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 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.

Keywords  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 AII 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 within 48 hours of MI in sinus rhythm. Recruitment was restricted to patients of Caucasian origin. Exclusion criteria were exist-
sed during the study. 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 Pearson 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.