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ACE inhibitors unmask incoordinate diastolic wall motion in restrictive left ventricular disease

Michael Y Henein, Aham Amadi, Christine O'Sullivan, Andrew Coats, Derek G Gibson

Abstract

***Objective*—To assess the effect of ACE inhibition on left ventricular filling and wall motion in patients with a clinical diagnosis of heart failure.**

***Design*—Prospective examination of left ventricular systolic and diastolic function using M mode echocardiography and pulsed and continuous wave Doppler before and three weeks after starting an ACE inhibitor.**

***Setting*—A tertiary referral centre for cardiac disease equipped with non-invasive facilities.**

***Subjects*—30 outpatients with a clinical diagnosis of heart failure in whom treatment with an ACE inhibitor was started; age 61 (SD 11) years; 27 male; 3 female; 21 healthy controls of similar age.**

***Results*—Left ventricular cavity was dilated both at end systole and end diastole, and fractional shortening reduced. Although mean isovolumetric relaxation time (IVRT) and transmitral E (early) to A (late) filling velocity (E/A) ratio were not different from normal, a value of 1·0 on the normal frequency plot of the E/A ratio divided the patients bimodally into two groups: 20 patients (group A) with E/A ratio > 1·0 and 10 patients (group B) < 1·0. In group A patients, IVRT was short as was transmitral E wave deceleration time compared to normal ($P < 0·001$), fulfilling the criteria of restrictive left ventricular physiology. Left ventricular wall motion during IVRT was coordinate and left ventricular end diastolic pressure was raised on the apexcardiogram ($P < 0·001$). In group B, E wave deceleration time was longer, relaxation incoordinate, and apexcardiogram normal. With an ACE inhibitor: in group A, left ventricular dimensions fell at end diastole ($P < 0·05$) and end systole ($P < 0·01$) but fractional shortening did not change; long axis total excursion ($P < 0·01$) and peak rate of shortening ($P < 0·05$) both increased; IVRT increased ($P < 0·001$) with the appearance of markedly incoordinate wall motion, minor axis lengthening, and long axis shortening ($P < 0·001$ for both); A wave amplitude also consistently increased ($P < 0·001$); finally, transmitral E wave velocity fell and A wave velocity increased. ACE inhibition did not alter any of the left ventricular minor and long axis or transmitral Doppler variables in patients in group B.**

***Conclusions*—Patients with a clinical diagnosis of heart failure differ in their presentation and response to ACE inhibition according to baseline haemodynamics. In restrictive left ventricular physiology, ACE inhibition reduces cavity size and prolongs IVRT, compatible with a fall in left atrial pressure. At the same time, ventricular relaxation becomes very delayed and incoordinate, greatly reducing early diastolic left ventricular filling velocity. Thus ACE inhibition unmasks major diastolic abnormalities in patients with restrictive left ventricular disease.**

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Keywords: ACE inhibitor; restrictive left ventricular physiology; diastolic incoordination; heart failure

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Angiotensin converting enzyme (ACE) inhibitors have been shown to improve exercise tolerance and prolong life expectancy in patients with left ventricular disease.[1 2] However, the nature of the disturbance of ventricular function in patients presenting with the clinical syndrome of heart failure is very variable and is itself likely to have a major effect on drug action. It was our purpose in the present study, therefore, to describe left ventricular pathophysiology in a group of patients thought to merit treatment with ACE inhibitors on the ground of a clinical diagnosis of heart failure and to determine its effects on these abnormally functioning ventricles, using non-invasive methods based on echocardiography.

Patients and methods

SUBJECTS

We studied 30 outpatients in whom a clinical diagnosis of heart failure had been made and an ACE inhibitor was considered to be indicated. All the patients were symptomatic with dyspnoea, class II-IV (New York Heart Association), limiting exercise tolerance, along with cardiac enlargement on chest *x* ray, and ventricular cavity size—determined by echocardiography—increased to 5·8 cm or more (the upper 95% confidence limit of normal) at end diastole. No patient had evidence of structural valve disease, pericardial disease, more than mild functional mitral regurgitation, or significant arrhythmia. They were all in sinus rhythm. The drug (captopril,

Table 1 Clinical details

Variables	*Group A (n = 20)*	*Group B (n = 10)*
Age (years)	61 (12)	62 (10)
Gender	19 male, 1 female	8 male, 2 female
Aetiology:		
Ischaemic heart disease	6	2
Coronary bypass surgery	3	2
Dilated cardiomyopathy	4	1
Aortic valve disease	2	1
Hypertension	2	3
Sarcoidosis	1	0
Unknown	2	1
Treatment (daily dose)		
Captopril	10 (25 mg)	5 (25 mg)
Enalapril	5 (5mg)	3 (5 mg)
Lisinopril	5 (2·5 mg)	2 (2·5 mg)

enalapril, or lisinopril) and initial dose prescribed were determined by the referring physician. Echocardiographic measurements were made before and at least three weeks after the start of treatment. Between the two echocardiographic studies other baseline drugs were not altered, including diuretics. Clinical details, aetiology, and treatment are summarised in table 1.

Twenty one normal subjects, age 58 (SD 11) years, served as control. None had a history of hypertension, shortness of breath, or valvar or ischaemic heart disease.

PROCEDURES

All patients were studied at rest. Cross sectional guided M modes were obtained using a Hewlett Packard Sonos 1500 echocardiograph with a 2·5 MHz transducer interfaced to it. With the patient in the left semilateral position, M modes of the left ventricular minor axis were recorded from the parasternal long axis view with the cursor by the tips of the mitral leaflets. M modes of mitral valve leaflets themselves were also recorded from the same view, with the cursor at the tips of the leaflets. Long axis M modes of the left and septal segments were recorded from the apical four-chamber view, with the cursor positioned at the corresponding angles of the mitral ring.[3] All records were made during quiet expiration. Transmitral pulsed Doppler records of the forward flow velocities were obtained using the same echocardiograph with the sample volume at the tips of the mitral valve leaflets, in the apical four-chamber view. Continuous wave Doppler recordings of mitral regurgitation was detected by colour flow and recorded with a Doptek system (Colchester, UK), using a 2·5 MHz non-imaging transducer. Blood pressure was taken with a sphygmomanometer. The apexcardiogram was recorded using Cambridge equipment (time constant 4 s). An electrocardiogram and phonocardiogram were superimposed on all traces. Studies were recorded photographically at a paper speed of 100 mm/s. M mode traces were digitised off line.[4]

From the left ventricular minor axis M mode trace we measured ventricular dimensions using leading edge methodology. End diastole was taken as the onset of the Q wave of the electrocardiogram and end systole as A2—the first high frequency vibration of the aortic component of the second heart sound—on the phonocardiogram. Fractional shortening was calculated as the fall in cavity dimension divided by the end diastolic dimension (%). We also measured the total amplitude of epicardial systolic excursion. Isovolumetric relaxation was measured as the time interval from the aortic component of the second heart sound to mitral cusp separation on the M mode trace.

From the long axis traces we determined the total amplitude of excursion. The A wave was taken as the amplitude of backward ring motion (towards the atrium) after the P wave of the electrocardiogram. From the digitised short and long axis traces we measured peak rates of shortening (in systole) and of lengthening (in diastole) and the time intervals between the Q wave of the electrocardiogram and peak shortening and between A2 of the phonocardiogram and peak lengthening. From the pulsed Doppler traces of the transmitral forward flow velocity we measured peak early and late diastolic filling velocities—both from the baseline—and hence calculated E/A ratio. We also measured transmitral E wave deceleration time and the time interval between A2 and the onset of transmitral early diastolic flow using linear extrapolation to baseline of the acceleration phase. The presence or absence of functional mitral regurgitation on continuous wave Doppler was noted. Systolic and diastolic blood pressures were recorded and the relative height of the left ventricular end diastolic point with respect to the total amplitude on the apexcardiogram was measured and expressed as a percentage.

STATISTICAL ANALYSIS

Baseline results from all patients are presented as mean (SD). A normal frequency plot of transmitral E (early) to A (late) diastolic left ventricular filling velocity ratio (E/A ratio) was constructed for the whole group of patients and departure from a unimodal distribution sought. Baseline results from the two patient groups defined on this basis were compared with normal controls using Student's unpaired *t* test. Individual results, before and after treatment with an ACE inhibitor, were compared using paired *t* test. A P value of less than 0·05 was considered significant.

REPRODUCIBILITY

The reproducibility of the digitising process was assessed in a sample of 20 patients from duplicate determinations of long axis excursion, peak velocities, and timing with respect to the Q wave and A2. Within and between observer values were determined independently. Reproducibility was assessed as root mean square (RMS) difference between duplicate measurements, and the corresponding value of coefficient of variation as the ratio RMS difference/absolute value (table 2).

Results

CLINICAL DETAILS (TABLES 1 AND 3)

The patients studied proved to have a mean age of 61 years, and to be almost all males.

Table 2 Intra- and interobserver reproducibility

Variables	Intraobserver CV (%)	Interobserver CV (%)
Total excursion	3·2	4·0
Shortening during isovolumetric relaxation	11·5	15
Peak shortening rate	4·2	5·4
Peak lengthening rate	5·0	6·0
Q to onset of shortening	6·0	7·0
A2 to onset of lengthening	5·5	6·0

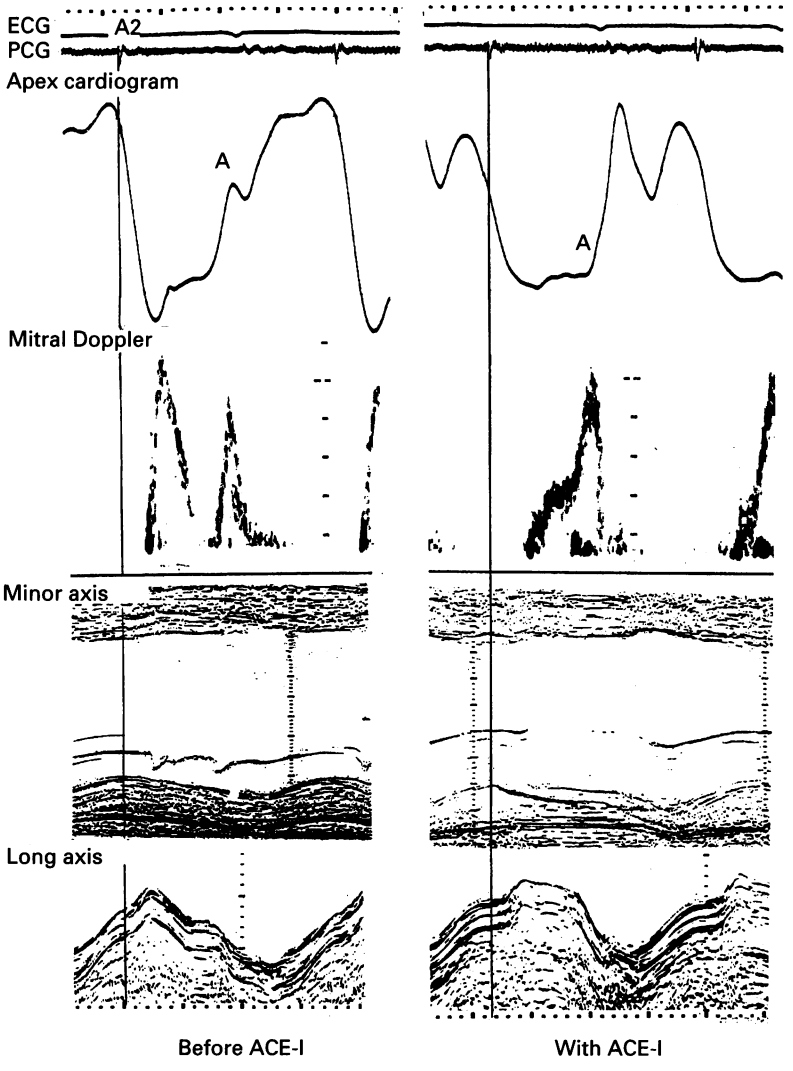
CV, coefficient of variation.

Table 3 Overall left ventricular function

Variables	Normal (n = 21)	Patients (n = 30)
Left ventricular		
End diastolic dimension (cm)	4·9 (0·5)	6·9 (1·2)
End systolic dimension (cm)	3·3 (0·5)	5·8 (1·5)†
Fractional shortening (%)	30 (5)	17 (10)†
Isovolumetric relaxation time (ms)	60 (10)	45 (37)
Mitral regurgitation (No of patients)	0	22
Transmitral E/A ratio	1·4 (0·4)	1·8 (1·7)

E, early; A, late diastolic left ventricular filling velocities.
†P < 0·001.

Coronary artery disease and its complications were the commonest diagnoses. End diastolic dimension, increased by definition, had a mean value of 6·9 cm. In addition, end systolic dimension—5·8 cm—was significantly increased and fractional shortening reduced to 17% with respect to normal. The majority of the patients had mild functional mitral regurgitation as estimated by colour doppler. By contrast, mean values of isovolumetric relaxation time and transmitral E/A ratio did not differ significantly from normal, although the scatter was wide. In order to investigate the possibility that this wide scatter concealed more than one discrete group within the sample as a whole, we constructed a normal frequency plot of values of E/A ratio. This departed significantly from a unimodal distribution [observed $r = 0{\cdot}871$, expected $r = 0{\cdot}949$ ($n = 30$) for $P < 0{\cdot}01$]. The cut off value between the two populations was 1·0, which we used to divide the patients into two groups.



A composite representing different pressure, flow velocities, and wall motion changes occurring in early and late diastole from a patient with dominant E wave before ACE inhibitor and dominant A wave after. Note: (a) the drop in left ventricular end diastolic pressure on the apexcardiogram (top trace) after treatment was associated with a reduction in early diastolic and an increase in late diastoic filling velocities; (b) the increase in the isovolumetric relaxation time during which minor axis lengthened and long axis continued to shorten all through early and mid diastole. ECG, electrocardiogram; PCG, phonocardiogram; A2, second heart sound, which was recorded on all traces and used to align them.

BEFORE TREATMENT

Minor and long axis function and transmitral Doppler

These are shown in tables 4–6.

In the 20 patients (group A) in whom the E/A ratio was > 1·0, left ventricular cavity size was larger at both end diastole and end systole, and fractional shortening was less than that in the remaining patients (group B). Though the timing and velocity of systolic shortening of both short and long axes were similar, there were major differences in diastolic function. Apart from the differences in E/A ratio, used to define the groups, E wave deceleration time in group A was 75 (20) ms, a value well within the range previously described as being characteristic of a restrictive pattern of filling.[5] That in group B was significantly longer, though still shorter than normal. While left ventricular wall motion was coordinate during isovolumetric relaxation in group A, minor axis increased and septal long axis reduced in group B, indicating a change in left ventricular cavity shape. Finally, relative height of the late diastolic A wave on the apexcardiogram was significantly increased in group A, but not in group B.

Effect of ACE inhibition in group A

With treatment, left ventricular dimensions at end diastole and end systole both fell significantly, though fractional shortening did not change (table 4). Systolic total excursion and peak rate of shortening of left ventricular long axis both increased (table 5). Isovolumetric relaxation time was greatly prolonged, and wall motion became incoordinate during this period with an increase in left ventricular minor axis, and a fall in long axis, compatible with a change in cavity shape. Though the rate of early diastolic left ventricular long axis lengthening did not change, A wave amplitude consistently increased (table 5). Left ventricular filling pattern as shown by pulsed Doppler changed strikingly (table 6). Transmitral peak E wave velocity fell and its deceleration time increased. A wave also increased so that the E/A ratio was consistently reduced. Finally, the relative height of the A wave on the apexcardiogram fell.

Table 4 Minor axis function: comparison of groups. Values are mean (SD)

Variables	Normal	Group A, n = 20		A v B (pre)	Group B, n = 10		A after ACE v B before
		Pre	ACE		Pre	ACE	
R-R interval (ms)	940 (200)	740 (135)	800 (170)	NS	800 (140)	820 (190)	NS
Systolic BP (mm Hg)	120 (10)	128 (24)	112 (20)	NS	134 (24)	120 (25)	NS
Diastolic BP (mm Hg)	80 (10)	75 (10)	72 (10)	NS	80 (9)	76 (12)	NS
EDD (cm)	4·9 (0·5)	7·2 (1·2)‡	6·7 (1·1)[a]	< 0·05	6·1 (0·7)‡	6·4 (0·7)	NS
ESD (cm)	3·3 (0·5)	6·3 (1·3)‡	5·6 (1·1)[b]	< 0·001	4·6 (1·2)‡	4·7 (1)	< 0·05
Shortening fraction (%)	30 (5)	13 (6)‡	16·5 (7)	< 0·001	24 (12)	27 (9)	< 0·05
Systolic epicardial motion (cm)	0·9 (0·1)	0·47 (0·15)‡	0·5 (0·17)[b]	< 0·001	0·7 (0·16)‡	0·8 (0·2)	< 0·01
Total excursion (cm)	1·7 (0·3)	1·1 (0·3)‡	1·13 (0·5)	NS	1·3 (0·5)*	1·4 (0·5)	NS
Peak short rate (cm/s)	9·0 (3·0)	4·7 (2·0)‡	5·5 (1·6)	NS	5·6 (2·0)†	7 (1·8)	NS
Peak length rate (cm/s)	10·4 (2·6)	7·8 (3·1)†	7·4 (2·8)	NS	7·9 (5·1)	7·8 (4·5)	NS
A2 to peak lengthen (ms)	115 (40)	95 (40)	97 (30)	NS	110 (40)	100 (40)	NS

EDD, end diastolic dimension; ESD, end systolic dimension; A2, second heart sound; BP, blood pressure.
*P < 0·05; †P < 0·01; ‡P < 0·001; [a]P < 0·05 *v* pre ACE; [b]P < 0·01 *v* pre ACE.

Table 5 Long axis function: comparison of groups. Values are mean (SD)

Variables	Normal	Group A, n = 20		A v B (pre)	Group B, n = 10		A after ACE v B before
		Pre	ACE		Pre	ACE	
Systole							
Total excursion (cm)							
Left	1·5 (0·25)	0·74 (0·3)¶	0·9 (0·2)[b]	< 0·001	1·2 (0·3)*	1·3 (0·3)	< 0·01
Septal	1·5 (0·3)	0·56 (0·2)¶	0·72 (0·2)[c]	< 0·01	0·8 (0·27)¶	0·92 (0·2)	NS
Peak shortening rate (cm/s)							
Left	8 (1·5)	3·4 (1·0)¶	3·9 (1·0)[a]	< 0·001	5·6 (1·5)‡	5·6 (1·9)	< 0·01
Septal	7·5 (1·2)	2·6 (0·9)¶	2·6 (1·4)	NS	2·7 (1·2)¶	2·9 (2·1)	NS
IVRT							
Time (ms)	60 (10)	17 (24)¶	80 (40)[c]	< 0·001	79 (20)¶	76 (35)	NS
Dimension change (cm)							
Minor axis	0·1 (0·07)	0·1 (0·1)	0·3 (0·2)[c]	< 0·05	0·22 (0·14)‡	0·25 (0·14)	NS
Long Axis							
Left	0·1 (0·07)	−0·07 (0·1)¶	−0·18 (0·15)[a]	NS	−0·01 (0·14)†	−0·07 (0·1)	< 0·01
Septal	0·1 (0·06)	−0·04 (0·14)¶	−0·2 (0·15)[c]	< 0·001	−0·21 (0·1)¶	−0·13 (0·13)	NS
Diastole							
Peak lengthening rate (cm/s)							
Left	10 (2·5)	3·6 (2·4)¶	3·2 (2·7)	< 0·05	6·0 (2·6)¶	5·7 (3·0)	< 0·05
Septal	6·5 (1·0)	1·4 (1·9)¶	1·4 (2·7)	NS	1·8 (1·5)¶	2·3 (2·4)	NS
A2 to peak lengthening (ms)							
Left	115 (25)	115 (55)	150 (50)[a]	NS	110 (30)	110 (10)	NS
Septal	120 (25)	105 (45)	145 (45)[c]	< 0·05	140 (40)	130 (30)	NS
A wave amplitude (cm)							
Left	0·4 (0·1)	0·3 (0·14)*	0·5 (0·17)[c]	< 0·001	0·57 (0·15)‡	0·63 (0·15)	NS
Septal	0·5 (0·15)	0·3 (0·1)¶	0·42 (0·1)[c]	< 0·001	0·5 (0·2)	0·59 (0·1)	NS

−, Abnormal shortening during IVRT; IVRT, isovolumetric relaxation.
*P < 0·05; †P < 0·01; ‡P < 0·005; ¶P < 0·001 *v* normal; [a]P < 0·05 *v* pre ACE; [b]P < 0·005 *v* pre ACE, [c]P < 0·001 *v* pre ACE.

Table 6 Transmitral Doppler and apexcardiogram: comparison of groups. Values are mean (SD)

Variables	Normal	Group A, n = 20		A v B (pre)	Group B, n = 10		A after ACE v B before
		Pre	ACE		Pre	ACE	
Transmitral Doppler							
E wave velocity (m/s)	0·7 (0·1)	0·8 (0·2)*	0·5 (0·2)[a]	< 0·001	0·43 (0·25)‡	0·4 (0·4)	NS
A wave velocity (m/s)	0·5 (0·1)	0·3 (0·3)†	0·8 (0·2)[a]	< 0·001	0·78 (0·15)‡	0·8 (0·05)	NS
E/A ratio	1·4 (0·4)	2·5 (1·7)†	0·8 (0·8)[a]	< 0·001	0·6 (0·5)‡	0·5 (0·4)	NS
E deceleration (ms)	160 (20)	75 (20)‡	125 (35)[a]	< 0·001	130 (32)†	155 (30)	NS
Mitral regurgitation (patients)	0	18	12		4	4	
Apexcardiogram							
A wave/total pulse (%)	15 (5)	47 (20)‡	16 (8)[a]	< 0·001	15 (8)	13 (3·5)	NS

E, early diastolic filling; A, late diastolic filling.
*P < 0·05; †P < 0·01; ‡P < 0·001; [a]P < 0·001 *v* pre ACE.

Effect of ACE inhibition in group B (tables 4–6)
With the same dose of ACE inhibition given for the same period of time, there was no significant change in any of the measurements obtained from left ventricular minor or long axes, transmitral Doppler, or apexcardiogram in the patients in group B.

Comparison between group A after ACE inhibitors and group B before ACE inhibitors
Since ACE inhibition led to the pattern of left ventricular function in patients in group A resembling that seen under control conditions in group B, we compared the two states formally (tables 4–6). This resemblance applied to all measurements except left ventricular end systolic dimension and fractional shortening, which were more reduced in group A, and free wall long axis, where total excursion ($P < 0·01$), peak shortening ($P < 0·01$), and peak lengthening ($P < 0·05$) velocities were lower with more incoordination during isovolumetric relaxation, $P < 0·01$.

Discussion

The syndrome of heart failure is well recognised clinically, although formal definitions have proved very unsatisfactory.[6-9] The patients identified in the present study were similar to those described in western published reports as having the syndrome: they were

elderly, predominantly males, and suffering from the complications of coronary artery disease. By definition, left ventricular cavity size was enlarged, and significant valve disease and rhythm disturbances were absent. Echocardiographic analysis of these patients showed, however, that they were not a homogeneous group, but were bimodally distributed in terms of their diastolic function. The majority (group A) had an abnormally short isovolumetric relaxation time, and a dominant E wave, on transmitral Doppler, with a reduced deceleration time.[10] In the remainder (group B), isovolumetric relaxation time was long, wall motion incoordinate, E wave amplitude reduced or absent altogether, and the left ventricular long axis showed a series of major disturbances of relaxation.[11] Since the effects of any drug in disease are likely to depend on the baseline characteristics of the patients to whom it is given, we elected to investigate the two groups separately.

In patients in group A, oral administration of an ACE inhibitor had clear cut effects. Left ventricular cavity size fell with no change in systolic shortening velocities, isovolumetric relaxation time increased, and transmitral E wave amplitude fell. Left ventricular wall motion during diastole became strikingly incoordinate, with complementary changes in major and minor ventricular axes during the isovolumetric relaxation period. At the same time, the incidence of functional mitral regurgitation fell, and the amplitude of long axis changes during atrial systole increased. By contrast, in group B patients similar doses of the same drugs given for a similar period of time caused no measurable effect on left ventricular haemodynamics. Not only were the patients bimodally distributed with respect to their baseline characteristics, therefore, but this dichotomy was directly reflected in the response to treatment.

Several mechanisms have been suggested to explain the beneficial effects of ACE inhibition on exercise tolerance and prognosis. These have included a reduction in left ventricular afterload,[12] lowering of left atrial pressure,[13] improvement of cardiac pump function resulting from arteriovenous dilatation,[14] or remodelling of the heart without improving intrinsic pump function.[15] We found no change in arterial blood pressure. At least part of the response seen in our study in the group A patients can be explained in terms of a fall in left atrial pressure. The very short values of isovolumetric relaxation time present in control circumstances suggest that it was initially raised, and its increase, along with a change in the pattern of transmitral flow from a dominant E wave to a dominant A wave, would be compatible with a substantial fall in early diastolic atrioventricular pressure gradient. A reduction in left atrial pressure would also explain the fall in left ventricular end diastolic dimension in the absence of any change in shortening rate. In addition, left ventricular long axis relaxation became very incoordinate, with striking prolongation of tension, often throughout early diastole and diastasis, until the onset of atrial systole. At the same time the minor axis enlarged before any detectable transmitral flow, suggesting that the termination of wall tension within the myocardium had become asynchronous and that the cavity shape was changing.

These results might be explained in more than one way. It is possible that ACE inhibition has a primary action in inducing incoordinate left ventricular diastolic function, thus explaining why isovolumetric relaxation time increased, the E wave was suppressed, and long axis tension development was prolonged. However, there is no experimental basis for such an action. Alternatively, one can note that disturbances to ventricular physiology in group A after ACE inhibition became very similar to those in group B before treatment, particularly with respect to isovolumetric relaxation time and filling characteristics, though different in the extent. Further, ACE inhibition in the latter group was without effect on ventricular mechanics. It seems therefore, that the underlying physiology in all patients approximated to that seen in group B, but superimposed on this, in group A patients, was an additional factor sensitive to ACE inhibition. We cannot define this additional factor precisely, but a major component of it appears to be a high left atrial pressure. Increased end diastolic ventricular stiffness and abnormalities of ventricular relaxation are both widely held to increase left atrial pressure. However, passive ventricular compliance—determined largely by myocardial collagen—is unlikely to change with short term drug administration, while ventricular relaxation became even more abnormal with ACE inhibition. Two additional possibilities require more consideration. Mild functional mitral regurgitation was common, though not invariable, in group A patients, and its incidence declined somewhat with treatment. In addition, left atrial pressure may rise due to an increase in central blood volume and thus reflect the properties of the peripheral circulation, explaining its response to a vasodilator. Regardless of the mechanism of the increase in left atrial pressure, we believe that a high early diastolic atrioventricular pressure gradient leads to an apparently normal pattern, not only of filling, as is well recognised,[5] but also of wall motion, by overriding disturbances of relaxation. Abnormal relaxation only becomes apparent when it is unmasked as atrial pressure falls, although the effects of these disturbances on ventricular filling in patients with restrictive physiology can readily be appreciated. The greater effects of ACE inhibition—seen in our study—compared with those of nitrates[16] may reflect the effect of chronic compared with acute administration, since it is established that their beneficial effects on exercise may require several weeks to appear.[12]

Our study had obvious limitations. In order to reflect the clinical use of ACE inhibition, we did not fix drug or dose nor did we attempt to establish rigid entry criteria to define heart failure, since it was our aim to study both the nature of ventricular disease and drug use as it

occurs in cardiological practice. The doses used were initial ones, and were thus low. Once a patient is established on the drug, it is standard practice to increase the dose until an optimal clinical response is achieved. This may explain persisting differences between group A after treatment with an ACE inhibitor and group B. The study was an exploratory one, and thus designed to be non-invasive. It would clearly have been of interest to have correlated direct measurements of left atrial pressure with the echocardiographic changes that we have described. However, no mechanism other than raised left atrial pressure has ever been found to underlie an abnormally short resting isovolumetric relaxation time. It would also have been of interest to have determined the time relations of the change in filling pattern during the period between our two sets of observations and also to exercise tolerance. In common with previous clinical trials of the effects of ACE inhibition,[2 17 18] we did not consider patients with atrial fibrillation, although they form a significant proportion of those eligible for treatment. Finally, all our patients were already on diuretic treatment and the dose was not altered for the study, so we are unable to distinguish a primary effect of ACE inhibition on ventricular loading conditions from a secondary one potentiating diuretic action. Both, though, are likely to contribute to the effects of ACE inhibition in clinical practice.

Our observations seem to have a number of general consequences. They illustrate the varied nature of left ventricular disease encompassed within the clinical syndrome of heart failure, and underline difficulties that arise when any rigorous definition is attempted. The dependence of the response to ACE inhibition on baseline physiology stresses the significance of allowing for the protean nature of ventricular disease in assessing drug effects. It is clear that an intervention documented as increasing exercise tolerance and improving prognosis may make measurements of left ventricular relaxation more abnormal. Whether the changes we observed contribute directly to the known therapeutic effects of ACE inhibition we cannot say, although we note that a low E/A ratio has been linked both to a greater exercise tolerance[19] and a better prognosis[20] than a high one. We have previously noted the bimodal distribution of the E/A ratio.[21] Its genesis is unclear, but its apparent stability seems worthy of note. Simple control system theory suggests a positive feedback mechanism whereby the additional factor we have assumed to be its basis aggravates the conditions that give rise to it in the first place, thus leading to a bistable system. Finally, our results raise the possibility that among the large numbers of patients with the clinical diagnosis of heart failure, there may be considerable variation in response to ACE inhibition, a significant minority showing no effect at all. As long as ACE inhibition is thought to be without important side effects, this finding would be of little practical consequence other than reducing the overall cost-effectiveness of treatment, but should any clinically significant interaction be demonstrated, for example with aspirin,[22] then the case for more discriminating drug use would be clear.

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