Br. J. clin. Pharmac. (1982), **14**, 179S–186S

REGIONAL CIRCULATORY RESPONSE TO CONVERTING-ENZYME INHIBITION IN CONGESTIVE HEART FAILURE

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1 To determine the distribution of flow, the regional haemodynamic response to 100 mg of captopril was determined in 36 patients with refractory cardiac heart failure. Measurements included forearm blood flow by venous occlusion plethysmography (eight patients), splanchnic blood flow by indocyanine green clearance (10 patients), and coronary blood flow by thermodilution (12 patients).

2 Cardiac index significantly rose in one hour (1.9 ± 0.1 to 2.2 ± 0.1 l/m/m^2, $p < 0.01$) while forearm blood flow rose slightly (2.9 ± 0.8 to 3.2 ± 0.3 ml/100 ml/min). Renal blood flow rose significantly by 30% (344 ± 48 to 533 ± 82 ml/min, $p < 0.02$). Despite a fall in rate pressure product (8.8 ± 0.7 to 7.1 ± 0.5 mm Hg bt $\times 10^3$, $p < 0.02$), coronary blood flow did not significantly change (160 ± 20 to 133 ± 12 ml/min), indicating an improved supply–demand relationship.

3 External myocardial efficiency improved (19 ± 3 to $26 \pm 6\%$, $p < 0.05$). Coronary blood flow is unaffected and converting-enzyme inhibitor improves myocardial efficiency. This strategic reduction in vascular impedence distinguishes converting-enzyme inhibitors as a unique class of vasodilators in the treatment of coronary heart failure.

Introduction

Converting-enzyme inhibitors benefit patients with severe congestive heart failure, both acutely and chronically (Gavras *et al.*, 1978; Davis *et al.*, 1979; Faxon *et al.*, 1980, 1981; Creager *et al.*, 1982). These drugs lower systemic vascular resistance, reduce left ventricular filling pressure, and increase cardiac output. Such salutary effects appear to relate to inhibition of the renin–angiotensin system and support the hypothesis that angiotensin is a cause of excessive vascular impedance in heart failure (Curtis *et al.*, 1978).

The peripheral vasoconstriction in heart failure occurs unequally in various regional circulations (Wade & Bishop, 1972). The cutaneous renal and splanchnic circulations have the greatest vasoconstriction such that the fractional distribution of flow falls in these vascular beds and is preserved in the coronary and cerebral beds. The effect of vasodilators on the fractional distribution of cardiac output is complex and depends on the basal levels of neural, humoral, and intrinsic factors (Zelis *et al.*, 1979).

This study reports on the effect of captopril, an orally active converting-enzyme inhibitor, on the distribution of cardiac output in patients with severe congestive heart failure. The findings suggest that the renin-angiotensin system impairs renal blood flow and diminishes urinary sodium excretion, and has little effect on limb, splanchnic, or coronary flow. The restoration of renal blood flow and natriuresis associated with reduction in vascular impedance makes captopril a unique vasodilator in the treatment of congestive heart failure.

Methods

Thirty-six patients with chronic congestive heart failure (New York Heart Association functional classes III–IV) were studied after a stay in hospital of at least 48 hours. The average age was 57 ± 12. Twenty-eight were men and eight women. Coronary artery disease was clinically or angiographically documented in 30, and six had an idiopathic cardiomyopathy. Twelve were thought to show clinical deterioration over a three-month period before study, and 24 were thought to be stable. The average ejection fraction determined by radionuclide gated blood pool scan was $24 \pm 6\%$. Details of long-term follow-up have been reported elsewhere (Creager *et al.*, 1982).

After in-hospital stabilisation on a 2 g sodium diet, digoxin and frusemide dosages, and discontinuation of other vasodilators, an acute haemodynamic study

0306–5251/82/100179–08 $01.00

was undertaken. On the day of study all medication was withheld. A right-heart catheterisation with a Swan-Ganz flow directed catheter was performed and radial artery cannulation was placed. Pressures were measured by using Bentley model 508 strain-gauge transducers recorded on a direct writing Hewlett-Packard multigraph. Mean pressures were obtained by electrical integration with zero reference at the mid-axillary line. Cardiac output was determined by thermodilution using an Instrumentation Laboratory model 601 cardiac output computer averaging at least three replicate determinations varying less than 10%. Plasma renin activity was quantified in systemic venous blood by radioimmunoassay of angiotensin I generation (Sealey *et al.*, 1972) and noradrenaline by a modified radioenzymatic assay (Ben-Jonathan & Porter, 1976). Plasma aldosterone concentration was determined in twelve patients with a direct radioimmunoassay (St Cyr *et al.*, 1972).

Regional blood flow was measured in separate patient groups. Limb blood flow was measured in eight patients, coronary blood flow in 12, and splanchnic and renal blood flow in 9 and 11, respectively. In addition, limb blood flow was measured in eight normal volunteers for comparison.

Limb blood flow was measured by venous occlusion forearm plethysmography by a Whitney mercury/silastic strain gauge placed circumferentially around the forearm and connected to a modified Park Electronics Laboratories model 270 plethysmograph in connection with a Hewlett–Packard multichannel recorder. Each subject was positioned so the arm was above the level of the heart. A sphygmomanometric cuff was placed around the wrist and inflated to at least 50 mm Hg above systolic blood pressure to exclude hand vasculature. To examine the effect of dynamic exercise, eight patients with heart failure and eight volunteers were asked to squeeze a hand dynamometer to 100 mm Hg for five seconds, four times a minute for five minutes, as described by Zelis *et al.*, (1974). Measurements were made between each squeeze. Venous volume, forearm blood flow, and forearm vascular resistance were determined as reported (Faxon *et al.*, 1980).

Coronary sinus blood flow was measured in eleven patients with ischaemic cardiomyopathy by using a thermodilution technique after placement of a No 7F Ganz thermodilution catheter into the coronary sinus. The catheter was placed 2–3 cm from the coronary sinus ostium and its position verified by periodic injections of radio-opaque contrast under fluoroscopy. Coronary sinus flow was determined using a Wheatstone bridge (Wilton Webster Laboratories, Altadena, California) and recorded as described by Ganz *et al.* (1971). Flow was calculated from the change in temperature of the coronary sinus blood during infusion of 5% dextrose in water at 20°C at a rate of 50 ml/min. Oxygen saturations from the arterial and coronary sinus blood were determined according to the method of Gordy and Dratkin (1957) using a Beckman spectrophotometer. Total coronary resistance was calculated as the ratio of arteriovenous pressure gradient to coronary sinus flow. Myocardial oxygen consumption was determined by the product of flow and oxygen extraction. External myocardial efficiency was calculated as the ratio of left ventricular work index to myocardial oxygen consumption.

Hepatomesenteric blood flow was estimated by determination of the clearance of indocyanine green (C_{ICG}) according to the method of Wiegand *et al.* (1960). A single bolus of indocyanine green (0.5 mg/kg) was injected into the pulmonary artery and blood sampled from the right atrium at five-minute intervals for 20 min.

Renal blood flow was calculated from the effective renal plasma flow determined from the clearance of *p*-aminohippurate (C_{PAH}) (Smith *et al.*, 1945). After injection of 0.04 mg/kg, a constant infusion of 2 mg/min was begun. After 45 minutes of equilibration, three 20-minute collections of urine via a Foley catheter and four simultaneous venous samples were obtained to determine the C_{PAH}. Determination of glomerular filtration was made by measurement of the clearance of endogenous creatinine and urine sodium excretion ($U_{Na}V$) quantified. Renal vascular resistance was defined as the systemic pressure gradient divided by renal blood flow. Filtration fraction was calculated as the ratio of glomerular filtration rate to renal plasma flow × 100.

Systemic haemodynamic data was collected until three successive determinations 15 min apart demonstrated homeostatis. Regional blood flow was determined simultaneously with the systemic haemodynamics. Captopril, 25 mg or 100 mg, was given orally as a single dose and repeat measurements were made 30, 60, 90, and 120 min afterwards. Coronary blood flow or limb blood flow was measured simultaneously with the systemic haemodynamics. Five of 11 patients, in whom coronary blood flow was measured, received teprotide (1 mg/kg) (Squibb) instead of captopril. Indocyanine green clearance was determined before and one hour after captopril and renal plasma flow, creatinine clearance and urine sodium excretion were determined before and one to two hours after captopril.

Haemodynamic indices were derived from standard formulae (Yang *et al.*, 1978). Data before and over the hour of peak effect were averaged. Peak effect was defined as the maximal fall in systemic vascular resistance. Measurements were evaluated by the paired Student's *t*-test and the Wilcoxon–Mann–Whitney rank-sum statistic for Gaussian and non-Gaussian distributions, respectively, and expressed as the mean ± s.d. The Pearson product moment correlation coefficient was

computed along selected variables. Statistical significance was accepted at the 95% confidence level ($p < 0.05$).

Results

Central haemodynamic response

As reported (Creager *et al.*, 1982), captopril resulted in a reduction in mean blood pressure (85.0 ± 14 to 72.4 ± 17 mm Hg, $p < 0.001$) and fall in heart rate (87 ± 13 to 81.7 ± 10, $p < 0.01$). The systemic vascular resistance decreased 27% (2028 ± 664 to 1499 ± 620 dyne/s/cm^{-5}, $p < 0.001$), while cardiac index significantly improved from 1.78 ± 0.44 to 2.10 ± 0.48 l/min/m^2 ($p < 0.001$). Stroke work index rose slightly from 33.3 ± 14.8 to 35.8 ± 15.3 gm/m^2 ($p < 0.05$). Concomitant with these changes in arterial impedance, pulmonary capillary wedge pressure fell 27% from 27 ± 8 to 19.6 ± 6.9 mm Hg ($p < 0.001$) and right atrial pressure fell from 11.8 ± 6.1 to 9.5 ± 6.3 mm Hg ($p < 0.001$). Although mean pulmonary pressure fell, pulmonary arteriolar resistance did not significantly change.

Hormonal changes

Pretreatment plasma renin activity was raised in most patients, averaging 15.9 ± 19.8 ng/ml/h. After captopril, the level rose to 40.2 ± 38.1 ng/ml/h ($p < 0.001$). The change in plasma noradrenaline concentration from 957 ± 880 to 800 ± 545 pg/ml was not significant. Plasma aldosterone was measured in nine patients who had renal blood flow measured and averaged 30.5 ± 6.5 μg/dl before and 11.3 ± 1.2 μg/dl after ($p < 0.01$).

Regional blood flow (Figure 1)

Forearm vascular response (Figure 2) In patients with congestive heart failure, forearm blood flow was normal at rest and rose threefold during dynamic exercise. Captopril caused no significant change at rest or during exercise. In contrast, normal volunteers showed an increase in resting flow after captopril (2.8 to 5.9 ml/100 ml tissue/min, $p < 0.02$), but captopril did not significantly augment exercise blood flow. The level of vasodilatation achieved during exercise was greater in the normal subjects than in those with heart failure ($p < 0.01$). Venous volume showed no significant change after captopril in normal subjects or patients with heart failure.

Coronary haemodynamic response (Figure 3) Coronary sinus blood flow did not significantly change in the 11 patients in whom it was measured (160 ± 20 to 133 ± 12 ml/min, NS), although there was a relationship between the change in flow and the change in arterial perfusion. Likewise, coronary

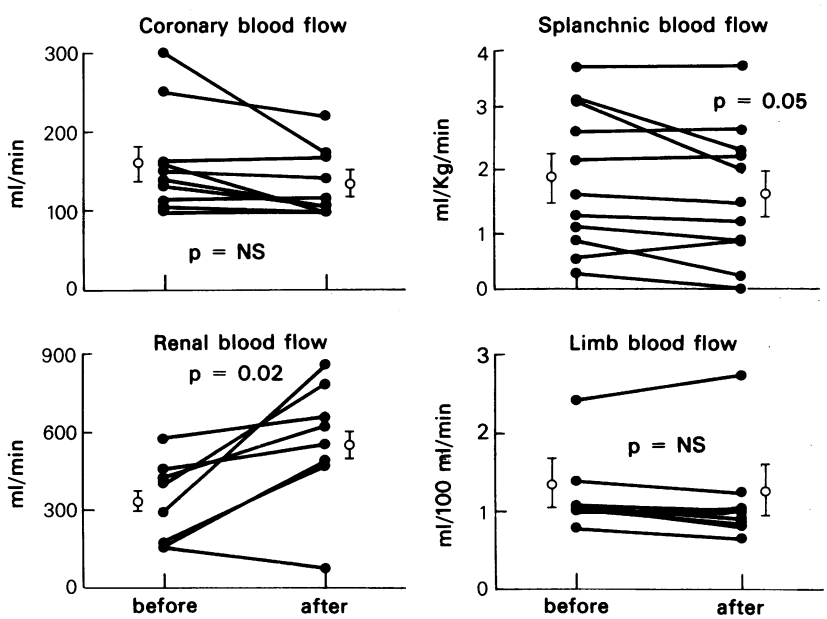

Figure 1 The acute regional circulatory response to captopril is illustrated. The values before and at peak effect after are shown. The mean ± SEM is indicated for each group. A significant fall in splanchnic flow as determined by the clearance of indocyanine green occurred while renal blood flow doubled. Coronary and limb blood flow was unaltered.

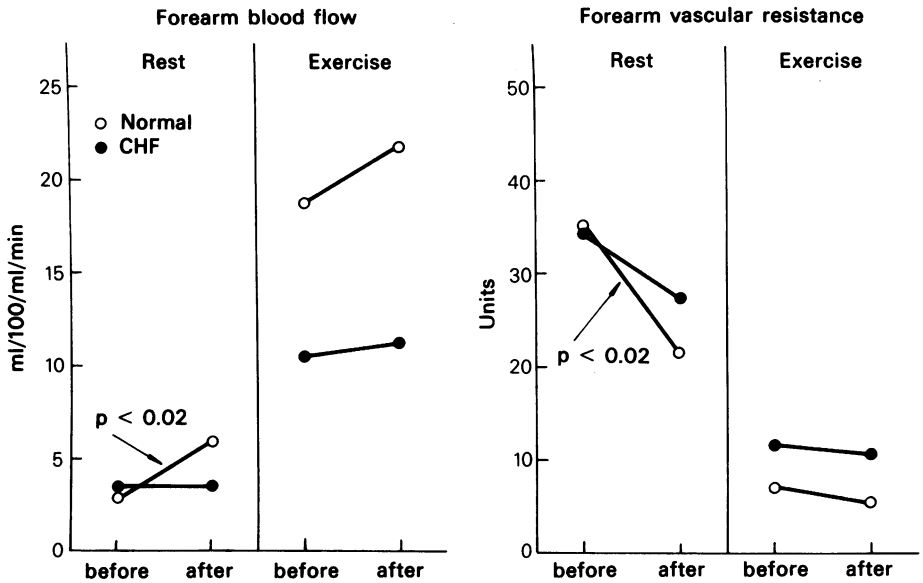

Figure 2 The changes in forearm blood flow and forearm vascular resistance at rest and after dynamic exercise are shown. The open circles depict normal volunteers and the closed circles represent patients with heart failure. Only the normal subjects showed an increase in flow at rest and neither normal subjects nor patients with heart failure showed a response to captopril during exercise.

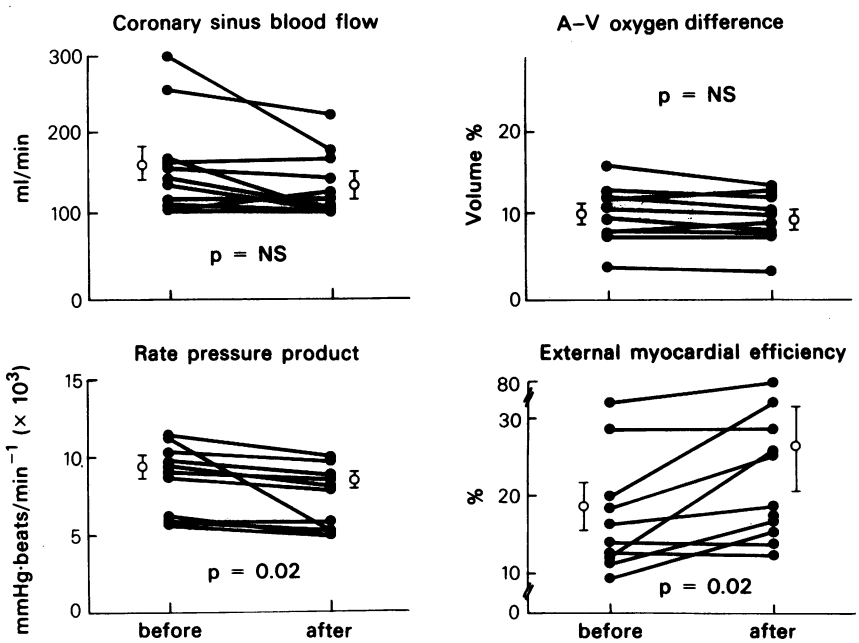

Figure 3 The coronary haemodynamic response to captopril in 11 patients with ischaemic cardiomyopathy is shown. While coronary sinus blood flow and arteriovenous oxygen difference did not change, rate pressure product fell and external myocardial efficiency rose.

vascular resistance and coronary arteriovenous oxygen difference did not change. Thus, myocardial oxygen consumption remained constant (16.4 ± 1.9 to 13.9 ± 1.6 ml/min, NS), despite a fall in the heart rate—systolic blood pressure product (8,824 ± 703 to 7,078 ± 514 beats/mm Hg, $p < 0.02$). A derived index of external myocardial efficiency improved 37% (19 ± 3 to 26 ± 6%, $p < 0.05$), reflecting left ventricular work without increased oxygen demand.

Splanchnic vascular response (Figure 1) Pretreatment clearance of indocyanine green ranged widely; after captopril, however, it declined 17%, paralleling the fall in arterial pressure. These changes would suggest that no splanchnic vasodilatation occurred.

Renal haemodynamic results (Figure 4)

Renal plasma flow showed a significant increase after captopril from 202.8 ± 28.8 to 323.7 ± 42.7 ml/min ($p < 0.01$). Glomerular filtration rate did not change significantly; filtration fraction, however, fell towards normal (41.3 ± 3.8 to 33.4 ± 4.5, $p < 0.05$). Urinary sodium excretion doubled from 34.5 ± 9.6 to 68.2 ± 19.6 μmol/min ($p < 0.05$).

The fractional distribution of cardiac output delivered to the kidney rose towards normal after captopril (10 ± 1 to 14 ± 2%, $p < 0.05$).

Discussion

Converting-enzyme inhibition with captopril improves cardiac function in patients with congestive heart failure, and our results are consistent with those of previous reports (Gavras *et al*, 1978; Davis *et al.*, 1979; Faxon *et al.*, 1980; Faxon *et al.*, 1981; Creager *et al.*, 1982). The haemodynamic benefit appears to be due to a reduction in ventricular afterload and preload without pulmonary vascular effects through interruption of the renin–angiotensin axis. It is also accepted that converting-enzyme inhibitors block the degradation of bradykinin (Johnston *et al.*, 1982), and we cannot exclude the accumulation of bradykinin as a cause of vasodilatation. The fall in preload and afterload does not precisely indicate the magnitude or location of the peripheral changes that occur after angiotensin inhibition, since central reflex (Zelis *et al.*, 1978), compliance (Alderman & Glanz, 1976), or contractile changes could confuse the interpretation of the central haemodynamic response.

It is generally accepted that abnormalities of the peripheral circulation occur commonly in patients with congestive heart failure (Zelis & Longhurst, 1975). The abnormal increase of vascular impedance further impairs cardac function, and vasodilators benefit patients by relieving this excess vasoconstriction. Blood flow to many organs is reduced in heart

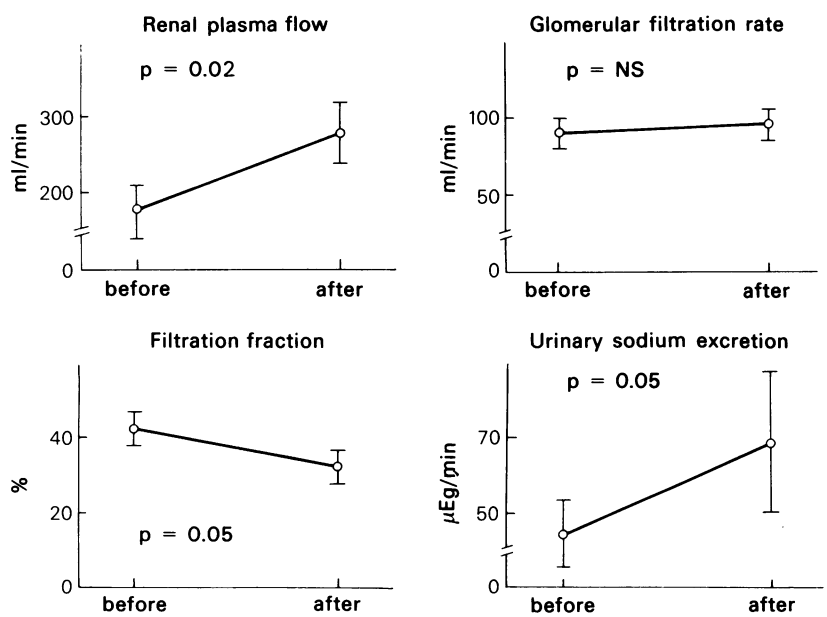

Figure 4 A significant rise in renal plasma flow occurred following captopril. This was accompanied by a fall in filtration fraction and a significant rise in urinary sodium excretion. Glomerular filtration rate did not change significantly.

failure. The greatest reduction occurs in the cutaneous, renal, and splanchnic circulations (Wade *et al.*, 1962). The mechanism of this regional vasoconstriction is complex. Zelis & Mason (1970) showed that these changes are, in part, due to augmentation of sympathetic tone and to increased sodium and water content in the arterial wall. What role other humoral, neural, or local autoregulatory factors have has not been carefully studied.

In normotensive sodium-depleted dogs not in heart failure, angiotensin inhibition enhances renal perfusion at the expense of cutaneous, skeletal, muscular, and hepatomesenteric flow (Gavras *et al.*, 1978). The evidence reported here and previously (Faxon *et al.*, 1980, 1981; Creager *et al.*, 1981; Halperin *et al.*, 1982) would support these observations and suggest that the renin–angiotensin system plays an important part in the redistribution of flow and the renal vasocontriction that occurs in heart failure.

The lack of a response of the limb vasculature to converting-enzyme inhibition distinguishes captopril from the actions of other vasodilators. Nitroprusside, phentolamine, nitroglycerine, prazosin, and hydralazine all reduce limb vascular resistance or increase limb venous volume, or both (Awan *et al.*, 1978; Miller *et al.*, 1976). Given the potent vasoconstrictor effects of angiotensin (Wood, 1961), the lack of a response in the arterioles or veins seems paradoxical. The absence of an effect may be due to reflex increase in sympathetic activity, local factors, or limited peripheral vasoconstrictor response to angiotensin. The lack of a response to captopril during exercise would also confirm this observation. Although vasodilation was less than normal during exercise in patients with heart failure, angiotensin inhibition did not improve nutrient flow. This observation suggests that other factors are responsible for the abnormal limb vascular response to exercise (Zelis *et al.*, 1974).

The hepatomesenteric vascular bed is one of the largest blood pools, and little is known of its response to vasodilators (Rowell, 1975). The lack of a response in this study would argue against a major effect of angiotensin on splanchnic flow. We did not, however, measure the hepatic extraction of this indicator, nor did we measure hepatic venous capillary pressure, so precise changes in blood flow or vascular resistance could not be calculated.

Coronary blood flow is usually preserved in patients with congestive heart failure. It has, however, been suggested that vasodilator therapy might be deleterious to patients with coronary artery disease due to either a fall in perfusion pressure or a redistribution of coronary flow away from the areas of ischaemia (coronary steal) (Mann *et al.*, 1978). Since most patients with congestive heart failure have coronary artery disease these issues are of utmost importance. This study and our previous reports (Halperin *et al.*, 1982) suggest that angiotensin inhibition does not have a major effect on the coronary vasculature. This may reflect either limited coronary vascular reserve in the setting of coronary artery disease, or an effect upon myocardial oxygen consumption, which in turn would maintain coronary flow through autoregulation (Weber & Janick, 1978; Klocke & Ellis, 1980). Nevertheless, the improvement in heart failure in these patients developed without evidence of myocardial ischaemia, since a balance was maintained between oxygen supply and demand. The improvement in ventricular performance did not result in an increase in oxygen utilisation, as shown by an increase in external myocardial efficiency.

Unlike the limb, splanchnic, and coronary circulations, renal perfusion rose 60% after converting-enzyme inhibition. This increase accounted for half of the rise in cardiac output and increased the fraction distribution of cardiac output to the kidney (10 to 14%), unlike the response reported with other vasodilators (Cogan *et al.*, 1980). The renin–angiotensin system has been implicated in the regulation of renal plasma flow, filtration fraction and glomerular filtration (Hollenberg *et al.*, 1977; Brenner *et al.*, 1982). It has been suggested that the renin–angiotensin system might explain the decrease in urinary sodium excretion known to occur in heart failure. The improvement in renal plasma flow, reduction in filtration fraction, and significant natriuresis reported here would support this contention. The fall in aldosterone could also contribute to this natriuresis. Our observations are supported by the findings of Dzau *et al.* (1980), who showed an improvement in renal blood flow sodium excretion after one week's treatment with captopril. The renal response to captopril differs from that in other studies of vasodilators in heart failure, in which a fall in filtration fraction was not accompanied by an increase in sodium excretion (Cogan *et al.*, 1980). In addition, sodium retention often accompanies treatment with prazosin or minoxidil.

We consider that the evidence provided in this study substantiates the hypothesis that converting-enzyme inhibition results in a strategic reduction in vascular impedance through selective peripheral vasodilatation. The renal vasculature appears to be most benefited, and significant improvement in renal haemodynamics and sodium excretion results. The splanchnic, limb, and coronary vascular beds show little effect of converting-enzyme inhibition in the setting of heart failure. The lack of coronary vasodilation may reflect the presence of limited coronary vascular reserve in the setting of coronary artery disease. The preservation of coronary flow supports the use of these agents in ischaemic cardio-

myopathies. This regional circulatory selectivity distinguishes converting-enzyme inhibitors as unique vasodilators in the treatment of severe congestive heart failure.

We are indebted to Dr Haralambos Gavras, James Melby, Jay Coffman, and Thomas J. Ryan for their assistance in these studies. We also thank Caroline Melidossian, R.N., for her technical help in accomplishing this project.

Supported in part by USPHS grants HL-18318-05, HL-22172 and HL-23304 from the National Institutes of Health.

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