European Heart Journal (1998) **19,** 1371–1376 Article No. hj981099

Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients

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Aims The purpose of this study was to examine, in chronically treated heart failure patients vs control subjects, the influence of neurohumoral activation and aldosterone escape on arterial elastic behaviour, assessed by non-invasive mathematical lumped-parameter modelling of the compliance of the arterial system.

Methods and Results Radial arterial pulse waves were recorded non-invasively for 30 s with an arterial tonometer sensor array in 13 chronic heart failure patients (mean age, $59 \pm 2{\cdot}5$ years) in New York Heart Association class II. The patients had been taking digoxin, furosemide, captopril and aspirin for more than 3 months. Thirteen healthy subjects (mean age, $50 \pm 4{\cdot}0$ years) acted as controls. Compliance of the proximal (aorta and major branches, C1) and distal parts (C2) of the circulation were derived from a third order four-element modified Windkessel model which can reproduce arterial pressure waveforms, including both exponential and oscillatory sections. Active renin, angiotensin II and aldosterone levels were determined on venous blood samples in the supine position and after 30 min active standing. There was decreased proximal (C1, $1{\cdot}51 \pm 0{\cdot}11$ ml . mmHg^{-1}, $P<0{\cdot}01$) and distal (C2, $0{\cdot}050 \pm 0{\cdot}011$ ml . mmHg^{-1}) arterial compliance in the chronic heart failure patients vs controls (C1, $1{\cdot}71 \pm 0{\cdot}16$ ml . mmHg^{-1}; C2, $0{\cdot}054 \pm 0{\cdot}006$ ml . mmHg^{-1}). The chronic heart failure patients were characterized by an aldosterone escape phenomenon which was inversely correlated with the proximal arterial compliance in both supine ($r = -0{\cdot}795$, $P=0{\cdot}002$) and standing ($r = -0{\cdot}628$, $P=0{\cdot}029$) positions.

Conclusions In chronically treated heart failure patients with full angiotensin-converting enzyme-inhibition and diuretics, there is decreased compliance of the aorta and its major branches, which is inversely correlated with the aldosterone escape phenomenon.
(Eur Heart J 1998; 19: 1371–1376)

Key Words: ACE-inhibition, arterial compliance, chronic heart failure, conduit arteries, renin–angiotensin–aldosterone system.

See page 1273 for the Editorial comment on this article

Introduction

Chronic heart failure is a syndrome characterized by a vasoconstrictor response of the vasculature at rest and during exercise to abnormalities in left ventricular function[1–3]. Progression of chronic heart failure has been associated with vasoconstriction in the smallest arteries and arterioles, leading to elevated systemic vascular resistance[4] and increased impedance to ventricular outflow. However, the specific contribution of the changes in the larger conductance arteries are less known in humans. Large arteries serve as a conduit to deliver blood to organs, and the distensibility of both the large and small arteries serve as a cushion to buffer pulsatile pressure and flow. Reduced buffering capacity by the arteries leads to amplification of reflected pressure waves and more rapid pulse wave velocity. This may increase end-systolic pressure and left ventricular work leading to ventricular hypertrophy. The concomitant stiffness of the large artery wall will decrease large artery distensibility[5–7].

Pepine *et al.* found increased characteristic input impedance in chronic heart failure, suggesting that the human aorta stiffens with this condition and that pressure and flow wave reflections are increased[8].

Revision submitted 6 April 1998, and accepted 14 April 1998.

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0195-668X/98/091371+06 $18.00/0

According to these authors, the changes observed in the frequency-dependent section of the impedance spectrum indicate that aortic distensibility is reduced in patients with heart failure. Many mechanisms have been suggested for the less distensible vascular behaviour in chronic heart failure such as sodium retention, water-logging and sympathetic nervous system stimulation[9,10]. This may be accompanied by prominent neurohumoral activation with increased circulatory plasma catecholamines and renin–angiotensin–aldosterone concentrations[11].

Since the introduction of vasodilators as standard therapy in the treatment of chronic heart failure, the patient treated with diuretics and ACE inhibitors is characterized by a very high plasma renin and low concentrations of angiotensin II and aldosterone. Nevertheless, in chronically treated chronic heart failure patients, the suppressive effect of ACE inhibitors on aldosterone level is weak, variable and unsustained and an aldosterone escape mechanism has been documented[12–14]. At present, it is still unknown if there is a relationship between impaired large artery elastic behaviour in chronic heart failure and neurohumoral activation or the aldosterone escape mechanism in the chronically treated patient.

In the literature, several methodologies have been introduced to estimate large artery distensibility and compliance. These include the invasive volume–pressure relationship and non-invasive evaluation of the regional diameter–pressure relationship. These were recorded by echocardiogram, Doppler signal processing, pulse wave velocity and mathematical estimations based on either distributed parameters or lumped-parameter engineering models[15–24]. The latter offer the opportunity to study global arterial compliance of the large artery system (aorta and its major branches).

This study aimed to examine the influence of the renin–angiotensin–aldosterone system and aldosterone escape in chronically treated chronic heart failure patients vs controls on arterial elastic behaviour assessed by non-invasive mathematical lumped-parameter modelling of the compliance of the arterial system.

Methods

Patients

Thirteen caucasian patients with chronic heart failure, aged 59 ± 2·5 years, were enrolled in the study. All were in NYHA class II and had been stabilized on digoxin 0·025 mg o.d., furosemide 40 mg o.d., captopril 50 mg t.i.d. and aspirin 160 mg o.d. All patients were in sinus rhythm and the aetiology of heart failure was ischaemic in all patients. None of the patients had other overt cardiovascular disease and none had taken nitrates or other non-ACE vasodilator therapy during the last 24 h prior to the study. None of the patients suffered from endocrinological, renal or hepatic disease.

Control subjects

A total group of 13 apparently healthy caucasian volunteers, age 50 ± 4·0 years, were enrolled in the same study protocol. All had attended the Policlinic of Internal Medicine for a general check-up. None had taken any medication for at least 3 months before the examination. All subjects gave oral informed consent to be enrolled in the study protocol. The study protocol was approved by the local medical ethical committee.

Study protocol

The experiments were carried out, after an overnight fast, between 0800 and 1000h. The patients took their last medication the night before the experiment.

The subjects lay down for 30 min. After 30 min, arterial blood pressure was measured with a mercury sphygmomanometer and heart rate was derived from beat-to-beat analysis of the ECG. This was followed by the recording, non-invasively, of radial arterial pulse waves, and finally venous blood samples were taken before and after 30 min of active standing to determine neurohumoral activation of the renin–angiotensin–aldosterone axis.

Arterial compliance

Radial arterial pulse waves were recorded non-invasively with an arterial tonometer sensor array (model N-500, Nellcor Inc., Colin, San Antonio, Tx, U.S.A.). The waveform was calibrated by the oscillometric method with a cuff on the opposite arm and a calibration system internal to the Nellcor device. The tonometer sensor array adjusts itself automatically to obtain the optimal waveform and repeats its calibration until the waveform is stable. At that point, 30-s-long analog tracings of the radial artery waveform were digitized at 200 samples per second and stored in a personal computer system for compliance analysis (Hypertension Diagnostics, Inc. Minneapolis, Mn, U.S.A.). The pulse wave of an average beat representative of the 30 s period was constructed, as described by Cohn *et al.*[25]. Compliance of the proximal (aorta and major branches, C1) and distal parts (C2) of the circulation were derived from a third order four-element modified Windkessel model which can reproduce arterial pressure waveforms including both exponential and oscillatory pressure decays observed during the diastolic portion of the cardiac cycle[26].

Cardiac output was estimated from an algorithm developed in the laboratory of Cohn *et al.* (US Patent No 5241966, 1993). It is a multivariate function of ejection time, heart rate, body surface area and age and can be determined from the arterial pressure waveform, with the following formula developed from an

experimental set of 'learning' data and validated in an independent set of 'test' data:

$$\text{Stroke Volume} = -6{\cdot}6 + 0{\cdot}25\ \text{ET} - 0{\cdot}62\ \text{HR} + 40{\cdot}4\ \text{BSA} - 0{\cdot}51\ \text{Age},$$

where ET is ejection time in ms, HR is heart rate in beats . min^{-1} and BSA is body surface area in mm^2.

Hormone measurements

Active renin, angiotensin II and aldosterone levels were determined on venous blood samples obtained in the supine position and after 30 min active standing. Active renin (PR) was measured using a commercial immunoradiometric assay from Nichols Institute Diagnostics (R active renin test). Angiotensin II (Ang II) was estimated by a radioimmunoassay procedure (Amersham Int.) after isolation from plasma by solvent extraction chromatography (Bond Ulut, Analytichem Int) and purification by HPLC (Nucl 10-C18 column). Aldosterone was assayed with a commercial radioimmunoassay from Radim (Pomezia).

Statistical analysis

All study parameters are given as mean ± s.e.m. The study parameters were compared between controls and patients and between supine and standing positions using the Mann–Whitney U test. Pearson's correlation coefficients were calculated between aldosterone in the supine and standing position and, respectively, age, arterial blood pressure and C1 and C2. A P value <0·05 is considered as statistically significant.

Results

Morphometric characteristics, haemodynamic parameters, proximal and distal arterial compliance in chronic heart failure patients and controls are given in Table 1. Chronic heart failure patients had significantly lower systolic (P<0·01) and diastolic (P<0·05) blood pressure, but significantly higher heart rate (P<0·01). Estimated cardiac output and systemic vascular resistance were respectively, lower (P<0·01) and higher (P<0·05) in the chronic heart failure patients. By contrast, C1 was significantly (P<0·01) lower in patients than in controls, while no statistically significant differences were observed for C2. In the group of chronic heart failure patients treated with captopril, digoxin and furosemide, renin concentration was highly elevated (P<0·0001, Table 2) and increased even further (P<0·05) after 30 min of active standing. Angiotensin II and aldosterone concentrations were significantly higher in patients than in controls in the supine position and after 30 min active standing. Angiotensin II tended to be higher after 30 min active standing, while aldosterone was significantly (P<0·05) increased after standing, not only in the control group but also in the patient group.

Table 1 Characteristics of the study population

	CHF (n=13)	CON (n=13)	*P*
Age (years)	59 ± 2·5	50 ± 4·0	ns
Length (cm)	168 ± 2	166 ± 2	ns
Weight (kg)	69 ± 3·0	70·8 ± 3·8	ns
SBP (mmHg)	116 ± 8	138 ± 4	<0·01
DBP (mmHg)	69 ± 4	75 ± 2	<0·05
HR (beats . min^{-1})	78 ± 3	67 ± 2	<0·01
CO (l . min^{-1})	3·64 ± 0·23	5·03 ± 0·18	<0·01
SVR (dynes . s . cm^{-5})	1954 ± 136	1623 ± 87	<0·05
C1 (ml . $mmHg^{-1}$)	1·51 ± 0·11	1·71 ± 0·16	<0·01
C2 (ml . $mmHg^{-1}$)	0·050 ± 0·011	0·054 ± 0·006	ns

CHF = chronic heart failure; CON = control subjects; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistance; C1 = compliance of the proximal part of the circulation; C2 = compliance of the distal part of the circulation.

Table 2 Renin–angiotensin II–aldosterone axis in the supine and standing position in the study population

	CHF	CON	*P*
Renin (μU . ml^{-1})			
Supine	1400 ± 828*	33 ± 7	<0·0001
Standing	1624 ± 997	40 ± 8	<0·0001
P	<0·05	<0·05	
Angiotensin II (pg . ml^{-1})			
Supine	26·3 ± 4·3	17·1 ± 1·5	<0·05
Standing	29·3 ± 4·7	19·7 ± 2·3	<0·05
P	ns	ns	
Aldosterone (ng . ml^{-1})			
Supine	15·4 ± 2·6	10·7 ± 2·1	<0·05
Standing	20·5 ± 3·4	13·5 ± 3·4	<0·01
P<0·05	<0·05	<0·05	

CHF = chronic heart failure; CON = control.
*data are obtained under 150 mg captopril, 0·025 mg digoxin and 40 mg furosemide.

As we aimed to investigate the aldosterone escape mechanism in chronic heart failure patients treated with ACE inhibitors, we correlated aldosterone concentrations in supine and standing positions with morphometric characteristics and haemodynamic and arterial compliance data (Table 3). There were no significant correlations between aldosterone concentrations and age or blood pressure. Also, in the controls, significant correlations between aldosterone concentrations and C1 and C2 were absent. Nevertheless, in chronic heart failure, significant correlations were found between C1 and aldosterone concentrations in the supine ($r = -0{\cdot}795$, $P = 0{\cdot}002$, Fig. 1) and standing ($r = -0{\cdot}628$, $P = 0{\cdot}029$) positions. There were no significant correlations between C2 and aldosterone concentrations in chronic heart failure. In controls or chronic heart failure patients, neither in the supine or standing

Table 3 Correlations of aldosterone during postural changes with baseline haemodynamic parameters in the study population

Aldosterone concentration	Correlates				
	Age	SBP	DBP	C1	C2
CHF					
Supine	ns	ns	ns	−0·795 (P=0·002)	ns
Standing	ns	ns	ns	−0·628 (P=0·029)	ns
CON					
Supine	ns	ns	ns	ns	ns
Standing	ns	ns	ns	ns	ns

SBP = systolic blood pressure; DBP = diastolic blood pressure; C1 = arterial compliance of the proximal part of the circulation; C2 = arterial compliance of the distal part of the circulation; CON = controls; CHF = chronic heart failure.

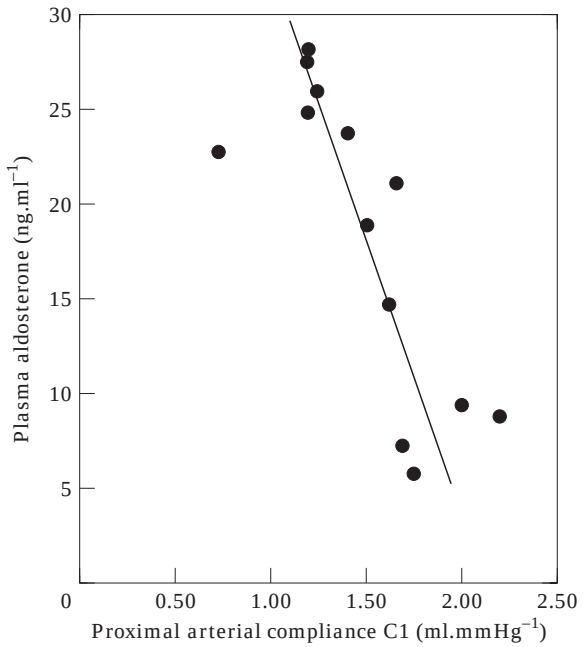

Figure 1 **Inverse relationship between aldosterone and C1 in chronically treated chronic heart failure patients. r = −0·795; *P* = 0·002.**

position, were there any statistically significant correlations between renin or angiotensin II and respectively age, blood pressures and C1 and C2.

Discussion

In chronic heart failure, proximal and distal arterial compliance assessed by non-invasive pulse wave contour analysis is lower in comparison to the arterial compliance in controls of comparable age, despite lower blood pressure in the chronic heart failure group and full chronic ACE inhibitor therapy. Moreover, the chronic heart failure patients were characterized by an aldosterone escape phenomenon and in both supine and standing positions aldosterone concentrations, but not renin or angiotensin II, were inversely correlated with the proximal arterial compliance.

Arterial compliance is markedly reduced in severe congestive heart failure and a less pronounced but clear-cut compliance abnormality occurs also in mild chronic heart failure[5]. This has important pathophysiological implications because a reduction in arterial compliance leads to an increase in arterial impedance and cardiac afterload[6].

Our findings in fully treated chronic heart failure patients with ACE inhibitors are still in accordance with these well-accepted principles. In particular, the proximal arterial compliance (C1), which is mainly representative of the elastic behaviour of the aorta and its major side branches, is impaired in our study group; the distal arterial compliance (C2), which is mainly representative for the elastic behaviour of the smaller vessels, was proportionally less reduced in chronic heart failure than the proximal arterial compliance. Giannattasio *et al.*[27] demonstrated the beneficial effects of angiotensin-converting enzyme inhibitor therapy on the arterial compliance of the small-sized (radial) artery in chronic heart failure patients. The results in the present data on heart failure patients fully treated with captopril 150 mg daily are the opposite of the results in a previous heart failure study, where the patients received no ACE inhibitor therapy[9]. In the latter paper, insignificantly reduced C1 and very low C2 were observed. The best explanation for this discrepancy is that our patients were receiving captopril, which is known to increase C2, but probably not C1.

Several investigators examined arterial compliance at different arterial sites using different methodologies. In chronic heart failure patients secondary to idiopathic dilated cardiomyopathy mainly treated with ACE inhibitors, Lage *et al.*[28] demonstrated that carotid artery distensibility was reduced, but did not study other vascular territories. Using pulse wave velocity as a measure of elastic behaviour, conflicting data have been observed in chronic heart failure. Arnold *et al.*[5] reported increased pulse wave velocity and decreased brachial artery compliance, while earlier studies of Merillon *et al.*[29] and Eliakim *et al.*[19] could not demonstrate differences between chronic heart failure patients and controls. In addition, using characteristic impedance as a study parameter resulted in conflicting data. The increase in characteristic impedance in chronic heart failure demonstrated by Pepine *et al.*[8] could not be confirmed either by Merillon *et al.*[29] or by Laskey *et al.*[30]. Khder *et al.*[31] reported on increased cross-sectional compliance and volumic distensibility, but unchanged isobaric compliance at the radial artery and concluded that radial artery intrinsic wall stiffness was unchanged, which is in contrast to the paradoxical behaviour of this artery described in hypertension[32]. Giannattasio *et al.*[33] studied radial artery compliance in chronic heart failure and described impaired arterial compliance using A-mode ultrasound echotracking.

Although more marked in severe congestive heart failure, the impairment was also manifest in mild congestive heart failure.

Earlier, Finkelstein *et al*., using invasively recorded brachial artery pressure waveforms and cardiac output determined by thermodilution[9] addressed the problem of haemodynamic impedance parameters. In their study, all vasodilator therapy was withdrawn for at least 72 h and digitalis and diuretics were withheld for at least 12 h. Their results implicated that chronic heart failure has a more highly damped vascular system than normal subjects and that distal compliance assessed from invasive pulse contour analysis is a more sensitive and specific index than systemic vascular resistance to the vascular changes in chronic heart failure. However, more recently the authors introduced a non-invasive methodology to assess proximal and distal arterial compliance, based on arterial waveforms recorded at the radial artery and making use of a third order four-element modified Windkessel mathematical model[26]. Our results are the first obtained non-invasively with this technique in chronically treated chronic heart failure patients.

The method for calculating cardiac output has been validated by Cohn *et al*.[25] in the cardiac output range between 3 and 8 $l \cdot min^{-1}$. The authors described an over-estimation of 10 to 15% of the calculated cardiac output values vs the indocyanine green method in the lower cardiac output range of 3 to 5 $l \cdot min^{-1}$. Values in heart failure may be unreliable because of a change in velocity of ejection that may alter the relationship between stroke volume and ejection time. Although the calculated cardiac output method has not been validated per se in heart failure patients, the observed values appear to be appropriate and an over-estimation of cardiac output in the heart failure patient would have tended to raise, not reduce, the compliance values.

In an animal model of early systolic dysfunction, reduced conduit vessel compliance preceded peripheral vasoconstriction[34]. Moreover, it has been demonstrated that the increase in circulating angiotensin II participates in changes in both aortic compliance and peripheral vascular resistance. In an animal model of hypertension, it has been demonstrated that angiotensin II antagonism improved aortic characteristic impedance[34]. In the setting of chronic heart failure, therapy with ACE inhibitors generally reduces serum aldosterone levels acutely. However, long-term ACE inhibition is associated with aldosterone suppression that is weak, variable and unsustained (aldosterone escape mechanism)[35]. Increased serum aldosterone levels in chronic heart failure may have several deleterious effects, including potentiation of catecholamines, induction of ventricular arrhythmias, alteration of baroreflex function, stimulation of myocardial fibrosis and disequilibrium of ion balances. However, there may be an alternative mechanism. The angiotensin II levels in chronic heart failure are still elevated despite ACE inhibition. This suggests that ACE inhibition in chronic heart failure does not chronically suppress angiotensin II and that the increased aldosterone may be due to residual angiotensin increase, rather than to aldosterone escape induced by another mechanism. In our study, the study question of the relationship between the aldosterone escape phenomenon and the altered arterial compliance in chronic heart failure was examined. Our results pointed towards a less compliant aorta and its major side branches with increasing aldosterone escape. Our observation holds true in both the supine and standing position. It should be noted that under control conditions a significant relationship between aldosterone and proximal compliance was absent.

Although a direct causative relationship between aldosterone escape and impaired arterial compliance is still uncertain, there are several arguments which may support this hypothesis. First, sodium retention and waterlogging and the potentiation of catecholamines due to aldosterone escape may be responsible for stiffer, less distensible vascular behaviour. Second, recently the expression of the aldosterone receptor (type I mineralocorticoid receptor) gene in vascular smooth muscle and to a less extent to endothelial cells[36] has been demonstrated, which makes a direct relationship more plausible. Third, Weber and Brilla demonstrated that aldosterone acts directly as a circulating hormone to induce collagen synthesis in the ventricle[37]. This observation may also constitute an argument in favour of increased arterial stiffness in aldosterone escape, provided the authors' findings are extended from the myocardium to the arterial wall.

In conclusion, in chronically treated chronic heart failure patients with ACE inhibitors we observed aldosterone escape associated with reduced arterial compliance of the aorta and its major side branches, which in turn could lead to a further worsening of the heart failure process due to increased impedance to ventricular outflow. Future studies should address the question whether aldosterone antagonists, in combination either with ACE inhibitors or angiotensin II receptor antagonists, will be able to improve large artery compliance.

We would like to thank Mrs Linda Packet for her excellent secretarial assistance.

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