and nine women undergoing elective diagnostic cardiac catheterisation were included in the study. Ages ranged from 21 to 70 years. Five patients with chest pain but no clinical evidence of congestive heart failure were labelled controls. The other 18 had clinical evidence of congestive heart failure of at least one year's duration. The severity of heart failure was graded as follows: class II patient comfortable at rest, ordinary activity result-

ing in dyspnoea; class III less than ordinary activity causing dyspnoea; class IV inability to carry on any physical activity without dyspnoea (New York Heart Association, Criteria Committee, 1964). The evaluation of each patient included left ventriculography and coronary arteriography.

The study was approved by the Hospital Ethics Committee. Informed consent was obtained from each patient after the nature and purpose of the study were explained.

All patients were admitted to the cardiology division. They received a constant dietary regimen containing 3 to 5 g NaCl per day for at least 3 days before the study. After 12 hours overnight fast, they were brought to the catheterisation laboratory. On the morning of the study, no premedication was given but the patient's usual oral digitalis preparation was administered. A Swan-Ganz flow-directed balloon-tipped catheter was introduced through an antecubital vein. A short polyethylene catheter (Seldicath) was placed percutaneously into a radial artery for the continuous monitoring of arterial pressure and arterial blood sampling.

After the placement of the catheters the patients were allowed to rest for 45 minutes. At that time, control haemodynamic measurements were obtained. Saralasin was then administered intravenously by a constant infusion pump (Sage Mod. 355). The initial rate of infusion was 1 $\mu\text{g}/\text{kg}$ per min. This was subsequently increased stepwise to a maximum of 10 $\mu\text{g}/\text{kg}$ per min or until mean arterial blood pressure fell by 20 mmHg. This maximal dose was chosen to assure complete blockade of angiotensin. After 45 minutes at the maximal infusion rate, all measurements were repeated.

Pressures were monitored using Statham transducers (P23Dd) and inscribed on a Hewlett Packard 14560 recorder. Mean pulmonary capillary wedge pressure was used as an index of left ventricular end-diastolic pressure.

Cardiac output was assessed by the direct Fick method. Oxygen consumption was measured with a Fleisch Metabograph (Metabo-Epalinges) (Fleisch, 1954). During the middle period of the timed respiratory collection, duplicate blood samples of 2 ml were drawn from the pulmonary and radial arteries into heparinised syringes. Blood oxygen saturation was determined on a co-oximeter (IL 182 Instrumentation Lab. Inc.). For the measurements of plasma renin activity, 7 ml blood were drawn in chilled tubes containing EDTA. We handled plasma at 4°C because we have been unable to confirm the observation that chilling of the blood before separation can lead to a variable but often considerable rise in plasma renin activity (Sealey *et al.*,

1977). After centrifugation the plasma was immediately frozen and stored at -28°C . Renin activity was quantified by radioimmunoassay of angiotensin I generated during incubation under standard conditions (Sealey *et al.*, 1972).

CALCULATIONS

Mean pressures were obtained from electronically integrated records. The systemic vascular resistance (SVR) in $\text{dyne s}^{-1} \text{cm}^{-5}$ was calculated from the

formula $\frac{\text{MAP} - \text{RA}}{\text{CO}} \times 80$, where MAP = mean

arterial pressure; RA = mean right atrial pressure; CO = cardiac output; and 80 is the factor for converting resistance units to $\text{dyne s}^{-1} \text{cm}^{-5}$.

Mean and standard error of the mean were calculated and the data were compared by Student's paired and unpaired *t* test. Correlation coefficients were obtained for plasma renin activity and the various haemodynamic measurements. In all cases, *P* values of less than 0.05 were considered significant.

Results

CLINICAL CHARACTERISTICS

The clinical data of the 23 subjects are summarised in Table 1. Three of the 5 controls without congestive heart failure were found to have coronary artery disease and 2 had no evidence of disease. The diagnoses of the 18 patients with congestive heart failure included mitral and aortic valvular disease, coronary artery disease, and cardiomyopathy. According to the New York Heart Association criteria for congestive heart failure, one patient was class IV, 11 were class III, and 6 were class II. All but 3 of the patients with congestive heart failure were receiving a digitalis preparation and 11 had, in addition, diuretic therapy; in 2 frusemide was stopped 5 and 3 days before study (cases 16 and 17). Plasma sodium and potassium concentrations were similar whether the patients were on diuretic therapy or not.

INITIAL HAEMODYNAMIC AND RENIN MEASUREMENTS

Individual haemodynamic and plasma renin data are shown in Table 2. Resting mean arterial pressure averaged 91 ± 3.5 mmHg (mean $\pm$ SEM), for the 18 patients with congestive heart failure and 99 ± 4.3 mmHg for the 5 controls. Mean right atrial pressure for the two groups was identical, 3.6 ± 0.6 mmHg, while mean pulmonary arterial pressure was 28 ± 3.2 and 12.8 ± 0.6 mmHg, respectively ($P < 0.025$). In the group with heart failure, mean pulmonary capillary wedge pressure was $19 \pm$

Table 1 *Clinical and biochemical characteristics*

Case no.	Age (yr)	Sex	Diagnosis	CHF class	Digitalis (mg/day)	Diuretic (mg/day)	Serum electrolytes mmol/l	
							Na	K
1	63	M	Coronary artery disease	—	—	—	142	3.8
2	63	F	Chest pain	—	—	—	143	3.5
3	56	F	Chest pain	—	—	—	139	3.7
4	54	M	Coronary artery disease	—	—	—	141	4.3
5	67	F	Coronary artery disease	—	—	—	140	4.2
6	59	M	Aortic regurgitation	III	Digoxin 0.25	Furosemide 40 Spironolactone 50	136	4.1
7	70	M	Mitral regurgitation	IV	Digoxin 0.25	Furosemide 40 Spironolactone 100	143	4.3
8	60	M	Coronary artery disease	II	—	Furosemide 40 Spironolactone 75	141	4.0
9	57	F	Aortic regurgitation and stenosis	II	—	—	142	4.0
10	58	M	Aortic regurgitation and stenosis	III	Digoxin 0.25	Furosemide 40 Spironolactone 25	140	4.1
11	50	M	Coronary artery disease	III	Digoxin 0.25	—	139	4.1
12	50	M	Cardiomyopathy	III	Digoxin 0.25	Hydrochlorothiazide 50 Amiloride 5	140	4.0
13	53	M	Aortic regurgitation and stenosis; coronary artery disease	II	Digoxin 0.25	Hydrochlorothiazide 50 Amiloride 5	142	3.9
14	63	F	Mitral regurgitation	III	Digoxin 0.25	Spironolactone 75 Furosemide 40	140	3.7
15	21	M	Aortic regurgitation	II	—	—	139	4.0
16	70	M	Aortic stenosis	III	Digoxin 0.25	Furosemide 40 Chlorthalidone 100	133	4.2
17	64	F	Mitral regurgitation	III	Digoxin 0.50	Furosemide 80/week	142	4.1
18	55	M	Mitral regurgitation	II	Digoxin 0.25	—	141	4.0
19	58	F	Mitral regurgitation	III	Digitoxin 0.3	Chlorthalidone 100	143	4.0
20	70	F	Aortic regurgitation	II	Digoxin 0.25	—	141	4.4
21	61	F	Mitral regurgitation and stenosis	III	Digoxin 0.25	—	144	4.2
22	51	M	Mitral stenosis	III	Digoxin 0.5	Hydrochlorothiazide 50 Amiloride 5	140	3.6
23	65	M	Mitral regurgitation	III	Digoxin 0.25	—	139	4.7

Table 2 *Haemodynamic and renin data before and during saralasin infusion*

Case no.	Mean arterial pressure (mmHg)		Mean right atrial pressure (mmHg)		Mean pulmonary artery pressure (mmHg)		Mean pulmonary capillary wedge pressure (mmHg)		Heart rate (beats/min)		Cardiac index (l/min per m ²)		Stroke volume index (ml/syst per m ²)		Systemic vascular resistance (dyne s ⁻¹ cm ⁻⁵)		Plasma renin activity (ng/ml per hr)	
	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S
1	85	90	5	4	13	12	7	7	75	75	2.9	2.5	38	33	1140	1419	2.0	1.6
2	95	98	3	3	14	14	6	5	73	77	2.5	2.6	34	33	1636	1617	3.2	1.6
3	110	110	5	5	14	15	8	8	68	75	2.7	2.3	40	30	1615	1909	2.7	2.4
4	105	100	3	1	12	9	6	4	75	75	4.0	3.3	53	44	1118	1320	3.7	3.5
5	98	—	2	—	11	—	5	—	72	—	3.3	—	46	—	1182	—	1.3	—
6	70	62	—2	—2	10	9	5	2	52	55	1.6	2.2	31	41	2074	1305	9.4	32
7	130	110	4	5	50	55	37	24	83	85	2.0	2.0	25	24	3064	2625	1.9	2.2
8	120	110	4	3	28	21	17	12	110	94	3.5	2.9	32	30	1428	1630	9.0	19
9	92	70	—2	—3	12	7	6	3	75	75	2.9	4.4	38	59	1478	732	14	46
10	77	70	6	8	47	41	27	25	90	82	3.1	2.8	34	35	1183	1127	8.1	40
11	92	72	2	2	18	12	12	6	77	84	3.3	3.7	43	45	1270	862	5.6	6.7
12	90	87	2	0	31	21	23	15	58	50	3.2	2.6	56	52	1235	1513	3.3	9.5
13	91	87	0	—2	12	8	8	3	82	80	2.9	2.8	36	35	1348	1392	13	40
14	80	<50	—2	—	11	—	5	—	90	—	2.1	—	23	—	2060	—	5.8	—
15	97	97	4	0	18	14	14	9	63	75	2.8	3.7	45	50	1550	1232	2.3	2.1
16	80	79	2	2	42	37	25	22	60	50	2.1	1.9	35	38	1570	1722	4.6	12.5
17	87	87	6	2	48	47	29	17	85	90	1.3	1.9	15	21	3411	2429	1.5	2.3
18	80	85	3	1	39	35	26	20	75	77	2.7	2.5	36	32	1081	1258	1.8	1.5
19	83	98	6	7	23	25	16	20	80	85	2.0	2.0	25	24	1785	2141	1.2	1.1
20	105	155	8	—	28	—	23	40	65	60	2.4	—	37	—	2156	—	0.53	0.67
21	93	—	1	—	34	—	27	—	75	—	4.2	—	56	—	1168	—	2.3	—
22	85	—	4	—	34	—	23	—	90	—	3.1	—	34	—	1117	—	2.4	—
23	85	—	6	—	20	—	14	—	70	—	3.4	—	49	—	1170	—	2.2	—

C, Control; S, During saralasin infusion.

Fig. 1 Relation between plasma renin activity and cardiac index, mean arterial pressure, mean right atrial pressure, and pulmonary capillary wedge pressure. Controls ($\square$) and patients with congestive heart failure ($+$). Correlations are calculated only for the heart failure patients. Cardiac index did not correlate with renin values. The most significant correlation was observed between plasma renin activity and pulmonary capillary wedge pressures.

2.2 mmHg as compared with 6.4 ± 0.5 mmHg ($P < 0.01$) in the controls. Average heart rate at rest was nearly the same in the two groups, being 77 ± 3.3 and 73 ± 1.3 beats per min, as were the mean cardiac indexes of 2.7 ± 0.2 and 3.1 ± 0.3 l/min per m^2 , respectively. The stroke volume index of 36 ± 2.6 in the patients with heart failure was slightly less than 42 ± 3.3 ml/syst per m^2 in the controls. Systemic vascular resistance averaged 1675 ± 157 in the congestive heart failure patients and 1338 ± 118 dyne $s^{-1} cm^{-5}$ in the controls. Mean plasma renin activity of 4.9 ± 1.0 in the heart failure group was nearly twice that of 2.6 ± 0.4 ng/ml per hr in the control group.

RENIN AND HAEMODYNAMIC CORRELATES

Fig. 1 illustrates the relation between initial plasma renin activity and various haemodynamic indices for the 18 patients with congestive heart failure. The haemodynamic correlates examined were cardiac index, mean arterial and right atrial pressures, and mean pulmonary capillary wedge pressure.

Plasma renin activity and cardiac index did not correlate; the r value (excluding the controls) was

0.12. There was an inverse correlation ($P < 0.05$) between renin and mean arterial pressure and renin and mean right atrial pressure; the r values were -0.48 and -0.52 , respectively. The best correlation ($r = -0.61$) for the patients with congestive heart failure was obtained between initial plasma renin activity and mean pulmonary capillary wedge pressure ($P < 0.01$).

The values of the 5 control patients are also plotted on the figure but not included in the calculations. For cardiac index, mean arterial, and right atrial pressures they appear to be interspersed among the values of the patients with congestive heart failure. For the relation of renin to pulmonary capillary wedge pressure, however, the controls form a homogeneous group separate from the patients.

HAEMODYNAMIC RESPONSES TO SARALASIN

Fifteen patients with congestive heart failure received an infusion of saralasin. Nine (cases 6 to 14) responded with a decrease in mean arterial pressure, while in 6 (cases 15 to 20) it increased or did not change. Two types of pressure responses are illustrated in Fig. 2. In the patient shown in the left

Fig. 2 Responses of mean arterial and pulmonary capillary wedge pressure to saralasin infusion in 2 patients with congestive heart failure. Case 7 with 'normal' plasma renin levels had decreased pressures and case 20 with 'low' plasma renin activity had increased pressures.

panel (case 7) saralasin induced a decrease in mean arterial pressure of 20 mmHg. Simultaneously, mean pulmonary capillary wedge pressure fell by 13 mmHg. An opposite response is shown in the right panel of the same figure. In this patient (case 20) saralasin caused a progressive increase in mean arterial pressure of 50 mmHg, which returned to baseline within 30 minutes after stopping the infusion. Concurrent with mean arterial pressure, mean pulmonary capillary wedge pressure increased by 17 mmHg. In both patients heart rate hardly changed despite substantial changes in blood pressure (Table 2).

During saralasin infusion at a maximal rate of 10 µg/kg per min one patient (case 14) experienced profound hypotension which required immediate discontinuation of the procedure; subsequent recovery was uneventful. This patient is not included in the following analysis of the data. For the 8 others who experienced lower blood pressure in response to saralasin (Fig. 3), the mean decrease was 11.8 ± 2.8 mmHg ($P < 0.005$). The remaining 6 taken together had increases in their mean arterial pressure of 11.8 ± 8.0 mmHg. This overall increase was the result of a pressor response to saralasin in 3 (cases 18-20).

In the 8 patients in whom blood pressure fell, mean pulmonary capillary wedge pressure also decreased significantly from 17 ± 4.0 to 11 ± 3.1 mmHg ($P < 0.005$) during saralasin infusion (Fig. 3). In the same group right atrial pressure, cardiac index, heart rate, and stroke volume index hardly changed in response to saralasin. In the group of the 6 patients in whom blood pressure

Fig. 3 Haemodynamic correlates before (C, open symbols) and after (Sar, closed symbols) saralasin infusion. This shows patients who had decreases in blood pressure (circles) in response to saralasin and patients who experienced no change or an increase in their blood pressure (triangles). Pulmonary capillary wedge pressure decreased significantly ($P < 0.005$) in the patients whose mean arterial pressure decreased.

increased or did not change during saralasin, mean pulmonary capillary wedge pressure and heart rate remained unchanged. Right atrial pressure, cardiac index, and stroke volume index were not measured during saralasin infusion in case 20; in the remaining 5 patients these indices did not change significantly. Though not shown in Fig. 3, the haemodynamic indices of 4 controls did not change during saralasin infusion (Table 2).

Left ventricular function curves of all 13 patients in whom cardiac index was determined in response to saralasin are shown in Fig. 4. In a majority of the patients saralasin induced a distinct shift to the left, with either no change or even some increase in

Fig. 4 Left ventricular function curves of 13 patients who had an infusion of saralasin. Open symbols before and closed symbols after saralasin. (Circles and triangles: see Fig. 3). All but one patient who had increased arterial pressure experienced improvement in left ventricular function.

stroke volume index, thus indicating improvement of their left ventricular function.

PLASMA RENIN ACTIVITY IN SUBGROUPS DEFINED BY SARALASIN RESPONSE

Fig. 5 shows initial plasma renin levels of all

Fig. 5 Initial plasma renin activity of controls ($\square$), and patients with congestive heart failure who had a decrease ($\circ$) or no change or an increase ($\triangle$) in arterial pressure in response to saralasin infusion. The patients who had a decrease in blood pressure had significantly higher renin levels ($P < 0.01$).

patients replotted according to their arterial pressure response to saralasin. The 6 who did not decrease their arterial pressure showed a mean plasma renin of 2.0 ± 0.58 ng/ml per hr. In contrast, the 8 patients who responded to saralasin by a fall in arterial pressure had a significantly higher initial mean plasma renin activity of 8.1 ± 1.6 ng/ml per hr ($P < 0.01$). Mean renin level for the 5 controls was 2.6 ± 0.43 ng/ml per hr.

Not shown in Fig. 5 is the renin response to saralasin infusion. The 6 patients hardly increased plasma renin activity to 3.4 ± 1.8 ng/ml per hr whereas the 8 patients who had decreased arterial pressure showed a substantial increase to 24 ± 6.1 ng/ml per hr ($P < 0.02$). No significant change was observed in the controls.

Discussion

The purpose of this study was to assess the role of the renin-angiotensin system in patients with congestive heart failure by measuring renin levels and by determining the effect of specific angiotensin II blockade on various haemodynamic indices. No relation between initial plasma renin activity and cardiac index was found but some inverse correlations were observed between plasma renin and either mean arterial pressure or right atrial pressure. The strongest inverse correlation existed between initial plasma renin activity and mean pulmonary capillary wedge pressure. When saralasin was infused into 15 of the patients, 9 responded with a decrease in arterial pressure, 1 of whom developed acute hypotension which was quickly reversed by administration of saline. Three had no change in their arterial pressure and 3 had increases, thus exhibiting an agonistic response to saralasin. Heart rate was not predictably influenced by the change in arterial pressure. Mean plasma renin activity of the patients who lowered blood pressure in response to saralasin was significantly higher than that of the patients who either did not change or increased it. Plasma renin activity in the latter group was not different from that of the 5 controls. The 2 patients who experienced the most striking agonistic response to saralasin had the lowest renin values of all. In all but these 2 patients, saralasin decreased mean pulmonary capillary wedge pressure without reducing stroke volume in most. In some, left ventricular function was substantially improved by a simultaneous increase in stroke volume and reduction of mean pulmonary capillary wedge pressure.

Renin via angiotensin II plays a direct role in sustaining blood pressure in some patients with congestive heart failure. This is illustrated by those 9 patients with higher renin levels who responded to

saralasin with a blood pressure reduction. At the same time, the inverse correlation between plasma renin activity and arterial pressure suggests that the renin-angiotensin system in such patients may, at least in part, be stimulated by a relative decrease in arterial pressure. The majority of our patients had been treated with diuretics as shown in Table 1. Studies in animals (Gavras *et al.*, 1973), normal volunteers (Sancho *et al.*, 1976; Posternak *et al.*, 1977), and hypertensive patients (Brunner *et al.*, 1974b; Gavras *et al.*, 1976) have shown that blood pressure becomes more renin dependent during sodium depletion. However, it appears from Table 1 that previous administration of diuretics did not predict blood pressure responsiveness to saralasin. The effectiveness of diuretics varies among patients with congestive heart failure and therefore those 9 patients who responded to saralasin with a blood pressure drop could have developed more diuretic-induced hypovolaemia. This latter possibility is in part supported by the slightly lower mean right atrial pressure of these patients. Thus, blood pressure responsiveness to saralasin may have been accentuated by diuretic therapy and its influence on intravascular volume and renin secretion. However, 2 of the patients (cases 9 and 11) who had not received any diuretics also lowered their blood pressure, thus suggesting that renin dependency was not only the result of diuretic therapy. This is supported by findings in animals with experimental heart failure, which received no diuretics. In them blood pressure also was renin dependent unless excessive sodium and water were retained (Watkins *et al.*, 1976; Morris *et al.*, 1977).

Recently Nicholls and coworkers reported that diuretics other than spironolactone hardly increase renin levels when administered long term to patients with congestive heart failure (Nicholls *et al.*, 1976). Our data are in total agreement since renin levels did not differ when comparing patients treated with (4.3 ± 1.8) or without such diuretics (4.1 ± 1.7). Furthermore, the 5 patients on spironolactone had slightly higher renin levels (6.8 ± 1.4) though the difference was not statistically significant. If the observed correlation between plasma renin activity and pulmonary capillary wedge pressure is analysed similarly, it appears that the strongest correlation ($r = 0.75$) was seen in the patients receiving no diuretics and the weakest ($r = 0.60$) in the 5 patients on spironolactone. Thus, taken together, there is strong evidence suggesting that the observed relation between renin and cardiac function is physiologically meaningful.

Mean pulmonary capillary wedge pressure reflects left ventricular function and venous return. Venous return is determined by total blood volume and its

fractional distribution between the arterial and venous sides of the circulation. In our study, the strongest inverse correlation was observed between plasma renin activity and pulmonary wedge pressure; renin was high unless pulmonary capillary wedge pressure was much increased. Thus, it seems that renin levels of patients with congestive heart failure are inappropriately high but may be returned toward normal by the compensatory mechanism of increasing preload. This is supported by recent findings in experimental heart failure (Watkins *et al.*, 1976; Morris *et al.*, 1977). In stable, chronic congestive heart failure it would then be understandable that renin levels do not correlate with cardiac index when compensating mechanisms are in full play. This is because cardiac output at rest is often kept at normal levels by a compensatory rise in preload which in turn modulates renin secretion, possibly via cardiopulmonary receptors (Zehr *et al.*, 1976).

The decrease in mean pulmonary capillary wedge pressure in response to saralasin seen in 12 of 14 patients may be attributed in 8 to the concomitant reduction of arterial pressure which is the principal determinant of afterload. In 4 others however, pulmonary capillary wedge pressure decreased in spite of no change or even a slight increase in arterial pressure. Enhanced left ventricular contractility could explain this decrease, but experimental evidence available to date suggests that angiotensin II, if it has any effect on myocardial contractility *in vivo*, would tend to increase it (Downing and Sonnenblick, 1963; Koch-Weser, 1965). Hence, saralasin should reduce inotropy unless it exerts an agonistic effect on the myocardium. To our knowledge no data are available demonstrating a direct effect of saralasin on myocardial contractility. Another possible explanation of the decrease in mean pulmonary capillary wedge pressure could be an increase in left ventricular compliance. The respective roles of changes in compliance and in left ventricular end-diastolic volume cannot be differentiated by the method used in the present study (Braunwald and Ross, 1963).

The most tempting interpretation of the results would be that saralasin blocks a direct vasoconstrictor effect of renin via angiotensin II on the venous capacitance vessels. Reduced venous tone would explain the simultaneous decrease in cardiac index and mean arterial pressure in the face of an increase in systemic vascular resistance observed in some patients, for example cases 8 and 12. A direct vasoconstrictor effect of angiotensin II on the veins was described by some workers (Emerson *et al.*, 1965; Dollery *et al.*, 1963), but others were unable to confirm these observations (Borucki *et al.*, 1976).

Our results nevertheless suggest that this mechanism may be operative in patients with congestive heart failure.

Improvement in cardiac function during saralasin infusion observed in many of our patients raises the question whether angiotensin antagonists have therapeutic potential in congestive heart failure. In recent years, several studies have shown the benefit of afterload reduction by drugs such as glyceryl trinitrate, nitroprusside, and phentolamine (Chatterjee and Parmley, 1977). It is now known that these agents also affect preload to a variable degree, thus accounting for disparate modification of left ventricular function (Miller *et al.*, 1976). Depending on the initial haemodynamic status, changes may result predominantly from a decrease in preload or in impedance, or both. It should be noted that most of these studies (Franciosa *et al.*, 1972; Gold *et al.*, 1972; Chatterjee *et al.*, 1973; Gould *et al.*, 1974; Perret *et al.*, 1975) were done in patients with acute heart failure after myocardial infarction. Such patients, who often have reduced cardiac output, differ from those included in our study who had stable chronic congestive heart failure.

Recent work has shown a therapeutic benefit of vasodilators even in chronic congestive heart failure (Cohn *et al.*, 1974; Kovick *et al.*, 1976). Angiotensin inhibition by its inherent specificity may have the advantage of fewer side effects. The one severe problem encountered, that is a blood pressure increase of 50 mmHg in case 20, would probably have been avoidable by using smaller doses of saralasin, for example 1 to 2 µg/kg per min.

Even more promising could be the use of specific antagonists of angiotensin converting enzyme rather than saralasin (Ondetti *et al.*, 1971). They lack agonistic properties which would avoid a major adverse effect that we encountered with saralasin, that is, blood pressure increase. Furthermore, converting enzyme inhibition has been shown in hypertensive patients to be more effective in lowering blood pressure (Gavras *et al.*, 1974; Case *et al.*, 1976; Gavras *et al.*, 1977). Accordingly, even more load reduction might be expected with these compounds in patients with congestive heart failure. A new specific antagonist of angiotensin converting enzyme has recently been tested which has the additional advantage of being orally active (Ferguson *et al.*, 1977; Ondetti *et al.*, 1977). Thus, this agent will allow prolonged specific angiotensin inhibition. Prolonged rather than acute blockade of the renin-angiotensin system could provide the further advantage of reducing angiotensin-dependent aldosterone secretion. Angiotensin inhibition may then combine a direct effect on vasomotor tone with simultaneous decrease in blood volume.

Taken together, patients with chronic congestive heart failure appear to have inappropriately high plasma renin activity which tends to return toward normal depending on the compensatory rise in preload. This points to an interaction between cardiac function and venous return modulating renin secretion, possibly via cardiopulmonary receptors. Inhibition of the renin-angiotensin system may decrease preload and impedance and thereby improve cardiac function. Specific angiotensin inhibitors deserve further trials to evaluate their usefulness for the treatment of congestive heart failure.

Grant support for this study came in part from the Swiss National Science Foundation. R.K.F. was supported in part by the Roche Research Foundation for Scientific Collaboration with Switzerland.

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