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Vasopressin and angiotensin II contribute equally to the increased afterload in rabbits with heart failure

Leonard Arnolda, Barry P McGrath, Colin I Johnston

Abstract

***Study objective* – Vasopressin, like angiotensin, has both vasoconstrictor and fluid retaining properties and therefore may make an important contribution to the pathogenesis of low output congestive heart failure. The study aimed to examine the relative importance of the renin-angiotensin system and vasopressin in an animal model of heart failure.**

***Design* – The acute haemodynamic effects of vasopressin receptor blockade with a selective antagonist, $d(CH_2)_5DAVP$ (AVPA) (30 $\mu g \cdot kg^{-1}$) and angiotensin converting enzyme inhibition with captopril (1 $mg \cdot kg^{-1}$) were compared. The effect of combined blockade (ie, vasopressin receptor antagonist + angiotensin converting enzyme inhibitor) was also examined.**

***Experimental material* – Rabbits, 2.5-3.5 kg, with doxorubicin induced cardiomyopathy and heart failure (n = 20) were used. There were 15 controls.**

***Measurements and main results* – Both AVPA and captopril produced significant increases in cardiac output (11% and 13% respectively) and falls in peripheral vascular resistance (21% and 17% respectively). Inhibition of the two vasoconstrictor systems was additive and resulted in a fall in peripheral vascular resistance to levels found in normal animals.**

***Conclusions* – Vasopressin and angiotensin II make equal contributions to the raised peripheral vascular resistance observed in this model of heart failure. Vasopressin inhibition may be useful in the treatment of heart failure either alone or as an adjunct to angiotensin converting inhibition.**

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The activation of a series of neural and hormonal mechanisms in heart failure produces the fluid retention and vasoconstriction which dominates the syndrome. So important are these neurohumoral mechanisms that therapeutic interventions directed at the compensatory changes (eg, diuretics, vasodilators) have proved far more successful in the long term than attempts to improve cardiac function (inotropes). Angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril have not only been effective symptomatically[1 2] but also prolongs life.[3]

Vasopressin, like angiotensin has dual vasoconstrictor and fluid retaining actions and may therefore play an important role in the pathophysiology of heart failure.

Doxorubicin produces a dose related cardiomyopathy and heart failure in man[4] and animal models.[5–7] We have previously shown that vasopressin has important vasoconstrictor actions in rabbits with doxorubicin cardiomyopathy and low output heart failure.[7] In this study we used a vasopressin V1 antagonist (AVPA) and an ACE inhibitor to compare the relative contributions of the renin angiotensin system and vasopressin to the vasoconstriction observed in this model. In addition combined blockade (ACE inhibition and AVPA) was used to explore possible interactions between these two vasoconstrictor systems in heart failure.

Methods

Rabbits of either sex, 2.5-3.5 kg in weight of a mixed strain derived from New Zealand White and English breeds, were obtained from the University central animal house. The animals were individually caged, kept in a standardised environment, and fed a laboratory diet and water ad libitum. The experiments were approved by the Monash University Research Advisory and Ethics Committee.

Doxorubicin (Farmitalia, Carlo Erba) was given via a marginal ear vein as a dose of 1 $mg \cdot kg^{-1}$ twice weekly for 8 weeks. This is a modification of the method described by Jaenke *et al*[5] and has been shown consistently to produce a cardiomyopathy and heart failure in rabbits.[6]

HAEMODYNAMIC MEASUREMENTS

Studies were carried out in conscious unrestrained rabbits. All animals had a chronically implanted aortic

thermistor catheter for measurement of cardiac output by the thermodilution technique as described by Korner and Hilder,[8] The animals were allowed to recover for at least two weeks before any measurements were performed. Doxorubicin treated animals were studied two weeks after the last dose of doxorubicin. Right atrial and central ear artery catheters were inserted under local anaesthesia (2% lignocaine) on the day of the study and the animals were allowed to recover for at least 1 h before any measurements were obtained.

Haemodynamic studies were carried out in resting conditions in 15 normal rabbits and 20 animals with congestive heart failure due to 8 weeks of doxorubicin therapy Five sets of the following measurements were made in each animal at each time point: mean blood pressure, right atrial pressure, cardiac output, and heart rate.

VASOPRESSIN AND ANGIOTENSIN BLOCKADE

[1- (β-Mercapto-β, β-cyclopentamethylenepropionic acid), 8-D-arginine] vasopressin[9] was used to block vasopressin vascular receptors. The dose of 30 $mg \cdot kg^{-1}$ intravenously was shown to abolish the pressor response to a bolus of vasopressin 100 $mg \cdot kg^{-1}$ for more than 1 h in a preliminary study.

The ACE inhibitor, captopril, was used in a dose of 1 $mg \cdot kg^{-1}$, sufficient to abolish the pressor response to 300 $ng \cdot kg^{-1}$ of angiotensin I for more than 1 h.

Both drugs were dissolved in 0.9% saline and given via the right atrial catheter as a bolus of 0.3 ml.

ALLOCATION TO TREATMENT

The 20 rabbits with heart failure were treated according to the schedule set out below. Group A (n = 5) received AVPA, group B (n = 5) received vehicle (saline). Groups C and D received captopril followed by AVPA (group C, n = 5) or vehicle (group D, n = 5).

In group A and B, haemodynamic measurements were made immediately before and 15 min after AVPA or vehicle. In groups C and D haemodynamic measurements were made before and 15 min after captopril. These animals were then given either AVPA (group C) or vehicle (group D) and a third set of haemodynamic measurements were made 15 min later.

Three groups of normal control rabbits were treated with AVPA (group E, n = 5), vehicle (group F, n = 5), or AVPA and captopril (group G, n = 5). Haemodynamic measurements were made before and 15 min after administration of drug or vehicle.

STATISTICS

The paired *t* test was used to analyse changes within groups and the unpaired *t* test to examine difference between groups. Statistical significance was assumed at $p<0.05$.

Results

The results of haemodynamic measurements in the four groups of rabbits with doxorubicin cardiomyopathy (A, B, C, and D; n = 20) were compared with the combined results from the three groups of normal rabbits (E, F, and G; n = 15) in table I. Resting cardiac output in rabbits with doxorubicin cardiomyopathy and heart failure was reduced to about 2/3 of the value observed in normal controls. Blood pressure was maintained despite the reduced cardiac output by a 48% increase in peripheral vascular resistance. Right atrial pressure and heart rate were not significantly different in heart failure and control animals.

Administration of AVPA to rabbits in heart failure (fig 1) resulted in an 11% increase in cardiac output and a 13% fall in blood pressure. Peripheral vascular resistance decreased by 21%. The administration of vehicle to group B produced no significant haemodynamic changes.

Captopril resulted in a significant increase in cardiac output and a decrease in peripheral vascular resistance (groups C and D). Blood pressure decreased slightly in both groups but the fall was significant in group C alone. Overall, cardiac output increased by 13%, blood pressure fell by 8%, and peripheral vascular resistance decreased by 17% (fig 2). The change in peripheral vascular resistance with captopril (95% confidence limits 11% to 23%) and AVPA (95% confidence limits 16% to 26%) were of similar magnitude.

When AVPA was given to rabbits who had received captopril (group C) cardiac output increased further (by 17%) and peripheral vascular resistance decreased to levels observed in normal animals. A small (4%) fall in blood pressure was not statistically significant. The change in peripheral vascular resistance induced by AVPA was similar before and after ACE inhibition, at 21 (SD 5)% *v* 21(4)%.

Cardiac output, blood pressure and peripheral

Table I Haemodynamic measurements in normal rabbits and rabbits with heart failure. Values are means (SD)

	Heart failure (n=20)	*Controls (n=15)*
Cardiac output ($ml \cdot min^{-1}$)	580(31)†	863(19)
Mean arterial pressure (mm Hg)	74(2)	76(2)
Peripheral vascular resistance ($dyne \cdot s \cdot cm^{-5}$)	10477(458)†	7091(217)
Right atrial pressure (mm Hg)	1.04(0.76)	-0.07(0.37)
Heart rate ($beats \cdot min^{-1}$)	236(12)	256(8)

†$p<0.01$ *v* controls

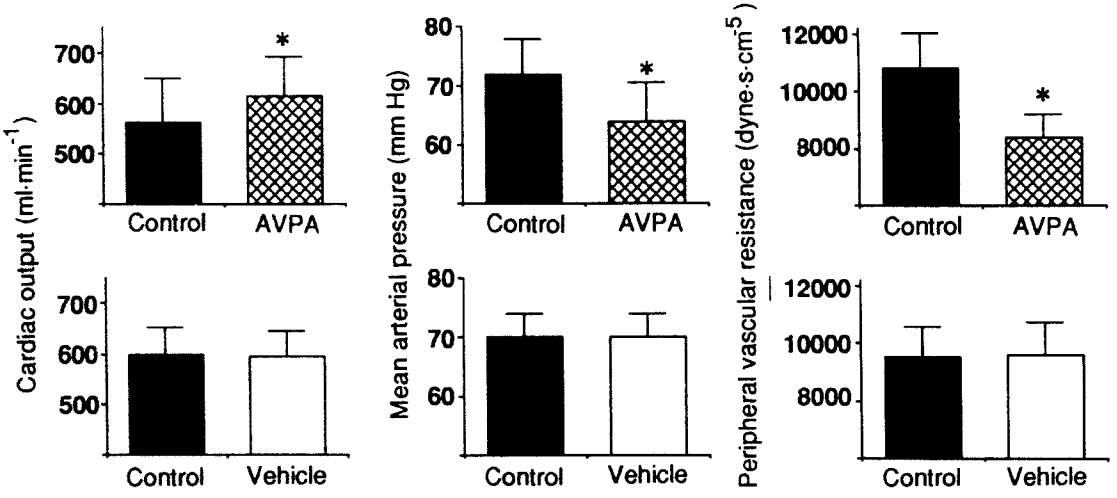

Figure 1 *Effects of a vasopressin V1 antagonist (AVPA, upper panel) or vehicle (lower panel) on cardiac output, mean arterial pressure, and peripheral vascular resistance in rabbits with doxorubicin cardiomyopathy and heart failure. Control (filled columns)=pretreatment values,* versus *AVPA (hatched columns) and vehicle (open columns). Bars=SD.*
**=p<0.05.*

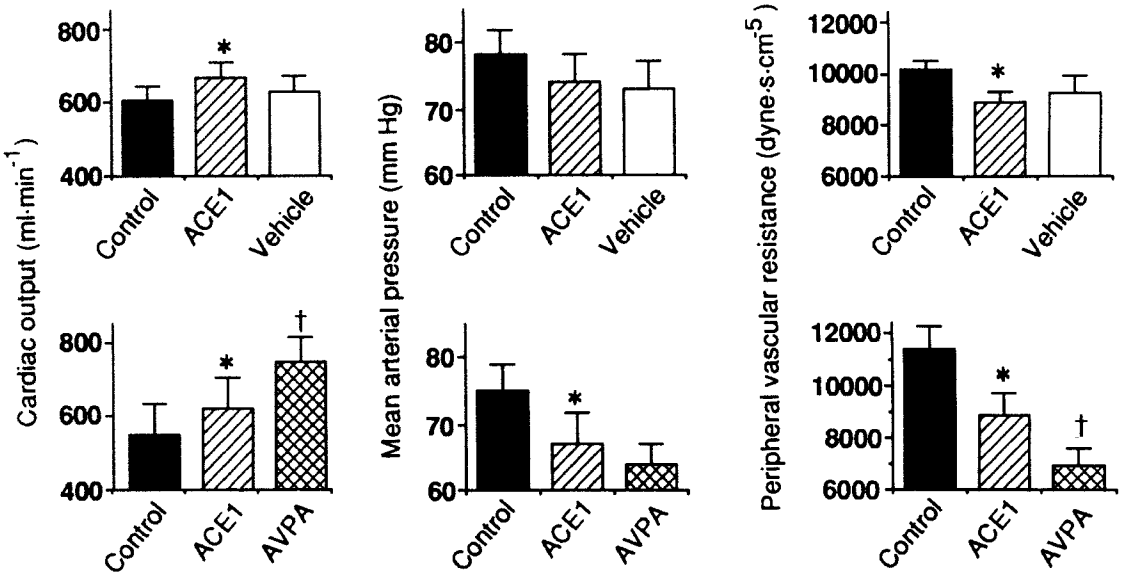

Figure 2 *Effects of angiotensin converting enzyme inhibition (ACEi) followed by a vasopressin antagonist (AVPA) or vehicle on cardiac output, mean arterial pressure, and peripheral vascular resistance in rabbits with adriamycin cardiomyopathy and heart failure. Control (filled bars)=pretreatment values,* versus *ACEi (single hatched bars), AVPA (cross hatched bars), and vehicle (open bars). Bars=SD.*
**p<0.05 v control, †p<0.05 v ACEi.*

vascular resistance were stable in the group treated with vehicle after ACE inhibiton (group D). This shows that the changes observed after AVPA in group C resulted from vasopressin blockade and did not simply reflect the time course of ACE inhibition.

The haemodynamic effects of treatement with AVPA, captopril + AVPA, or vehicle in normal control animals are shown in table II. There were no significant alterations in blood pressure, cardiac output, or peripheral vascular resistance in any group.

Discussion

Doxorubicin produces severe cardiomyopathy[5] and congestive heart failure in rabbits.[6] This is associated

Table II Haemodynamic effects of treatment with AVPA, AVPA + ACEi, or vehicle in normal control rabbits (n=5 in each group). Values are means (SD)

	Cardiac output ($ml \cdot min^{-1}$)	*Mean arterial pressure* (*mm Hg*)	*Peripheral vascular resistance* ($dyne \cdot s \cdot cm^{-5}$)
Control	868(34)	81(4)	7552(235)
AVPA	880(59)	85(4)	7877(570)
Control	897(32)	71(3)	6488(373)
AVPA+ACEi	880(23)	67(4)	6397(354)
Control	821(30)	74(3)	7234(391)
Vehicle	848(22)	75(1)	6985(125)

AVPA=$d(CH_2)_5$ DAVP 30 $\mu g \cdot kg^{-1}$; ACEi=captopril 1 $mg \cdot kg^{-1}$. There were no significant changes with treatment in any group.

with a decreased cardiac output and increased peripheral vascular resistance with evidence of activation of neural and hormonal vasoconstrictor mechanisms.[6 7] Renin levels are raised at 8 weeks.[6 7] While vasopressin levels are not increased, sensitivity to infused vasopressin is altered and vasopressin blockade results in vasodilatation.[7]

We observed a pronounced vasodilator response to captopril administration in keeping with the raised renin levels seen in this model and the proven efficacy of ACE inhibition in the treatment of heart failure.[1–3] The response to captopril may however overestimate the contribution of the renin angiotensin system because of possible effects on kinins and on prostaglandin metabolism[10] which may be activated in heart failure.[11]

In contrast, the AVPA used is a highly selective antagonist of the vascular actions of vasopressin and has only weak antidiuretic agonist activity.[9] The haemodynamic response to AVPA is therefore likely to reflect accurately the vasoconstrictor actions of vasopressin. The response to AVPA was of similar magnitude to that observed with captopril and implies that vasopressin and the renin-angiotensin system contribute equally to the vasoconstriction observed in this model. Neither AVPA nor AVPA + captopril produced any haemodynamic change in normal control animals, suggesting that vasopressin and angiotensin were not activated and providing further evidence that the responses observed in heart failure are not due to non-specific vasodilator actions of these compounds.

Other workers using different models of heart failure have also demonstrated vascular actions of vasopressin. Vasopressin V1 antagonists have been reported to lower blood pressure in cardiomyopathic hamsters,[12] in rats with myocardial infarction[13] or pulmonary stenosis,[14] and to produce renal vasodilatation in dogs with thoracic inferior vena caval constriction.[15] Vasopressin V1 antagonists had no discernible vasodilator effect on rats with aortocaval shunts.[16] However alterations in resistance in the native circulation in this model may be obscured by the dominant effect of a large shunt, and ACE inhibition also failed to alter peripheral vascular resistance in this study.

In rats with pulmonary stenosis the vasodilatation produced by AVPA was substantially less than with captopril.[14] The difference between that study and ours may reflect differences in the model (pulmonary stenosis produces pure right heart failure), the species used (rat or rabbit), or the severity of heart failure (cardiac output was more than 80% of normal and peripheral vascular resistance was not increased in rats with pulmonary stenosis). Perhaps vasopressin is only activated in severe heart failure.

Studies in humans with heart failure do not show a consistent response to AVPA. Nicod *et al*[17] observed a pronounced vasodilator response in one patient with severe heart failure and raised vasopressin levels, but not in nine others with less severe heart failure. Creager *et al*[18] reported a vasodilator response to AVPA in three of 10 subjects and found evidence of activation of the renin angiotensin system in five of these 10 patients. It should be noted however that the use of diuretics may have activated the renin-angiotensin system in these patients.

Sequential blockade (captopril followed by AVPA or vehicle) was used to examine the role of these two vasoconstrictor systems more closely. Angiotensin and vasopressin have overlapping vasoconstrictor functions in the maintenance of blood pressure during haemorrhage. Blockade of vasopressin V1 receptors magnifies the compensatory activation of the renin angiotensin system during haemorrhage[19] and may attenuate the fall in blood pressure. Indeed either vasopressin or angiotensin is able to support a normal constrictor response in the mesenteric vascular bed during haemorrhage.[20] In these circumstances the effects of inhibition of one vasoconstrictor is masked by activation of the other and a full appreciation of the role of each is only gained when both vasoconstrictors are blocked.

In this study AVPA produced a similar change in peripheral resistance before (group A) and after (group C) captopril. This suggests that neither the renin-angiotensin system nor vasopressin is able to compensate when the other is blocked. Renin and vasopressin appear to act independently rather than as part of a coordinated neural and hormonal response.

Abnormal baroreceptor reflexes in heart failure may

provide an explanation since they include blunted baroreceptor mediated renin and vasopressin release[21] as well as impaired heart rate and vasoconstrictor responses.[22] Whatever the mechanism, the effectiveness of ACE inhibition in the treatment of heart failure may lie in the inability of other vasoconstrictor mechanisms to compensate for its absence.

Doxorubicin cardiomyopathy in the rabbit produced severe heart failure with a substantially reduced cardiac output and increased peripheral vascular resistance. The acute response to pharmacological blockade suggests that vasopressin and angiotensin make quantitatively similar contributions to the raised peripheral vascular resistance observed in this model. Combined blockade indicated a simple additive interaction. If the effects of vasopressin blockade are sustained vasopressin antagonists may prove useful in the treatment of heart failure either alone or as an adjunct to ACE inhibition.

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