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RESEARCH ARTICLE

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The angiotensin-converting enzyme gene I/D polymorphism and heart rate variability following acute myocardial infarction

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Abstract *Aims* Heart rate variability (HRV) is a measure of cardiac autonomic control and is therefore subject to regulation by the renin-angiotensin system. The primary objective of this study was to determine the effect of an insertion/deletion polymorphism within the angiotensin-converting enzyme (ACE) gene on HRV in the early stages after a myocardial infarction at a time when cardiac autonomic control is deranged. The secondary objective was to determine whether this polymorphism affected the HRV response to inhibition of ACE. *Major Findings* 149 Caucasian subjects were studied 25 ± 16 h following MI using time and frequency domain measures of HRV derived from two 5-minute ECG recordings. Recordings were repeated at 182 ± 65 h following MI, when subjects had been stabilised on ramipril 2.5 mg bd. The study included 46 subjects with the DD genotype, 69 with the ID genotype, and 34 with the II genotype. No effect of the I/D polymorphism on short-term recordings of HRV was found. There was no difference in HRV response to the introduction of ramipril according to the genotypes. *Principal Conclusions* The I/D polymorphism within the ACE gene does not influence HRV after MI or the HRV response to ACE inhibitor therapy with ramipril. These findings may reflect the relative lack of importance of the I/D polymorphism and ACE activity in determining plasma and tissue angiotensin II concentration after a major stimulus to the renin-angiotensin system as occurs after myocardial infarction.

Key words Polymorphism · renin-angiotensin system · heart rate variability

Introduction

Cardiac autonomic control is profoundly deranged after myocardial infarction (MI) with evidence of impaired vagal control and high levels of sympathetic activity. The extent of this derangement, in particular subnormal vagal activity, can be assessed by the measurement of baroreflex sensitivity and heart rate variability (HRV). There is considerable evidence to show that low levels of these markers of cardiac autonomic control are strongly and independently associated with an adverse prognosis [1]. It is now widely believed that abnormal cardiac autonomic control after MI is not merely a consequence of the infarct but actively and deleteriously influences the clinical course of the disease.

Despite the evidence relating impaired autonomic control to an adverse prognosis, the cause of the autonomic dysfunction remains unclear. Part of the explanation may lie in the activation of the renin-angiotensin system after MI [2]. Angiotensin II (A II) exerts powerful vagal inhibitory and sympatho-facilitatory effects both within the brain stem and peripherally [3]. Recent human studies have demonstrated an inhibitory effect

of AII infusion on high frequency measures of HRV mediated by the vagus [4]. Plasma A II concentration is dependent not only upon the stimulus of renin production but on the activity of angiotensin-converting enzyme (ACE). The activity of this enzyme is known to be under genetic control as a result of the inheritance of the insertion-deletion (I/D) polymorphism within the ACE gene. This polymorphism is in close linkage disequilibrium with a functional variant which predicts serum and tissue ACE expression, with subjects homozygous for the D allele having serum ACE levels twice as high as subjects homozygous for the I allele [5]. It has been estimated that 39–65 % of the variation in HRV within the population may be attributable to influences on the autonomic nervous system of polymorphisms such as this [6]. In view of the evidence, albeit controversial, linking the D allele with cardiovascular disease we have investigated the possible link between the I/D polymorphism in the ACE gene and HRV in patients after MI. The reduction in HRV after MI is alleviated by treatment with ACE inhibitors and a secondary aim was to determine whether the I/D polymorphism within the ACE gene affected HRV response to treatment with ACE inhibitors [7].

Methods

Recruitment criteria

One hundred and forty-nine subjects were recruited from patients admitted to the coronary care units at three hospitals in the United Kingdom between 1998 and 2000. Patients were eligible if they presented within 48 hours of MI in sinus rhythm. Recruitment was restricted to patients of Caucasian origin. Exclusion criteria were existing treatment with ACE inhibitors, contra-indications to the use of ACE inhibitors, and established autonomic dysfunction. Drugs with a known impact on autonomic function were avoided during the study period unless a mandatory clinical indication arose. Patients who were commenced on β-blocker treatment during the study period were excluded from analysis. Patients stabilised on β-blocker treatment before study inclusion were eligible provided that there was no change to drug dose throughout the study. Written, informed consent was obtained prior to entry into the study, which was approved by the respective local clinical research ethics committees.

Experimental protocol

Blood samples were taken on admission for genotype analysis. HRV was examined first within 48 hours of admission at the bedside using methods previously described [8]. In brief, a 3-lead ECG signal was amplified, processed, and digitised at 500 Hz using a laptop computer. Two recordings of at least 256 consecutive RR intervals were made on each occasion. The ACE inhibitor ramipril (2.5 mg bd) was commenced following this study and HRV was re-assessed between day 6 and 10 after the MI. Studies were performed with subjects in the semi-supine position following a two hour fast and a minimum of 30 minutes' rest in bed. Blood pressure was measured using automated oscillometric sphygmomanometry following this rest period.

HRV analysis

HRV analysis was performed by a blinded investigator according to previously published methods [8]. In brief, ECG series containing less than 3 % of ectopic beats were manually reviewed and both non-sinus intervals and artefacts were deleted and replaced by interpolation from previous and following sinus intervals. Standard time domain measures were calculated including: SDNN (standard deviation of NN interval values – a prognostically important index expressing overall variability), pNN50 (% of successive NN interval differences > 50 ms) and rMSSD (root mean square of successive NN interval differences). Both pNN50 and rMSSD are measures of high frequency ("beat to beat") variation mediated principally by the vagus nerve [9]. Frequency domain analysis was performed on stationary RR interval series using autoregressive modelling as previously described [8], to determine spectral powers at low frequency (LF; centred at ~0.1 Hz) and at high frequency (HF; corresponding to the observed respiratory frequency) expressed in absolute and normalised units (nu = [power/total power > 0.04 Hz] x 100 %).

Genetic analysis

Deoxyribonucleic acid (DNA) was prepared from a small aliquot of whole blood collected in ethylenediamine tetraacetic acid by using a DNA extraction matrix (Instagene, Biorad, England) and was stored at –70 °C. The ACE gene D and I alleles were identified on the basis of polymerase chain reaction amplification of the respective fragments from intron 16 of the gene, with 5 % dimethylsulfoxide included in the reaction mixture to reduce mistyping of ID heterozygotes as previously described [10]. Amplified fragments were analysed on ethidium-bromide agarose gels by an individual blinded to the HRV data.

Data analysis

Power calculations for this study were based on change in SDNN. It was predicted that recruitment of the ID/II genotype would be twice as frequent as the DD genotype on the basis of previous studies within the local population [10]. As an effect related to the influence of angiotensin II was the subject of the study, we hypothesised that a difference in SDNN between the DD and ID/II groups of a similar magnitude to that obtained by treatment with an ACE inhibitor might be obtained. Data available from studies of the effect of ACE inhibitor therapy in heart failure suggest treatment effects of between 30 and 100 % [11, 12]. It was calculated that 124 subjects in total would be required to detect a difference in SDNN of 40 % with 80 % power at 5 % significance [7]. The study was designed to compensate for a 20 % drop-out rate (148 patients) to allow for recruitment of patients whose data might not be suitable for analysis (for example, in the presence of multiple ectopy).

Qualitative (nominal) descriptive data were analysed using Pearsons Chi-square test and quantitative descriptive data were analysed using three group one-way ANOVA. HRV data were assessed for normality. HRV data for the primary end-point of determining a difference between I/D polymorphisms following MI were assessed using three group one-way ANOVA. In addition, independent t-tests were used to compare the DD genotype with the ID/II genotypes combined. In order to assess the interaction between genotype and ACE inhibition, changes between the baseline measurement and measurement following ACE inhibition were calculated for each individual and the mean changes for each genotype were then compared using three group one-way ANOVA. In addition, independent t-tests were used to compare the DD genotype with the ID/II genotypes combined. Initial results were considered significant at the 5 % level but were then subjected to the Bonferroni correction for multiple testing.

Results

Study subjects

In total, 149 subjects were recruited: 45 subjects with the DD genotype, 69 subjects with the ID genotype, and 35 subjects with the II genotype. The subject population was in Hardy-Weinberg equilibrium for the I/D ACE polymorphism. There was no difference in the distribution of the I/D ACE genotypes according the location of recruitment ($p = 0.1$). Eighteen patients were excluded from the study after recruitment for the following reasons: an excess ectopic count preventing HRV analysis in both recordings in 8 subjects; introduction of β-blockers during the study period in 3 subjects; unavailable or poor quality ECG data preventing HRV analysis in 5 subjects; and 2 subjects withdrew consent. Within the group excluded from the study, there were 8 subjects with the DD genotype, 8 subjects with the ID genotype, and 2 subjects with the II genotype. No differences in the baseline characteristics of the patients excluded from analysis were found in comparison to the final study group.

The genotype groups were matched at baseline in terms of their demographic characteristics, including distribution of risk factors and previous history of cardiac disease. Matching was also achieved with respect to the extent and location of MI assessed by peak creatine kinase level, left ventricular ejection fraction on transthoracic echocardiography and ECG (Table 1). Overall, 87% of the study population received thrombolysis, 96% received aspirin and 35% received β-blockers. Comparing genotypes, there were no differences in terms of the treatment received, either in the use of thrombolysis or in the use of pharmacotherapy following infarction ($p > 0.1$ for frequency of thrombolysis, and for use of aspirin, β-blockers, calcium antagonists, nitrates and statins). Overall, 21% of the study population suffered from clinical cardiac failure and 15% had documented evidence of transient cardiac arrhythmias during the study period. There were no differences between genotype groups in terms of the rate of cardiac failure ($p = 0.18$), arrhythmia ($p = 0.34$), or other complications ($p = 0.51$).

Table 1 Demographic and clinical characteristics according to ACE genotype

	DD	ID	II	p
Age	63.7 ± 12.1	61.5 ± 11.9	64.9 ± 9.6	0.33
Male sex (%)	30 (65.2)	51 (73.9)	26 (76.5)	0.47
Type I DM (%)	1 (2.2)	1 (1.4)	1 (2.9)	0.88
Type II DM (%)	3 (6.5)	5 (7.2)	1 (2.9)	0.68
Hypertension (%)	16 (34.8)	22 (31.9)	11 (32.4)	0.95
Current smoker (%)	22 (46.4)	32 (46.4)	14 (41.2)	0.83
Positive FH (%)	10 (23.8)	17 (27.4)	10 (33.4)	0.67
Cholesterol	5.7 ± 1.1	5.8 ± 1.3	5.8 ± 0.8	0.89
Body mass index	25.7 ± 4.0	26.7 ± 4.0	27.1 ± 4.8	0.31
Previous cardiac disease (%)	6 (13.0)	13 (18.8)	6 (17.6)	0.70
Co-morbidity (%)	18 (39.1)	27 (39.1)	15 (44.1)	0.87
Anterior infarction (%)	22 (48.9)	39 (56.5)	15 (44.1)	0.42
Peak CK	1939 ± 1736	1960 ± 1496	1708 ± 1111	0.72
LV ejection fraction	51.1 ± 16.9	50.7 ± 14.3	52.5 ± 13.7	0.9

Numbers in parentheses are % of the total for each genotype.

Genetic effect on HRV following MI

There was no difference between the genotype groups in terms of their time to acquisition of HRV data following MI, measured from the start of thrombolysis or from the onset of symptoms in those subjects who did not receive thrombolysis (DD: mean 24 ± 16 h; ID: 26 ± 14 h; II: 25 ± 16 h, $p = 0.88$). There was no difference between the genotype groups in terms of their baseline blood pressure (DD: mean 96 ± 15 mmHg; ID: 97 ± 14 mmHg; II: 95 ± 13 mmHg, $p = 0.63$). There was no difference between the genotype groups in terms of their time to the final HRV recording (DD: mean 169 ± 57 h; ID: 191 ± 73 h; II: 187 ± 59 h, $p = 0.24$). Blood pressure fell in response to the introduction of ramipril by 5 ± 14 mmHg but there was no difference in the degree of change relative to the I/D ACE polymorphism ($p = 0.32$ for DD v ID v II).

There was no difference in HRV (first recording) during fixed frequency respiration between individual genotype groups following MI (Table 2) nor was there a difference when DD subjects were compared with ID/II subjects combined (Table 3). This also held true for HRV series recorded during uncontrolled respiration (data not shown).

Effect of ACE genotype on HRV response to ACE inhibition following MI

No differences were observed in HRV response to ACE inhibition following MI between the ACE genotypes (II v ID v DD; Table 4) during either free or controlled res-

Table 2 Differences in time and frequency domain HRV (fixed respiration) between ACE I/D genotypes

	DD	ID	II	p
Mean NN ms	805 ± 162	847 ± 171	853 ± 180	0.48
SDNN ms	24.1 ± 17.9	26.4 ± 17.9	30.7 ± 22.4	0.41
rMSSD ms	18.3 ± 19.1	23.0 ± 21.7	27.2 ± 21.5	0.28
pNN50 %	3.2 ± 10.5	6.3 ± 12.0	7.9 ± 12.9	0.29
LF ms^2	115 ± 220	113 ± 227	255 ± 724	0.32
LF n. u. %	29.8 ± 21.2	27.6 ± 16.7	29.5 ± 18.6	0.86
HF ms^2	240 ± 520	302 ± 480	384 ± 536	0.56
HF n. u. %	58.1 ± 20.7	58.9 ± 18.1	56.5 ± 19.8	0.87
LF ms^2/HF ms^2	1.0 ± 2.0	0.7 ± 0.8	0.8 ± 0.8	0.47
Total power ms^2	874 ± 1582	880 ± 1167	1430 ± 2203	0.31

$p < 0.05$ significant; Values given ± s. d.

Table 3 Differences in time and frequency domain HRV (fixed respiration) comparing the DD with the ID/II genotypes combined

	Mean difference	95% C. I.	p DD v ID/II
Mean NN ms	43.8	−28.1–115.8	0.23
SDNN ms	3.8	−4.1–11.8	0.34
rMSSD ms	6.2	−2.7–15	0.17
pNN50 %	3.7	−1.3–8.7	0.14
LF ms^2	50	−129–229	0.58
LF n. u. %	−1.5	−9.5–6.4	0.71
HF ms^2	92	−124–308	0.40
HF n. u. %	−0.1	−8.4–8.1	0.98
LF ms^2/HF ms^2	−0.3	−0.9–0.2	0.24
Total power ms^2	204	−487–895	0.56

$p < 0.05$ significant; Values given ± s. d.

Table 4 Comparison of the within-genotype changes in time and frequency domain HRV (fixed respiration) following treatment with ramipril

	DD	ID	II	p
δ Mean NN ms	−80.8 ± 109	−63.8 ± 148	−66.8 ± 196	0.9
δ SDNN ms	−0.5 ± 12.5	2.6 ± 16.9	7.5 ± 22.9	0.32
δ rMSSD ms	−3.1 ± 12.4	2.9 ± 26.3	11.6 ± 24.5	0.11
δ pNN50 %	−2.5 ± 8.2	3.6 ± 13.3	7.5 ± 15.0	0.03*
δ LF ms^2	5.5 ± 206.8	23.9 ± 288.7	236.1 ± 869.5	0.22
δ LF n. u. (%)	0.6 ± 26.2	−2.9 ± 19.2	−2.7 ± 21.1	0.81
δ HF (ms^2)	−67.9 ± 284.7	116.2 ± 502.4	284.5 ± 624.3	0.06
δ HF n. u. (%)	0.2 ± 26.5	0.9 ± 18.2	−4.1 ± 19.4	0.70
δ LF ms^2/HF ms^2	−0.1 ± 2.4	−0.2 ± 1.1	−0.1 ± 0.9	0.87
δ Total power ms^2	14.2 ± 981.2	167.6 ± 1296.4	965.4 ± 2401.1	0.11

$p < 0.05$ significant; *loses significance with Bonferroni correction. Values given ± s. d.

piration. No significant differences were observed when the DD subjects were compared with ID/II subjects combined (data not shown).

Discussion

Our results indicate that the I/D polymorphism within the ACE gene does not exert a major influence on either HRV after MI or the HRV response to ACE inhibitor therapy. This is surprising given the known effect of this polymorphism on ACE concentrations [5] and the powerful effects of the product of ACE activity, A II, on cardiac vagal activity and HRV [3]. However, the findings may reflect the relative lack of importance of the I/D polymorphism and ACE activity in determining plasma and tissue A II concentration after a major stimulus to the renin-angiotensin system such as occurs after MI. The functional significance of this polymorphism in relation to cardiovascular disease has been thrown into doubt by a recent large negative case-control study [13] and by the demonstration of publication bias in favour of studies reporting a significant effect of the ACE genotype in patients following MI [14].

There has been only one previous report investigating the association between the ACE I/D polymorphism and HRV [6]. This study assessed the influence of ACE polymorphisms in healthy, young (mean age 34 years) monozygotic and dizygotic twins, finding that the DD ACE genotype was associated with an increase in both time and frequency domain measures of HRV. Although it could be argued that the effect of inherited traits on HRV may be more powerful when cardiac vagal tone is high rather than when reduced by the effects of age and MI, the results of Busjahn et al. are difficult to explain biologically. Increased ACE in association with the D allele [5] results in a rise in A II (probably at a local 'tissue' level [15]) and a decrease in bradykinin [16]. Numerous human and animal studies have shown that A II facilitates sympathetic activity and inhibits vagal activity [3]. A decrease in bradykinin would be expected to reduce both baroreflex sensitivity [17] and vagal activity [18]. Thus, the D allele would be expected to result in a reduction in HRV. Whilst the absence of a clear biological explanation does not negate the findings of Busjahn et al. [6], the results of our study are consistent with those of Ylitalo et al. [19] who failed to find a significant interaction between the I/D ACE polymorphism and baroreflex sensitivity in healthy subjects.

Our study also sought to determine whether an interaction exists between the I/D ACE polymorphism and HRV response to ACE inhibition. There is evidence from a number of large studies of an early reduction in mortality following MI with ACE inhibitors that does not seem to be explained by a reduction in progressive left ventricular dilatation or a reduction of recurrent ischaemic events [20]. One explanation might be that treatment with ACE inhibitors improves cardiac autonomic control following MI, with a resulting improvement in prognosis probably as a result of a reduced susceptibility to ventricular arrhythmias [3]. In agreement with this, ACE inhibitors have been shown to improve HRV and reduce the occurrence of lethal arrhythmias and sudden death concurrent with a beneficial effect on neurohormonal imbalance following MI [3, 7, 21] in contrast to direct acting vasodilators [22]. There have been no previous studies of HRV response to ACE inhibition in relation to the ACE I/D genotype. We found no evidence of such an interaction adding to the lack of any consistent data to suggest any interaction between the ACE I/D polymorphism and physiologic responses to ACE inhibitor therapy [23–26]. In subjects with heart failure, a greater hypotensive response to therapy with captopril but not lisinopril has been found in association with the II genotype, which raises the possibility that pharmacogenic differences in response may depend upon the type of ACE inhibitor used [27].

A number of limitations exist relating to our study. Firstly, we cannot exclude a smaller effect of the polymorphism on HRV than the 40% that this study was

powered to detect. Secondly, the population studied was heterogeneous in terms of size and location of infarction. There is some evidence that anterior location of infarction, greater CK elevation, and lower ejection fraction are associated with a relatively low HRV, which may account for some within-group variability [28]. However, HRV does provide additional prognostic value beyond that attributable to infarct size and left ventricular function [1]. Thirdly, while the utility of HRV in determining prognosis is well established, the mechanisms behind the alterations in autonomic tone that occur following MI are not yet understood. Both neural and non-neural, including hormonal, influences may be responsible for the abnormalities in cardiac autonomic control after MI. Angiotensin II is an important modulator of autonomic control but it is possible that it has less effect after MI relative to the effects on HRV of changes in haemodynamics, cardiac afferent stimulation and psychological stress. If this were the case, differences in HRV response to MI according to the I/D genotype would be hard to reveal. It is conceivable that differences in HRV response to MI according to the I/D genotype were also concealed by the administration in about one third of patients of β-adrenergic antagonists (which inhibit renin secretion). However, analysis of the data excluding those subjects who received β-adrenergic antagonists did not alter the findings of the study.

Summary

This study of 149 patients with MI recruited at the time of infarction showed no significant effect of the ACE I/D polymorphism on HRV. No evidence was found of modulation of the HRV response to ACE inhibition with ramipril at a dose of 2.5 mg bd. The results of this study are consistent with recent evidence casting doubt upon the significance of the I/D polymorphism in cardiovascular disease and with the previously demonstrated lack of association between the ACE I/D polymorphism and malignant ventricular arrhythmias in ischaemic heart disease [29].

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