Determinants of the blood pressure response to the first dose of ACE inhibitor in mild to moderate congestive heart failure

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Aims To investigate the relationship in patients with heart failure between BP response to the first dose of ACE inhibitor and (1) plasma drug concentration and (2) baseline clinical and laboratory variables.

Methods We studied individual placebo-corrected BP responses to initiation of treatment with one of a number ACE inhibitor preparations in 132 patients with mild to moderate CHF. Various pharmacokinetic/pharmacodynamic models were compared. We assessed the strength of association between baseline physiological and laboratory variables and the BP response as assessed directly from the AUC(0,10 h) and indirectly from the slope of the PK/PD relationship. Predictive models for response variables were developing using regression analysis.

Results BP response was primarily related to plasma drug concentration. The association between the fall in BP and baseline variables was weak. The strongest single predictor of BP response was baseline mean arterial pressure ($r^2 = 5.8\%$, $P = 0.02$). The best combinations of predictor variables contained mean arterial pressure, plasma renin activity, creatinine concentration and age ($r^2 = 14.4\%$, $P = 0.37$). When the choice of ACE inhibitor was added, the predictive power of the model increased ($r^2 = 23.6\%$, $P < 0.01$) but left the majority of the variability in response unexplained.

Conclusions The first-dose blood pressure response to ACE inhibition cannot be accurately predicted from baseline pathophysiological variables in patients with mild to moderate CHF. The choice of ACE inhibitor accounts for a small proportion of the variability in response but wide inter-individual variability exists in the response to each treatment.

Keywords: ACE inhibitors, CHF, first-dose hypotension, regression analysis

Introduction

The angiotensin converting enzyme (ACE) inhibitors confer significant mortality and morbidity benefits in all functional grades of chronic congestive heart failure (CHF) [1–4] and in patients with left ventricular dysfunction following acute myocardial infarction [5, 6]. In this respect they are superior to currently available alternative therapeutic regimens [7]. In spite of this evidence, a significant proportion of patients who may benefit from treatment are not prescribed an ACE inhibitor [8–10]. Physicians' concerns regarding the possible occurrence of 'first-dose hypotension', a clinically significant fall in blood pressure on initiation of therapy, appears to be a major contributing factor to this under-utilisation of a proven treatment in both hospital [11] and primary care settings [12].

It has been suggested that the magnitude of the blood pressure response, and by inference the likelihood of first-dose hypotension, can be predicted from clinical and laboratory variables. A number of factors, which have in common their ability to increase angiotensin II levels, have been suggested to increase the risk of first-dose hypotension; namely low pre-treatment blood pressure, high diuretic

dose, hyponatraemia and renal artery stenosis [13]. High diuretic dose and associated hyponatraemia are associated with first-dose hypotension in severe CHF [14–16]. However patients with these high risk markers are now in a minority of those being commenced on therapy. Hyponatraemia and hypovolaemia are seldom found in those with mild to moderate CHF, for whom the predictors of a significant fall in blood pressure have proved more difficult to identify [17]. Further to this, direct comparisons of the haemodynamic responses to alternative ACE inhibitor agents are rare. We have previously shown qualitative and quantitative differences among agents in the pattern of blood pressure response to the first dose of treatment [18–21].

We have investigated whether the variability in pharmacodynamic response to acute ACE inhibition, as assessed by the change in systemic blood pressure, is determined by pharmacokinetic factors, and if differences among ACE inhibitors can be identified in this regard. We also sought to investigate the relationship between the blood pressure response and a variety of physiological variables in an attempt to identify clinically useful predictors of the magnitude of the blood pressure response. We studied: [i] the response to placebo; [ii] the response to the first dose of the ester ACE inhibitors enalapril, perindopril and quinapril, administered orally in their recommended starting doses in CHF; and [iii] the response to intravenous infusion

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of the active diacid metabolites, enalaprilat and perindoprilat. By studying the response to intravenous therapy we sought to eliminate differences in response due to interindividual heterogeneity in absorption, de-esterification and tissue distribution with oral dosing.

Methods

Patients

We utilised a database of 144 patients (51–88 years, 99 men) with CHF, each of whom was recruited to one of three randomised, double-blind, parallel-group, placebo-controlled studies of the haemodynamic and neurohumoral response to initiation of ACE inhibitor therapy with one of a number of preparations [18–21]. The design of each study is shown in Table 1. Due to the requirement for special preparation of plasma, plasma concentrations of captopril cannot be determined in the setting of a double-blind study. Individuals who received this drug were omitted from the analysis which is thus based on 132 patients. All studies were approved by the local ethics review committee and each patient gave written informed consent. All had stable, symptomatic CHF and doses of diuretic and other cardiovascular medication were unchanged for at least 14 days prior to the study. All patients had systolic BP ≥ 100 mm Hg, serum sodium ≥ 135 mmol l⁻¹ and stable hepatic and renal (serum creatinine ≤ 250 μ mol l⁻¹) function prior to the study.

Procedure

The procedure for blood sampling and for haemodynamic monitoring was identical in each study. Patients were admitted to hospital for commencement of ACE inhibition after 24 h supervised diuretic withdrawal. Each patient rested supine for 45–60 min immediately prior to administration of study therapy, during which time blood pressure (BP) was measured at 2 min intervals (Sentron semi-automatic sphygmomanometer, Bard, Sunderland, UK). Baseline BP was taken as the mean of readings over the final 30 min of this period. Mean arterial BP (MAP) was calculated as diastolic BP + 1/3 pulse pressure. Blood pressure at each time point was the mean of three readings. Supine haemodynamic observations and blood sampling for drug concentration were performed at 5, 10, 15, 20, 30, 40, 50 min and 1, 2, 3, 4, 5, 6, 8, 10, and 24 h after administration of a single dose of study medication.

For each study the mean placebo response was estimated by smoothing and averaging the individual baseline-corrected placebo MAP measurements. For each subject a baseline

correction was made to MAP at each time point by subtracting the baseline MAP. Baseline-corrected MAP values in the active treatment groups were further corrected by subtracting the appropriate baseline-corrected mean placebo response. High performance liquid chromatography of hippuric acid produced from the exogenous substrate Hip-His-Leu was used to measure plasma drug concentration, based on the method of Chiknas [22]. All samples were diluted as appropriate to lie within the calibration range of 0.16–20 ng ml⁻¹. Intra- and inter-assay coefficients of variation were consistently less than 10%.

Pharmacokinetic analysis

The following therapies were studied: oral perindopril 2 mg ($n = 24$); oral enalapril 2.5 mg ($n = 24$); oral quinapril 2.5 mg ($n = 12$); intravenous perindoprilat 0.167 mg h⁻¹ for 6 h ($n = 12$); intravenous perindoprilat 0.167 mg h⁻¹ for 1 h ($n = 12$); intravenous enalaprilat 0.25 mg h⁻¹ for 6 h ($n = 12$). Within each study a control group ($n = 12$) was administered oral and/or intravenous placebo as appropriate (Table 1). The pharmacodynamic (PD) effect of each of the orally administered ACE inhibitors studied is mediated by the diacid metabolite of the drug. Thus, for the purpose of pharmacokinetic (PK) modelling, only the profile of the diacid metabolite was considered. The PK profile of each drug was evaluated using one and two compartment models. Zero and first order methods were compared when modelling absorption and conversion to active metabolite. Model fitting was carried out using the computer package STATIS (Clydesoft, UK). The fit of each model to the data was assessed by the Akaike Information Criterion [23].

The PK analysis included 132 patients: 48 who received perindoprilat (24 perindopril orally, 24 perindoprilat i.v.), 36 patients who received enalaprilat (24 enalapril orally, 12 enalaprilat i.v.) and 12 who received quinaprilat (12 quinapril orally). A total of 36 patients received placebo.

Pharmacodynamic modelling

For each individual the area under the baseline and placebo corrected MAP curve up to 10 h after dosing AUC(0,10 h) was calculated using a linear trapezoidal method. This estimate (AUC(0,10 h)) was used as a direct measure of the magnitude of the PD response.

Pharmacokinetic/pharmacodynamic modelling

The PK parameters estimated for each individual were used to predict theoretical curves from which the relationship between plasma drug concentration and haemodynamic

Table 1 Design of studies 1–3.

Study 1	72 patients, $n = 12$	captopril 6.25 mg orally/enalapril 2.5 mg orally/ perindopril 2 mg orally/enalaprilat 0.25 mg h ⁻¹ i.v. (6 h)/perindoprilat 0.167 mg h ⁻¹ i.v. (6 h)/placebo
Study 2	48 patients, $n = 12$	enalapril 2.5 mg orally/perindopril 2 mg orally/ perindoprilat 0.167 mg h ⁻¹ i.v. (1 h)/placebo
Study 3	24 patients, $n = 12$	quinapril 2.5 mg orally/placebo

response was investigated. Three models of PD response were compared: a linear model, where effect is a linear function of drug concentration; and two $E_{\max}$ models, using the Langmuir and the more general Hill equations. All three models were fitted with and without a baseline term. An effect compartment was also considered to model the lag between drug concentration and blood pressure response profiles. Model fit was again assessed using AIC. The blood pressure response in general reflected plasma drug concentration and it was not possible to estimate the PK parameters associated with an effect compartment. A simple linear model with baseline error term provided the best description of the data. Thus a direct linear relationship between the PD effect and plasma drug concentration was derived:

$$\text{MAP}_{ij} = \alpha_i + \beta_i c_{ij},$$

where MAP_{ij} and c_{ij} are mean arterial pressure (baseline and placebo corrected) and plasma drug concentration for individual i at time j , and α_i and β_i are estimated intercept and slope of the fitted line for individual i . The β -coefficient, i.e. the estimated slope of the relationship, was taken as an indirect measure of the magnitude of the relationship between the observed drug concentration and MAP response, i.e. the PK/PD relationship.

Influence of physiological variables

We investigated the relationship between a number of baseline physiological variables and the magnitude of the MAP response, as assessed directly by the $\text{AUC}(0,10\text{ h})$ and indirectly by the slope of the PK/PD relationship (the β -coefficient). For the categorical variables gender (male/female), cardiac rhythm (sinus rhythm/other rhythm), aetiology of CHF (ischaemic heart disease/hypertensive heart disease/alcohol related/valvular heart disease) and New York Heart Association (NYHA) class (II of III or IV), the MAP responses were compared and 95% confidence intervals calculated for the differences in medians between groups for each variable. Patients with NYHA III and IV symptoms were considered together due to the small numbers in the latter category. The strength of association between the fall in MAP (as assessed by $\text{AUC}(0,10\text{ h})$ and β -coefficient) and each continuous variable (age, baseline values of MAP, diuretic dose, ACE activity, plasma renin activity, and serum sodium, potassium and creatinine concentration) was quantified using the Spearman rank correlation coefficient. Predictive models for the response variable under consideration ($\text{AUC}(0,10\text{ h})$ and β -coefficient) were developed using best-subset regression analysis, and by forward stepwise linear regression analysis. Statistical analysis was carried out using the computer package Minitab (Minitab Inc, PA, USA).

Results

General

Baseline clinical and laboratory features for each treatment group are summarised in Table 2. For each treatment at each time point, marked inter-individual differences in both plasma drug concentration and BP response were apparent

(Figure 1). In no case was initiation of study therapy associated with symptoms of hypotension. One patient, a 74 year old female who had received oral placebo as study treatment, was unable to tolerate subsequent open ACE inhibitor therapy (oral captopril 6.25 mg) due to symptomatic hypotension. All other patients left hospital on ACE inhibitor therapy and after reinstitution of diuretic and other therapy as appropriate.

Pharmacokinetic modelling

Intravenous dosing One- and two-compartment models with first order elimination were fitted to the intravenous infusion data. For 6 h infusions (enalaprilat and perindoprilat) the plot of concentration on a logarithmic scale against time shows, after the end of the infusion, the linear elimination of a one compartment model (Figure 1). Analysis of residual plots (i.e. (observed—predicted) *vs* predicted concentration) suggested in some cases that a two-compartment model would be more appropriate. With only four data points after the end of the infusion, there were insufficient data to justify the two compartment model. In contrast, it is clear from the 1 h infusion that elimination is not linear (Figure 1), the data being better described by a two compartment model, for which the Akaike Information Criterion was lower in all but one case (median fall in AIC between one- and two-compartment models = 25.2, inter-quartile range 12.3–30.2).

Oral dosing When the formation, disposition and elimination of each diacid metabolite ACE inhibitor were considered, concentration *vs* time plots revealed a lag phase before the start of absorption. This was incorporated into the model. Zero- and first-order methods were compared when modelling the phase of drug absorption and conversion to active metabolite. The lag and absorption/conversion phases were of the order of 6 h for enalapril and perindopril, 5 h for quinapril (Figure 1). There were again too few data points after this time to justify a two compartment model. In the cases of enalapril and quinapril the absorption/conversion phase was best described by a zero-order process; AIC was lower in 19 of 24 cases given enalapril (median fall in AIC between one and two compartment models = 8.9, interquartile range 0.5–19.8) and 10 of 12 cases given quinapril (median fall in AIC = 10.0, interquartile range 0.2–13.8).

It proved more difficult to model the data as regards oral perindopril in view of the much greater variation in PK parameters. In only 13 of the 24 individuals could PK parameters of a 1-compartment model be estimated, with little difference in AIC between zero- and first order absorption/conversion models.

Pharmacodynamic analysis

Summary plots of the $\text{AUC}(0,10\text{ h})$ showing the median, minimum, maximum and interquartile values are shown for each drug treatment in Figure 2, together with 95% confidence intervals (C.I.) for the median. The CI indicate that oral enalapril, intravenous enalaprilat, intravenous perindoprilat 1 mg over 6 h and oral quinapril each produced

Table 2 Summary of baseline clinical and laboratory variables. Values are mean (1 s.d.).

Patient characteristics	Age (years)	NYHA class (II/III/IV)	MAP (mmHg)	PRA (ng AI ml ⁻¹ h ⁻¹)	Sodium (mM)	Furosemide (mg day ⁻¹)	Aetiology of CHF (IHD/HT/AC/V)
Enalapril 2.5 mg orally (n=24)	68 (7)	10/12/2	97 (11)	8.2 (11.8)	138 (4.4)	93 (57)	19/3/2/0
Perindopril 2 mg orally (n=24)	69 (8)	8/16/0	94 (11)	5.3 (7.1)	140 (3.2)	93 (44)	18/3/3/0
Enalaprilat 1.5 mg i.v. (n=12) (0.25 mg h ⁻¹ for 6 h)	70 (6)	2/10/0	99 (15)	4.2 (3.7)	141 (2.4)	100 (43)	6/3/2/1
Perindoprilat 1 mg i.v. (n=12) (0.167 mg h ⁻¹ for 6 h)	69 (6)	5/7/0	89 (10)	4.5 (4.7)	140 (3.3)	85 (40)	8/0/4/0
Perindoprilat 0.167 mg i.v. (n=12) (0.167 mg h ⁻¹ for 1 h)	66 (8)	4/8/0	91 (12)	6.8 (8.4)	138 (3.7)	90 (41)	10/0/1/1
Quinapril 2.5 mg orally (n=12)	76 (8)	8/4/0	95 (12)	2.5 (1.6)	141 (3.1)	62 (18)	9/3/0/0
Placebo (n=36)	71 (8)	5/19/2	92 (14)	4.4 (2.7)	138 (2.5)	96 (69)	24/6/3/3

AC=alcohol related cardiomyopathy; HT=hypertension; IHD=ischaemic heart disease; CHF=congestive heart failure; MAP=mean arterial pressure; NYHA=New York Heart Association; PRA=plasma renin activity; V=valvular heart disease.

a significant fall in MAP as estimated by AUC(0,10 h). The median AUC(0,10 h) for perindoprilat given intravenously over 1 h or as oral perindopril could not be distinguished from zero.

Pharmacokinetic/pharmacodynamic modelling

Figure 3 shows summary plots for the β -coefficient of the PK/PD relationship and 95% CI for the median value within each group. The negative estimate of slope for oral enalapril and intravenous enalaprilat indicates a direct relationship between plasma drug concentration and fall in MAP. In keeping with the PK data the relationship of plasma drug concentration to MAP response with perindoprilat was more variable. For oral perindopril there was no direct relationship between concentration and effect (95% CI for median β -coefficient, -0.69 to 0.08 mmHg nmol⁻¹ l⁻¹). However a direct relationship was apparent for intravenous administration of perindoprilat over both 6 h and 1 h (95% C.I. for median β -coefficient -0.39 to -0.1 , and -1.1 to -0.27 mm Hg nmol⁻¹ l⁻¹ respectively). While the profile of MAP response with oral quinapril was qualitatively similar to that seen with oral enalapril, the magnitude of the fall was smaller. Thus the estimated slope defining the PK/PD relationship was of lesser magnitude than with oral enalapril (95% C.I. for the median β -coefficient, -0.08 to 0.01 mmHg nmol⁻¹ l⁻¹).

The results demonstrate clearly the more consistent response to intravenous as compared to oral administration of ACE inhibitor. However for each oral agent a close relationship between plasma concentration of the active diacid metabolite and MAP response was apparent in a number of patients.

Influence of physiological covariates

Both the direct pharmacodynamic response as measured by the AUC(0,10 h), and the indirect PK/PD relationship as measured by the β -coefficient of the linear model, were considered when determining factors which may be related

to the MAP response. The strength of each relationship was considered for all treatments combined and for each individual ACE inhibitor.

For the study population as a whole, for the β -coefficient of the PK/PD relationship, there was an association between abnormal cardiac rhythm (39 atrial fibrillation and 1 sinus rhythm plus frequent ventricular extrasystoles) and MAP response (95% CI for difference between medians 0.02–0.39, $P=0.03$, Mann-Whitney U-test). There was no relationship between MAP response and gender (95% CI -0.18 to 0.14 , $P=0.58$, Mann-Whitney), NYHA class (95% CI -0.12 to 0.21 , $P=0.69$, Mann-Whitney), or aetiology of CHF ($P=0.54$, Kruskal Wallis). Results were similar when individual drug treatments were considered. There was no association between any categorical variable and response as assessed by AUC(0,10 h) for the whole or any part of the study population.

As the distribution of some continuous variables was skewed, the Spearman rank correlation coefficient was used to assess the strength of association with MAP response. Although within each study significant correlations were identified, a number of such results can be expected by chance. No consistent relationship was apparent between any single continuous variable and either measure of MAP response.

To determine whether the blood pressure response can be predicted from a combination of baseline variables, forward stepwise regression analysis was carried out using age, gender, cardiac rhythm, NYHA class, diuretic dose, serum ACE activity, plasma renin activity, and serum sodium, potassium and creatinine concentrations as predictor variables, with AUC(0,10 h) and β -coefficient as response variables. Where data were skewed, logarithmic and reciprocal transformations were also considered. Baseline variables were included into the model in a stepwise manner. Individual variables were considered only if the amount of variability in response (adjusted r^2) was increased by their inclusion. The included predictors are shown in Table 3. From the results it can be seen that less than 15% of the variability in MAP response can be related to the considered

Figure 1 Individual drug concentration (nmol l^{-1}) and mean arterial blood pressure responses (MAP, mm Hg) following a single dose of ACE inhibitor in patients with mild to moderate chronic heart failure.

baseline factors. Best subsets regression analysis gave similar results. The results for individual drug treatments were similar to the overall analysis and are not presented. In no case did the inclusion of any further variable increase the value of the adjusted r^2 . When the choice of ACE inhibitor agent was included in a regression model with the previously identified predictor variables the adjusted r^2 values increased to 23.6% and 14.2% for $\text{AUC}(0,10 \text{ h})$ and β -coefficient respectively, improving the fit ($F=6.32$, $p<0.01$) but leaving over 75% of the variability in response unexplained.

Discussion

To our knowledge this study represents the most comprehensive analysis of the determinants of the blood pressure

response on initiation of ACE inhibitor therapy in mild to moderate CHF. Our results indicate that in this population the magnitude of the first-dose hypotensive response to oral ACE inhibitor therapy is primarily related to plasma drug concentration and cannot be predicted from baseline clinical or physiological variables. For oral therapy, pharmacodynamic differences appear to result from inter-individual differences in bioavailability of the active diacid, the MAP response reflecting the plasma drug concentration achieved. A simple linear relationship between pharmacodynamic response and plasma drug concentration was apparent. The sampling schedule for the studies was such that there was insufficient information to estimate the PK parameters of a two-compartment model. However the models developed adequately described the data in the period most relevant to

Figure 2 Summary plots showing median, quartiles and range of the pharmacodynamic response, as assessed directly from the area under the baseline and placebo corrected mean arterial blood pressure curve to 10 h (AUC_{0,10h}, mm Hg), following treatment with perindoprilat (oral perindopril or intravenous perindoprilat), enalaprilat (oral enalapril or intravenous enalaprilat) or oral quinapril. CI = 95% confidence interval for median value.

Figure 3 Summary plots showing median, quartiles and range of the pharmacodynamic response, as assessed indirectly from the slope (β -coefficient; mm Hg nmol⁻¹ l⁻¹) of the pharmacokinetic/pharmacodynamic relationship, following treatment with perindoprilat (oral perindopril or intravenous perindoprilat), enalaprilat (oral enalapril or intravenous enalaprilat) or oral quinapril. CI = 95% confidence interval for median value.

the current analysis of the determinants of the MAP response, i.e. up to 10 h after drug administration.

The studies upon which we have based the current analysis showed that, on average, the first dose of oral perindopril in patients with CHF does not lower MAP, in contrast to both captopril and enalapril [18, 21]. However in the latter study the mean maximum fall in MAP seen with perindopril 2 mg orally was as great as with enalapril 2.5 mg orally. The present study suggests that for all agents studied the MAP response depends upon the plasma drug concentration achieved. Observed differences in the average

MAP response to oral ACE inhibitor therapy are thus likely to reflect differences in the average plasma drug concentration achieved.

Previous statements regarding the value of markers such as hyponatraemia and high diuretic dose as predictors of first-dose hypotension are based largely on evidence from studies in severe CHF [14–16]. In the single study published to date in mild to moderate CHF, neither plasma sodium nor diuretic dose were predictive of the blood pressure response to a single oral dose of captopril [17]. We have now extended this finding to a large population treated with a variety of oral and intravenous ACE inhibitor agents. While Motwani was able to explain 74% of the variability in blood pressure response to a single dose of captopril, the only useful predictive baseline parameter was MAP, the others being the magnitude of the falls in plasma noradrenaline and angiotensin II after initiation of treatment [17]. Although in our study baseline MAP had the strongest association with subsequent MAP fall, only 6–7% of the variability in response could be explained on this basis. Moreover the best subset of baseline parameters could explain only 25% of the variability in response. When we eliminated interindividual differences in drug absorption and metabolism by intravenous administration of ACE inhibitor, an association emerged between baseline plasma renin activity and MAP response ($P=0.03$, Mann-Whitney). This suggests a central role for the renin-angiotensin system in maintaining systemic blood pressure in patients with mild to moderate CHF.

The incidence of symptomatic hypotension on initiation of ACE inhibitor therapy in CHF has been reported as approximately 5–10% [1, 3]; 2–5% of patients withdraw from treatment as a result. In the CONSENSUS II study mortality was higher among those patients who developed first-dose hypotension [24]. On the basis of this study and a number of case reports [14, 25], a variety of anecdotal protocols have been developed for the initiation of ACE inhibitor treatment in CHF [26]. While it has been suggested that the determinants of the response to chronic ACE inhibition may differ from those determining the acute response [26], the available evidence indicates otherwise [28, 29]. Recent guidelines for the treatment of CHF suggest that when initiating ACE inhibitor therapy, ‘...supervision for several hours with blood pressure control is advisable...’ [30]. Our data demonstrate wide inter-individual variation in the profile of the blood pressure response to each treatment studied. Moreover the magnitude of fall in blood pressure does not equate with the occurrence of symptoms. As hypotension following initiation of ACE inhibitor is of most significance when it results in organ hypoperfusion, our data call into question the rationale for monitoring of blood pressure for short, ill-defined periods after initiation of treatment.

It is of note that there was no relationship of diuretic dose to MAP response in our population. Our patients are likely to be representative of the population with mild to moderate CHF in whom an ACE inhibitor is indicated. Thus our results are relevant to the vast majority of patients. In this context the occurrence of a single episode of symptomatic first-dose hypotension in our population of 132 patients is reassuring.

Table 3 Forward stepwise regression.

Variables in model	Adjusted r^2	AUC(0, 10 h) For additional variable		Variables in model	Adjusted r^2	β -coefficient For additional variable	
		F	P value			F	P value
MAP	5.8	6.68	0.02	cardiac rhythm	5.8	6.69	0.02
MAP	10.6	5.88	0.03	cardiac rhythm	6.7	1.92	0.34
+ PRA				+ PRA			
MAP	13.6	4.17	0.09	cardiac rhythm	7.9	2.19	0.28
+ PRA				+ PRA			
+ 1/Cr				+ diuretic dose			
MAP	14.4	1.79	0.37	cardiac rhythm	8.8	1.96	0.33
+ PRA				+ PRA			
+ 1/Cr				+ diuretic dose			
+ Age				+ MAP			
Linear regression							
MAP	23.6	6.32	<0.01	cardiac rhythm	14.2	7.35	<0.01
+ PRA				+ PRA			
+ 1/Cr				+ diuretic dose			
+ Age				+ MAP			
+ Drug				+ Drug			

Regression analysis for MAP response as assessed by AUC₁₀ and β -coefficient of PK/PD relationship. r^2 = percentage variability in response explained by the value predictor variable(s). The r^2 value will increase as more predictor variables are added to the model. Adjusted r^2 takes account of the number of variables in the model and will decrease if too many predictor variables are included in the model. Abbreviations as for Table 2.

It is a perhaps a limitation of our study that we did not measure pre-treatment levels of atrial natriuretic factor, noradrenaline or angiotensin II. However none of these was predictive of the response to initiation of therapy in a previous study [17]. Moreover we wished particularly to assess the predictive value of routinely available parameters. A further possible criticism of our study is that we did not formally assess the influence of left ventricular ejection fraction. Once again no correlation between ejection fraction and blood pressure response was apparent in a previous study [17]. Information on ejection fraction is frequently not available to physicians caring for patients with heart failure, particularly in primary care. In the absence of information on ejection fraction, our identification of abnormal cardiac rhythm as a predictor of the MAP response may indicate a subgroup of patients with more severe CHF at risk of a greater fall in blood pressure.

In summary, the blood pressure response to the initiation of ACE inhibitor therapy in patients with chronic, stable CHF cannot be predicted from baseline pathophysiological variables. The time to maximum fall in blood pressure varies markedly among patients treated with any single ACE inhibitor agent. Symptomatic hypotension on initiation of ACE inhibitor in mild to moderate CHF is unpredictable but rare, and should not be perceived as limiting the use of this most appropriate therapy in this population.

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