Regulation of peripheral vascular tone in patients with heart failure: contribution of angiotensin II

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Abstract

Objective—To determine directly the contribution of angiotensin II to basal and sympathetically stimulated peripheral arteriolar tone in patients with heart failure.

Design—Parallel group comparison.

Subjects—Nine patients with New York Heart Association grade II–IV chronic heart failure, and age and sex matched controls.

Interventions—Forearm plethysmography, lower body negative pressure, local intra-arterial administration of losartan, angiotensin II, and noradrenaline, and estimation of plasma hormone concentrations.

Main outcome measures—Forearm blood flow responses, plasma hormone concentrations.

Results—Baseline blood pressure, heart rate, and forearm blood flow did not differ between patients and controls. In comparison with the non-infused forearm, losartan did not affect basal forearm blood flow (95% confidence interval −5.5% to +7.3%) or sympathetically stimulated vasoconstriction in controls. However, the mean (SEM) blood flow in patients increased by 13(5)% and 26(7)% in response to 30 and 90 µg/min of losartan respectively (p < 0.001). Lower body negative pressure caused a reduction in forearm blood flow of 20(5)% in controls (p = 0.008) and 13(5)% (p = 0.08) in patients (p = 0.007, controls *v* patients). Blood flow at 90 µg/min of losartan correlated with plasma angiotensin II concentration (*r* = 0.77; p = 0.03). Responses to angiotensin II and noradrenaline did not differ between patients and controls.

Conclusions—Losartan causes acute local peripheral arteriolar vasodilatation in patients with heart failure but not in healthy control subjects. Endogenous angiotensin II directly contributes to basal peripheral arteriolar tone in patients with heart failure but does not augment sympathetically stimulated peripheral vascular tone.

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Angiotensin II is a potent vasoconstrictor and pressor peptide, playing a fundamental role in the regulation of blood pressure and body sodium and water under circumstances of sodium and volume depletion.[1] All the major effects of angiotensin II are mediated through the angiotensin II type 1 (AT_1) receptor, and include arteriolar vasoconstriction, renal sodium reabsorption, and stimulation of adrenal aldosterone production.[1] Within minutes of acute hypovolaemia, renin secretion causes rapid generation of angiotensin II, leading to compensatory vasoconstriction and fluid retention that serves to sustain blood pressure and prevent circulatory collapse.[2] Even at doses insufficient to cause vasoconstriction directly, angiotensin II augments sympathetically mediated vasoconstriction[3] through a prejunctional adrenoreceptor mediated mechanism.[4 5] Thus angiotensin II has the potential to be a major contributor to the physiological regulation of vascular tone and blood pressure in man.

The renin-angiotensin system also plays a central role in the pathophysiology of heart failure. Decreased renal perfusion secondary to low cardiac output increases renin production, which in turn leads to increased generation of angiotensin II. The vasoconstrictor and salt and water retaining properties of angiotensin II increase cardiac work, leading to a vicious circle of worsening heart failure—hence the rationale for using ACE inhibitor treatment in patients with heart failure to interrupt this damaging maladaptive response. This paradigm has been confirmed in many clinical heart failure studies in terms of clinical status and exercise time,[6 7] and long term effects on morbidity and mortality.[8–11] However, ACE inhibitors not only block the generation of angiotensin II from angiotensin I, but also inhibit the degradation of other peptides such as bradykinin and substance P. Thus the mechanisms whereby ACE inhibition achieves these beneficial effects in heart failure are unclear and may not be directly attributable to a reduction in plasma angiotensin II concentrations.[12]

Systemic AT_1 antagonism in patients with heart failure causes a reduction in blood pressure and systemic vascular resistance.[13 14] However, when examining in vivo vascular responses in man, systemic drug administration causes concomitant effects on organs such as the brain, kidney, and heart, and influences neurohumoral reflexes through changes in systemic haemodynamics. Because of these confounding influences, vascular responses cannot be wholly attributed to a direct effect of the drug in blood vessels.[15 16] In contrast, the use of bilateral forearm blood flow measurements—with unilateral brachial artery infusion of vasoactive drugs at subsystemic, locally active doses—provides a powerful and reproducible method of directly assessing vascular responses in vivo.[15 16] This technique has been used very

successfully to demonstrate the major contribution of nitric oxide and endothelin-1 to the maintenance of basal peripheral vascular tone in healthy people.[17] [18]

Previous local forearm studies assessing the role of the renin-angiotensin system in the maintenance of basal peripheral vascular resistance[19] [20] have been confounded by the use of antagonists, such as saralasin, with partial agonist activity. However, losartan, a selective AT_1 receptor antagonist devoid of agonist activity, has recently become available for clinical use. The aims of our study were thus to investigate patients with heart failure and matched healthy controls as follows: first, to establish the role of endogenous angiotensin II in the maintenance of peripheral vascular tone; second, to determine the effect of sympathetically stimulated vasoconstriction in the presence and absence of angiotensin II antagonism; and third, to document the peripheral vascular responses to noradrenaline and angiotensin II.

Methods

SUBJECTS

We recruited nine patients with established chronic heart failure of New York Heart Association (NYHA) grade II–IV who were taking maintenance ACE inhibitor treatment. They had a left ventricular ejection fraction of < 35% or echocardiographic evidence of left ventricular impairment (shortening fraction of < 20% or left ventricular end diastolic diameter of > 5.6 cm), or both. Age and sex matched controls were also recruited. All studies were undertaken with the approval of the local research ethics committee and the written informed consent of each subject.

None of the control subjects received vasoactive or non-steroidal anti-inflammatory drugs in the week before each phase of the study, and all abstained from alcohol for 24 hours and from food and caffeine containing drinks for at least nine hours before each study. Patients were withdrawn from ACE inhibitor treatment for five drug half lives before each of the study days. All other concomitant drugs were omitted on the study day. All studies were performed in a quiet, temperature controlled room maintained at 23.5–24.5°C.

DRUGS

Losartan (Dupont-Merck, Wilmington, USA), noradrenaline (Levophed; Sanofi Winthrop, Guildford, UK), and angiotensin II (Clinalfa AG, Läufelfingen, Switzerland) were dissolved in physiological saline and given intra-arterially. To prevent its oxidation, noradrenaline was dissolved in saline containing 0.1% ascorbic acid (Evans Medical, Langhurst, UK). Doses of losartan (30–90 μg/min) were chosen to achieve an effective subsystemic and locally active concentration.[21] [22]

INTRA-ARTERIAL ADMINISTRATION

The brachial artery of the non-dominant arm was cannulated with a 27 gauge steel needle (Cooper's Needle Works, Birmingham, UK) under 1% lignocaine (Xylocaine; Astra Pharmaceuticals, Kings Langley, UK) local anaesthesia. The cannula was attached to a 16 gauge epidural catheter (Portex, Hythe, UK) and patency maintained by infusion of physiological saline through a syringe pump. The total rate of intra-arterial infusions was maintained constant throughout all studies at 1 ml/min.

FOREARM BLOOD FLOW AND BLOOD PRESSURE

Blood flow was measured in both the infused and non-infused forearms by venous occlusion plethysmography using mercury-in-Silastic strain gauges applied to the widest part of the forearm.[15] During measurement periods the hands were excluded from the circulation by rapid inflation of the wrist cuffs to a pressure of 220 mm Hg using E20 Rapid Cuff Inflators (D E Hokanson, Washington DC, USA). Upper arm cuffs were inflated intermittently to 40 mm Hg for 10 seconds in every 15 seconds to achieve venous occlusion and obtain plethysmographic recordings. Analogue voltage output from an EC-4 strain gauge plethysmograph (D E Hokanson) was processed by a MacLab analogue to digital converter and Chart *v*3.3.8 software (AD Instruments, Castle Hill, Australia) and recorded onto a MacIntosh Classic II computer (Apple Computers, Cupertino, USA). Calibration was achieved using the internal standard of the plethysmograph.

Blood pressure was monitored in the non-infused arm at intervals throughout each study, using a semi-automated non-invasive oscillometric sphygmomanometer[23] (Takeda UA 751, Takeda Medical, Tokyo, Japan).

LOWER BODY NEGATIVE PRESSURE

Subjects were rested supine in a plastic covered steel cage enclosing the lower body from the waist, as described previously.[3] Suction was applied using an industrial strength vacuum cleaner regulated by a servo control unit (Medical Physics Department, Edinburgh, UK) to produce a constant negative pressure of 15 mm Hg. Alteration to and from atmospheric pressure was attained within one to two seconds.

VENOUS SAMPLING AND ASSAYS

Ten minutes before giving losartan by infusion and 10 minutes after its completion, 30 ml of blood was withdrawn from the non-infused arm and 10 ml admixed with each of 1 ml of 1% disodium EDTA, 0.5 ml of 0.45% *O*-phenanthroline/4.65% disodium EDTA, and 1 ml of 1% disodium EDTA/2% sodium metabisulphite. The samples were placed on ice and immediately centrifuged at 2000 ×*g* for 15 minutes. Plasma was frozen and stored at −80°C before assay for plasma angiotensin II, endothelin-1, big endothelin-1, adrenaline, and noradrenaline concentrations. Following extraction using Bond Elut columns (Varian, Harbor City, California, USA),[24] concentration of plasma angiotensin II (Peninsula Laboratories Europe, St Helens, UK), endothelin-1 (Peninsula Laboratories Europe), and big endothelin-1 (Peninsula Laboratories Europe) were determined by radioimmunoassay as previously described.[25] [26] The intra-assay coefficients of variability were

5.2%, 7.0%, and 7.2%, respectively, and the interassay coefficients of variability were 8.6%, 9.0%, and 9.3%, respectively. The cross reactivities of the endothelin-1 assay were as follows: endothelin-1 (100%), endothelin-2 (7%), endothelin-3 (7%), big endothelin-1 (10.3%), C-terminal fragment (0%), angiotensin I (0%), and angiotensin II (0%). The cross reactivities of the big endothelin-1 assay were as follows: endothelin-1 (0%), endothelin-2 (0%), endothelin-3 (0%), big endothelin-1 (100%), C-terminal fragment (100%), and brain natriuretic peptide-32 (0%). Adrenaline and noradrenaline concentrations were determined by an electrochemical method after separation by reverse phase high performance liquid chromatography.[27]

STUDY DESIGN

Subjects attended at 09:00 and rested recumbent throughout each study. Strain gauges and cuffs were applied and the brachial artery of the non-dominant arm cannulated. Measurements of forearm blood flow were made for the last three minutes of each infusion period unless otherwise stated. Before participating in one of the following protocols, saline was infused for the first 30 minutes to allow time for equilibration, with forearm blood flow measurements being made every 10 minutes and basal blood flow being taken as the last of these measurements.

Eight patients with heart failure and eight matched healthy controls received saline, losartan 30 µg/min, losartan 90 µg/min,[21 22] and saline, each for 13 minutes and in that order. Forearm blood flow was measured continuously for the last six minutes of each infusion, with lower body negative pressure being applied for the last three minutes. Following 15 minutes of further saline infusion, noradrenaline was infused intra-arterially at doses of 20, 60, 180, and 540 pmol/min,[22] each for six minutes. At least one week later, subjects reattended and received incremental doses of angiotensin II (0.1, 1, 10, and 100 pmol/min),[22] each dose given into the brachial artery for six minutes. One patient withdrew after the first visit and was replaced.

DATA ANALYSIS AND STATISTICS

Plethysmographic data were extracted from the chart data files and forearm blood flows were calculated for individual venous occlusion cuff inflations by use of a template spreadsheet (Excel *v*5.0; Microsoft). Recordings from the first 60 seconds after wrist cuff inflation were not used because this causes reflex vasoconstriction.[15 16] Usually, the last five flow recordings in each three minute measurement period were calculated and averaged for each arm. To reduce the variability of blood flow data, the ratio of flows in the two arms was calculated for each time point, in effect using the non-infused arm as a contemporaneous control for the infused arm.[15 16] Percentage changes in the infused forearm blood flow were calculated[15 16] as follows:

$$\% \text{ Change in blood flow} = 100 \times \{I_t/NI_t - I_b/NI_b\} \, / \, I_b/NI_b$$

where I_b and NI_b are the infused and non-infused forearm blood flows at baseline (time 0), respectively, and I_t and NI_t are the infused and non-infused forearm blood flows at a given time point.

Data were examined by analysis of variance (ANOVA) with repeated measures, two tailed paired Student's *t* test, and regression analysis using Excel *v*5.0. All results are expressed as mean (SEM). Significance was taken at the 5% level.

Results

Patients had significantly higher plasma endothelin-1 and big endothelin-1 concentrations than controls (table 1), with a trend for higher plasma angiotensin II and adrenaline concentrations.

There were no significant differences in blood pressure, heart rate, or baseline forearm blood flows in the infused and non-infused arms between protocols, or between patient and control subjects. Throughout all studies there were no significant changes in heart rate or arterial pressure (table 2; data on file). Except during the application of lower body negative pressure, there were no significant changes in blood flow in the non-infused arm. Plasma angiotensin II concentrations did not change significantly during the study (table 1).

In the healthy control subjects, there were no significant changes in blood flow of the infused forearm during infusions of saline or losartan (fig 1). Student's *t* distribution gives 95% confidence intervals of −5.5% to +7.3% and −9.7% to +6.9% for percentage changes in forearm blood flow with 30 µg/min and 90

Table 1 Subject characteristics

	Control subjects	Patients with heart failure
Mean (SD) age (years)	61 (4)	64 (2)
Sex (M/F)	6/3	6/3
Aetiology ischaemic heart disease	–	9
NYHA grade II/III/IV	–	5/3/1
Left ventricular ejection fraction (%)	–	30 (2)
Echocardiography		
LVEDD (cm)	–	7.2 (0.5)
SF (%)	–	16 (2)
Concomitant treatment		
ACE inhibitor	–	9
Diuretic	–	9
Aspirin	–	9
Nitrates	–	5
β Blocker	–	3
Calcium antagonist	–	3
Digoxin	–	2
Amiodarone	–	1
Blood pressure (mm Hg)		
Systolic	132 (5)	132 (9)
Diastolic	82 (5)	81 (6)
Heart rate (beats/min)	66 (3)	64 (2)
Baseline blood flow (ml/100 ml/min)		
Infused	4.2 (0.7)	2.8 (0.3)⋆
Non-infused	3.7 (0.6)	2.6 (0.2)⋆
Plasma endothelin-1 (fmol/ml)	1.9 (0.3)	3.0 (0.1)†
Plasma big endothelin-1 (fmol/ml)	7.9 (2.0)	19.6 (3.5)‡
Plasma angiotensin II (fmol/ml)		
Basal	3.3 (0.3)	13.3 (9.6)§
After losartan	3.3 (0.4)	9.1 (3.9)§
Plasma noradrenaline (pmol /ml)	1.6 (0.5)	1.3 (0.1)
Plasma adrenaline (pmol/ml)	0.3 (0.1)	1.3 (0.6)¶

⋆p = 0.11; †p = 0.005; ‡p = 0.01; §p = 0.08; ¶p = 0.16.
ACE, angiotensin converting enzyme; LVEDD, left ventricular end diastolic dimension; NYHA, New York Heart Association; SF, shortening fraction.

Table 2 Systemic haemodynamics, forearm blood flow, and lower body negative pressure (LBNP) responses during saline and losartan infusions

	Control subjects (n = 8)				Patients with heart failure (n = 8)			
	Saline	*Losartan 30 μg/min*	*Losartan 90 μg/min*	*Saline*	*Saline*	*Losartan 30 μg/min*	*Losartan 90 μg/min*	*Saline*
Blood pressure (mm Hg)								
Systolic	129 (4)	132 (4)	128 (5)	133 (4)	134 (9)	134 (9)	139 (9)	133 (9)
Diastolic	86 (4)	86 (6)	85 (3)	83 (3)	83 (6)	85 (7)	85 (6)	81 (6)
Heart rate (beats/min)	74 (3)	68 (3)	65 (4)	63 (3)	64 (2)	63 (2)	62 (2)	63 (2)
Absolute forearm blood flow (ml/100ml/min)								
Non-infused arm	3.8 (0.7)	4.1 (1.0)	4.2 (1.0)	4.8 (1.2)	2.9 (0.5)	2.7 (0.3)	2.7 (0.2)	2.6 (0.2)
Infused arm	4.3 (0.8)	4.7 (1.2)	4.7 (1.2)	4.8 (1.1)	3.1 (0.5)	3.4 (0.5)	3.6 (0.4)	3.2 (0.5)*
Percentage change in								
forearm blood flow	1 (2)	1 (3)	−1 (4)	−5 (5)	0 (2)	13 (5)	26 (7)	12 (5)†
Absolute forearm blood flow with LBNP (ml/100ml/min)								
Non-infused arm	3.1 (0.6)	3.3 (0.8)	3.3 (0.8)	3.5 (0.9)	2.4 (0.3)	2.4 (0.3)	2.3 (0.2)	2.3 (0.2)
Infused arm	3.4 (0.7)	3.5 (0.9)	3.7 (1.0)	4.0 (1.2)	2.5 (0.3)	2.8 (0.4)	3.0 (0.2)	2.7 (0.3)
Percentage vasoconstriction with LBNP								
Non-infused arm	19 (4)	20 (4)	21 (2)	20 (5)‡	13 (5)	11 (4)	12 (5)	13 (3)
Infused arm	20 (5)	24 (3)	24 (4)	18 (4)‡	14 (6)	15 (4)	15 (5)	14 (5)

*p < 0.001 (two way ANOVA: infused *v* non-infused); †p < 0.001 (two way ANOVA: patients *v* controls); ‡p = 0.008 (two way ANOVA: basal *v* LBNP).

μg/min of intra-arterial losartan, respectively. During saline infusion, lower body negative pressure caused a 20(5)% and a 19(4)% reduction in the infused and non-infused forearm blood flow, respectively (table 2; p = 0.008). There were no significant differences between the vasoconstriction induced by the application of lower body negative pressure in the infused and non-infused arms across the saline and losartan infusion periods (fig 1 and table 2).

In patients with heart failure, blood flow increased by 13.3% (95% confidence interval +2.3 to +24.4%) and 25.6% (+9.1 to +42.2%) in the infused forearm with 30 μg/min and 90 μg/min of intra-arterial losartan, respectively (p < 0.001; fig 1). The increase in blood flow at 90 μg/min of losartan correlated with the baseline plasma angiotensin II concentration (*r* = 0.77; p = 0.03). Lower body negative pressure did not significantly reduce the blood flow in either arm (p = 0.08) and was unaffected by losartan in the infused forearm (fig 1 and table 2). The lower body negative pressure response was significantly less than that achieved in the control subjects (p = 0.007; fig 1 and table 2).

Angiotensin II and noradrenaline caused dose dependent vasoconstriction in both patients and controls (p < 0.001 for all; fig 2). There was no significant difference in the magnitude of the vasoconstriction response to noradrenaline or angiotensin II between patients and controls.

Discussion

We have previously shown in healthy volunteers[22] that intra-arterial losartan infusion, at doses of 30–300 μg/min, is locally active only and is able to reverse the vasoconstriction caused by angiotensin II infusion at 1 pmol/min within six minutes. This dose of angiotensin II is
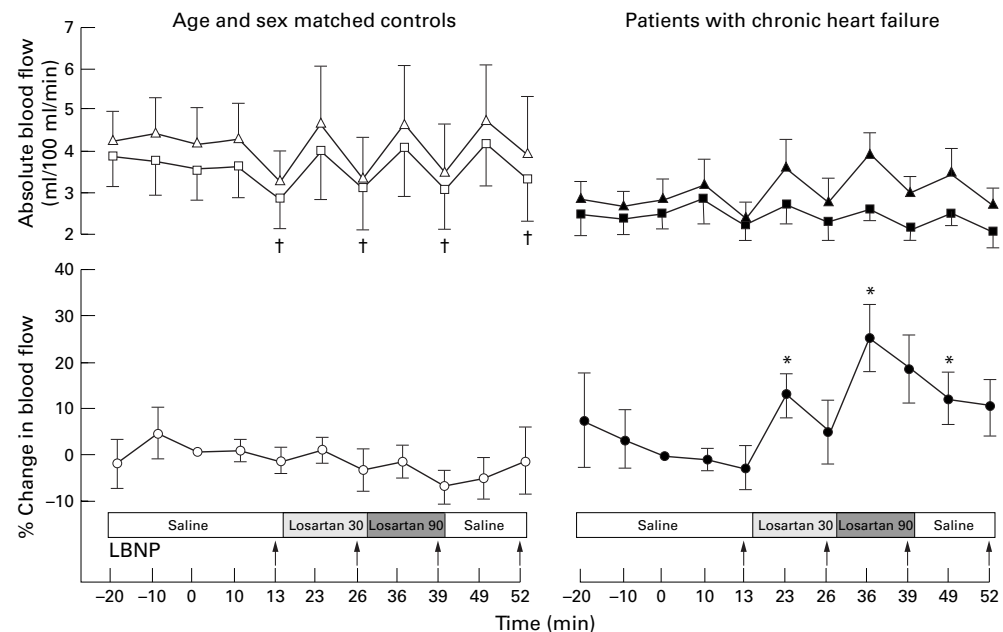

*Figure 1 Absolute (non-infused arm, squares; infused arm, triangles) and percentage change in forearm blood flow responses (circles), with intermittent application (arrows) of lower body negative pressure (LBNP), to saline and losartan (30 and 90 μg/min) infusion in healthy control subjects (empty symbols) and patients with heart failure (filled symbols). *p < 0.001 (one way ANOVA, v baseline saline infusion); †p = 0.008 (two way ANOVA, basal v LBNP).*
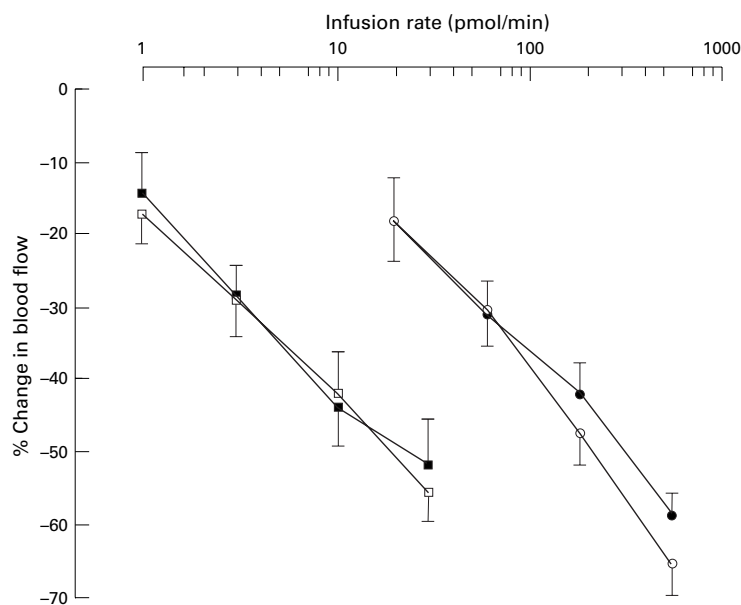
Figure 2   Forearm blood flow responses to infusion of angiotensin II (squares) and noradrenaline (circles) in healthy control subjects (empty symbols) and patients with heart failure (filled symbols); p < 0.001 (one way ANOVA for each response).

sufficient to cause a comparable increase in plasma angiotensin II to that seen in patients with heart failure and causes a reduction in blood flow of about 20%. In the present study, we have shown for the first time that brachial artery infusion of losartan causes an acute local increase in forearm blood flow by ~25% in patients with heart failure. This cannot be explained by an increased sensitivity to angiotensin II in these patients, given the normal dose–response relations to angiotensin II infusion. Moreover, the mean plasma angiotensin II concentrations tended to be higher in patients with heart failure and the maximum increase in blood flow in the infused arm significantly correlated with plasma angiotensin II concentrations. These findings suggest that in patients with heart failure, endogenous angiotensin II contributes to the maintenance of basal peripheral vascular tone. The observed reductions in systemic vascular resistance with oral losartan[13 14 28] would therefore appear to be related to the direct vasodilator action of AT$_1$ antagonism on peripheral resistance vessels.

One of the first vasodilator treatment trials in heart failure (V-HeFT I)[29] showed significant benefit for left ventricular function and mortality using the combination of isosorbide dinitrate and hydralazine, but not prazosin. It would appear, therefore, that all vasodilators are not equal and the precise mechanisms by which some agents, but not others, produce benefit remain unclear. In patients with heart failure, acute systemic AT$_1$ antagonism and ACE inhibition reduce systemic vascular resistance and blood pressure to a similar extent.[13 14 28] However, ACE inhibition also has the potential to cause the accumulation of endogenous vasodilating peptides such as bradykinin and substance P, which raises the possibility that the resultant vasodilatation may not be solely attributable to a reduction in angiotensin II generation. Indeed, there is evi-

dence that endogenous bradykinin may regulate arteriolar tone in some vascular beds[30] and that some of the beneficial effects of ACE inhibition in heart failure may be mediated through bradykinin.[12] However, our findings of a direct peripheral vasodilator action of losartan in patients with heart failure suggests that the vasodilatation induced by ACE inhibition is also probably caused, at least in part, through a reduction in the generation of angiotensin II. Recently, the ELITE study[31] has shown that AT$_1$ antagonism is associated with a lower mortality than ACE inhibition in elderly patients with heart failure. The mechanism of this benefit has not been fully elucidated but may be related to its more complete inhibition of angiotensin II action, and peripheral and systemic vasodilator actions may contribute.

In agreement with previous studies,[32–34] we have additionally shown an attenuation of forearm vasoconstriction to lower body negative pressure in patients with heart failure. The mechanism of this impaired response is not a result of a reduction in peripheral sensitivity to noradrenaline, given the normal responsiveness to noradrenaline infusion in these patients. Heart failure is associated with increased sympathetic nerve outflow[35] and suggests that the impaired response to lower body negative pressure may reflect increased basal activity attenuating the effect of further stimulation of the reflex. Alternatively, 15 mm Hg of lower body negative pressure in patients with high cardiac filling pressures may not be sufficient to reduce the pressure in the atria or pulmonary arteries to enable unloading of the cardiopulmonary baroreceptors and stimulation of the reflex. Finally, these observations are also in keeping with the beneficial haemodynamic effects of peripheral venous pooling, which reduces cardiac preload, thereby improving the tension–pressure relation of the failing heart, perhaps even leading to peripheral vasodilatation.[34]

A reduced cardiac output leads to increases in central sympathetic nerve outflow,[35] circulating noradrenaline concentrations,[36] and peripheral vascular resistance.[37] It is well established that angiotensin II facilitates release of noradrenaline from nerve terminals in vitro.[4] Even at doses insufficient to cause vasoconstriction directly, angiotensin II augments sympathetically mediated vasoconstriction in vivo[3] through prejunctional release of noradrenaline.[5] Thus there is an important potential for the renin-angiotensin and sympathetic nervous systems to act synergistically in the pathophysiology of heart failure. If basal concentrations of tissue or plasma angiotensin II augment normal sympathetically mediated vasoconstriction, then losartan would be expected to reduce the response to lower body negative pressure. Although this has been described in sodium deplete hypertensive patients, using the mixed antagonist and partial agonist saralasin,[20] we have not detected an effect of losartan on vasoconstriction induced by lower body negative pressure, either in patients with heart failure or in healthy control subjects. However, there are some inconsistencies in the responses to angiotensin II

infusion during lower body negative pressure[3] [38] [39] with some workers finding facilitation of prejunctional noradrenaline release only at high plasma angiotensin II concentrations of 25–97 fmol/ml.[38] Therefore, while the lack of an effect of losartan on the lower body negative pressure response may not have been unexpected in healthy controls with low plasma angiotensin II concentrations, it is perhaps surprising in patients with heart failure. Nevertheless, in the present study we were only able to show a trend for a reduction in blood flow with lower body negative pressure in patients with heart failure, so a small effect of losartan could have been missed. It also remains a possibility, though unlikely, that the induction of prejunctional noradrenaline release by angiotensin II is mediated by a non-AT$_1$-receptor mechanism.

We have studied patients with moderate chronic heart failure receiving maintenance diuretic and ACE inhibitor treatment. Given that diuretic treatment can stimulate the renin-angiotensin system, the acute withdrawal of ACE inhibition may cause a rebound increase in plasma angiotensin II. In this situation, the response to AT$_1$ antagonism might be expected to be greater. However, our patient population had only a moderate rise in plasma angiotensin II concentrations and a normal responsiveness to exogenous angiotensin II infusion.

We have also shown, in agreement with previous work,[21] [22] that intra-arterial losartan has no effect on basal forearm blood flow or vascular resistance in healthy control subjects. The 95% confidence intervals indicate that if angiotensin II provides any contribution to basal tone in peripheral blood vessels of healthy people then it is rather small. It would appear, therefore, at least in Western societies maintained on a relatively high sodium diet,[40] that angiotensin II is implicated in tonic adaptive responses rather than in the basal maintenance of peripheral resistance vessel tone in healthy man.

In summary, using intra-arterial losartan infusions, we have directly shown that angiotensin II makes an important contribution to the local maintenance of basal peripheral vascular tone in patients with heart failure but not in healthy controls. This would suggest that ACE inhibitors and angiotensin AT$_1$ receptor antagonists cause vasodilatation at least in part through a direct action. In addition, we have shown hyporesponsiveness to sympathetic nervous system activation through baroreceptor unloading, which does not appear to be augmented by angiotensin II.

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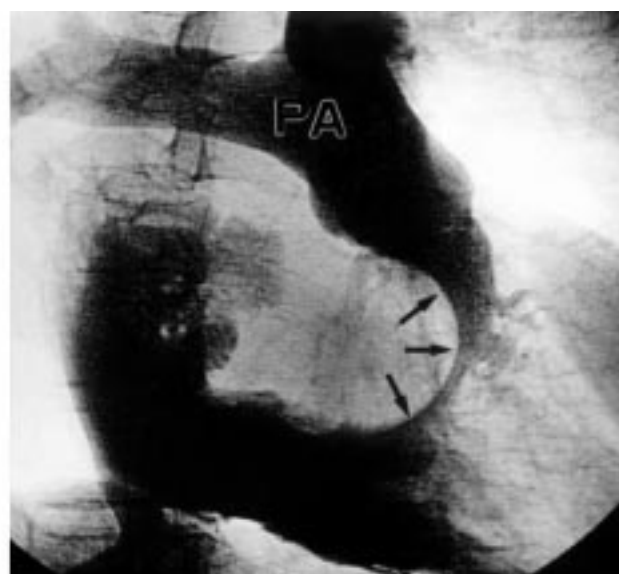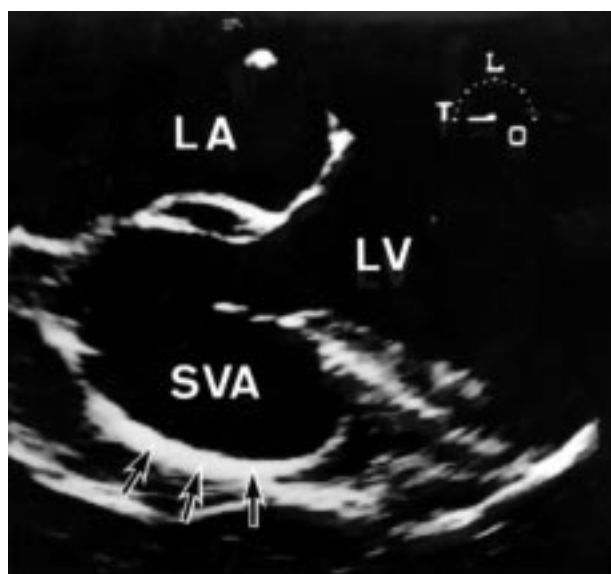
IMAGES IN CARDIOLOGY

Unruptured right sinus of Valsalva aneurysm

The diagnosis of sinus of Valsalva aneurysm is usually made when acute congestive heart failure occurs following a rupture of the aneurysm into the right ventricle or the right atrium. We report a rare case of unruptured right sinus of Valsalva aneurysm.

A 73 year old man was admitted to our hospital because of progressive dyspnoea on exertion. On examination his pulse was regular at 84 beats/min and blood pressure 150/46 mm Hg. To and fro murmur of Levine 2/6 grade was heard at the second right sternal border. ECG showed left ventricular hypertrophy with ST-T changes, and chest radiography showed moderate cardiomegaly (cardiothoracic ratio 0.74) and bilateral pleural effusion.

Aortic regurgitation was thought to be the cause of his congestive heart failure. However, transoesophageal echocardiography (left) revealed a large aneurysmal change of the right sinus of Valsalva as well as severe aortic regurgitation. A protrusion of the aneurysm into the right ventricle appeared to obstruct blood flow to the outflow tract. A shunt flow was not detected. Intravenous digital subtraction angiography confirmed the diagnosis of unruptured right sinus of Valsalva aneurysm, demonstrating an impressive large filling defect within the right ventricle (right). (LA, left atrium; LV, left ventricle; SVA, sinus of Valsalva aneurysm; PA, pulmonary artery.)

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