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Angiotensin-converting enzyme gene deletion polymorphism modulation of onset of symptoms and survival rate of patients with heart failure

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Abstract

Background: Angiotensin-converting enzyme is involved in the pathophysiology of heart failure. We hypothesized that clinical characteristics as well as survival rate in patients with heart failure of different etiologies may be modulated by functional variants DD, ID and II of the angiotensin-converting enzyme gene. *Methods:* We studied 333 patients with heart failure, aged 43.3 ± 10.5 years, 262 (78.7%) men and 71 (21.3%) women. Heart failure was ascribed to idiopathic dilated cardiomyopathy in 125 patients. Heart failure was caused by ischemic heart disease in 63 patients, Chagas' disease in 58, hypertensive heart disease in 41, alcoholic cardiomyopathy in 24, and was due to other etiologies in 22 patients. Statistical analysis was performed with the χ^2 test, Student's *t*-test, analysis of variance, Kaplan–Meier and Cox proportional hazards methods. *Results:* The DD genotype was associated with increased systolic left ventricular diameter ($p=0.031$). Earlier onset of symptoms was observed in patients with alcoholic cardiomyopathy and DD genotype ($p=0.033$, codominant D) and in patients with hypertensive cardiomyopathy and DD genotype ($p=0.048$, codominant D; $p=0.024$, recessive D). Mortality was higher in patients older than 50 years with DD genotype ($p=0.007$, codominant D; $p=0.002$, recessive D). Variables independently associated with higher mortality in patients older than 50 years were age, diabetes mellitus, Chagas' disease etiology and DD genotype. *Conclusions:* These results add evidence for an association of the DD genotype of the angiotensin-converting enzyme gene with earlier onset of symptoms and decreased survival rate of selected patients with heart failure.

Keywords: Angiotensin-converting enzyme; Polymorphism; Heart failure

1. Introduction

The functional variants DD, ID and II of the angiotensin I-converting enzyme (ACE) gene have been shown to be involved in the modulation of plasma ACE levels and activity [1–4]. The DD genotype was associated with higher ACE activity [3], which is related to an increased activity of angiotensin II [5,6], a key element in the pathophysiology of heart failure [7].

Higher frequency of the DD genotype was observed in patients with either ischemic or idiopathic dilated cardiomyopathy [8] and in patients with left ventricular dysfunction due to myocardial infarction [9]. In addition, DD genotype was recently suggested to be associated with increased susceptibility to alcoholic cardiomyopathy [10], with higher mortality in patients with heart failure due to idiopathic cardiomyopathy [11] and with poorer transplant-free survival in patients with systolic dysfunction [12].

Nevertheless, results from other studies have been inconclusive. An increased frequency of the DD genotype has not been observed in patients with dilated cardiomyopathy [13], while the DD genotype has not been associated with the severity or progression of heart failure [14].

Such different results may be ascribed to a number of factors including different genetic backgrounds of the study population, sample size, biased selection of the control group and deviation from the Hardy–Weinberg equilibrium [15].

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This study was performed to evaluate the insertion/deletion (I/D) polymorphism of the angiotensin I-converting enzyme gene in a Brazilian cohort of outpatients with heart failure of different etiologies relative to other clinical variables and survival rate.

2. Methods

2.1. Study population

Three hundred and thirty-three (333) patients with heart failure aged 13 to 68 (mean 43.3 years, standard deviation 10.5) years, 262 (78.7%) men and 71 (21.3%) women, were studied from March, 1995 to July, 1997.

The diagnosis of heart failure was made according to previously published criteria [16]. The classification of the etiologies of heart failure followed previous recommendations [17,18].

2.2. Inclusion criteria

Patients with symptomatic heart failure of different etiologies and left ventricular ejection fraction $<45\%$ on two-dimensional transthoracic Doppler echocardiography, or ejection fraction $<35\%$ by radionuclide ventriculography were eligible for the study. Patients were evaluated for surgical treatment of heart failure, including heart transplantation. Specifically, patients with valvular cardiomyopathy enrolled in the study were those with severe left ventricular dysfunction to the point that they would not be eligible for valve repair or replacement, but rather candidates for heart transplantation.

2.3. Exclusion criteria

Patients with valvular heart disease that would be candidates for conventional surgical treatment such as valve repair or replacement, patients with hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, recent myocardial infarction and unstable angina were excluded. In addition, patients with severe renal or hepatic dysfunction, severe peripheral arterial disease, cerebrovascular disease, active infection, coexisting neoplasm and active peptic ulcer disease were also excluded.

2.4. Clinical characteristics

Heart failure was ascribed to idiopathic dilated cardiomyopathy in 125 (37.6%) patients. Cardiomyopathy was due to ischemic heart disease in 63 (18.9%) patients, Chagas' disease cardiomyopathy in 58 (17.4%), hypertensive cardiomyopathy in 41 (12.3%), alcoholic cardiomyopathy in 24 (7.2%), valvular cardiomyopathy in 11 (3.3%) and peripartum cardiomyopathy in 11 (3.3%) patients.

There was a past medical history of arterial hypertension in 133 (39.9%) patients. One hundred sixty-two (49.2%) patients were smokers. Alcohol consumption was reported by 132 (39.6%) patients. Twenty-seven (8.1%) patients were diabetic, 5 (1.5%) had type I diabetes mellitus.

Baseline drug regimens were as follows: diuretics (mainly furosemide) in 327 (98.2%) patients, digoxin in 298 (89.5%), angiotensin-converting enzyme inhibitors in 318 (95.5%), nitrates in 43 (12.9%), hidralazine in 10 (3%), β-blockers (mainly carvedilol) in 12 (3.6%) and amiodarone in 51 (15.3%).

2.5. Genotype determination

The extraction of the genomic DNA was made from leukocytes separated from whole blood using a standard method [19]. The I/D polymorphism was detected by a polymerase chain reaction (PCR) technique using oligonucleotide primers flanking the respective fragments D and I from the intron 16 of the human angiotensin-converting enzyme gene [4]. Genotyping was undertaken in a blinded manner after the samples had been separated with electrophoresis on a 2% agarose gel and stained with ethidium bromide (1 μg/ml). Because of the preferential amplification of the D allele in heterozygous samples, each sample found to have the DD genotype was subjected to a second, independent PCR amplification with a primer that recognizes an insertion-specific sequence [20]. Misgenotyping using conventional ACE gene I/D polymorphism primer pairs occurred in 5.1% of patients in the present study.

2.6. Variables

The distribution of the DD, ID and II genotypes was analysed in relation to age, gender, etiology of heart failure, associated medical conditions, dimensions of cardiac chambers and ejection fraction estimated through echocardiography [21] and radioisotopic ventriculography [22], and survival rate. End-points regarding survival analysis were last medical evaluation, heart transplantation or other surgical treatment of heart failure, or death. The survival rate was evaluated considering the time elapsed: (a) from birth to the onset of symptoms, (b) from birth to death or surgical treatment of heart failure or last medical evaluation and (c) from the onset of symptoms to death or surgical treatment of heart failure or last medical evaluation. Furthermore, the time elapsed from birth to death were analysed according to age strata (younger than 25 years, between 25 and 50 years and older than 50 years).

2.7. Statistical analysis

The χ^2 test was used to evaluate associations between the I/D polymorphism and discrete variables. The Student's *t*-test was used for the comparison of means of two groups, and ANOVA was used for comparison of more than two

Table 1
Cardiac dimensions on echocardiography relative to I/D polymorphism

Variables*	DD	ID + II	p
Left atrium (mm)	46.9 ± 7.5	46.7 ± 7.8	NS
Aorta (mm)	34.0 ± 4.5	33.2 ± 4.0	NS
Left ventricle			
Interventricular septum thickness (mm)	8.1 ± 1.0	8.3 ± 1.1	NS
Posterior wall thickness (mm)	8.1 ± 1.0	8.3 ± 1.1	NS
End systolic diameter (mm)	65.9 ± 7.5	63.8 ± 8.7	0.031
End diastolic diameter (mm)	76.0 ± 7.9	74.1 ± 8.7	0.056
Ejection fraction (%)	34.5 ± 5.4	35.2 ± 6.3	NS

* Mean + standard deviation.

groups of continuous variables. The Kaplan–Meier method was used for survival analysis; death was considered an event, and surgical treatment of heart failure was considered a censored observation. Comparisons were made with the log-rank test. The Cox regression model was used for assessing the independent variables associated with prognosis; variables were selected through stepwise procedure.

The relation between the I/D polymorphism and the evolution of patients with heart failure was analysed in the light of the pattern of genetic inheritance conferred to the D allele [23]. In this way, assuming a codominant model for the D allele, the three genotypes were analysed separately (DD versus ID versus II), whereas assuming a recessive model of the D allele, patients with the DD genotype were compared with patients with the I allele (DD versus ID+ II). Finally, assuming a dominant model of the D allele, patients with the D allele were analysed in relation to homozygosity for the I allele (DD + ID versus II).

Statistical analyses were performed with SAS software [24]. A p value < 0.05 was considered significant.

2.8. Ethics

The study protocol was approved by the Ethics Committee for Medical Research of the Hospital das Clínicas from São Paulo University School of Medicine. Informed consent was obtained from all participants.

3. Results

3.1. Distribution of the alleles and genotypes

The frequency of the D allele was 0.58 and of I allele was 0.42. Frequencies of DD, ID and II genotypes were in accordance with Hardy–Weinberg equilibrium.

There was no statistically significant difference in the distribution of the genotypes relative to each etiology. Considering the small number of patients in some groups of acquired causes of cardiomyopathy, we analyzed the distribution of genotypes DD, ID, and II in two broad groups: idiopathic versus acquired causes of cardiomyopathy. The difference in the distribution of the three studied genotypes in both broad groups was not statistically significant.

In addition, there was no statistically significant difference in the distribution of the studied genotypes in relation to past medical history of arterial hypertension, diabetes mellitus, smoking or alcohol consumption.

3.2. Cardiac dimensions on echocardiography and ejection fraction

There was a tendency for increased ventricular diameters in patients with the DD genotype (Table 1). Particularly, left

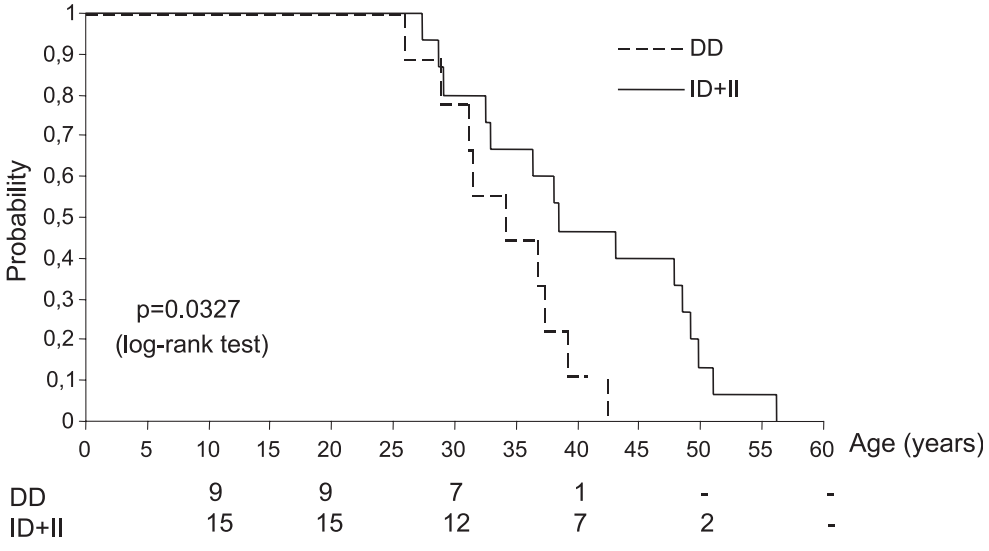

Fig. 1. Onset of symptoms and alcoholic cardiomyopathy relative to I/D polymorphism (recessive D allele model). The time in the abscissa refers to the time elapsed from birth to onset of symptoms. The numbers below the abscissa refer to the number of patients being followed up at the beginning of the subsequent interval.

ventricular systolic diameter on echocardiography was significantly higher in patients with DD genotype, assuming a recessive model of the D allele.

There was no statistically significant difference in the right ventricular ejection fraction on the radioisotopic ventriculography relative to the I/D polymorphism considering the codominant, recessive or dominant models of the D allele. In addition, there was no significant relationship between the genotypes and left ventricular ejection fraction on the radioisotopic ventriculography, considering the three patterns of inheritance.

3.3. Time elapsed up to the onset of symptoms

The time elapsed from birth until the onset of symptoms was shorter in patients with the DD genotype, in comparison to the patients with the ID and II genotypes for patients with alcoholic (Fig. 1) or hypertensive cardiomyopathy (Fig. 2).

3.4. Survival rate

A total of 61 patients died during follow-up: 18 with idiopathic cardiomyopathy, 18 with Chagas' heart disease, 16 with ischemic cardiomyopathy, 3 with hypertensive cardiomyopathy, 3 with alcoholic cardiomyopathy and 3 with valvular cardiomyopathy.

The comparison of the probability of survival relative to each etiology of heart failure did not reveal a statistically significant difference. We further tested the probability of survival of patients with idiopathic relative to acquired causes of cardiomyopathy; the difference in the survival rate was not statistically significant either.

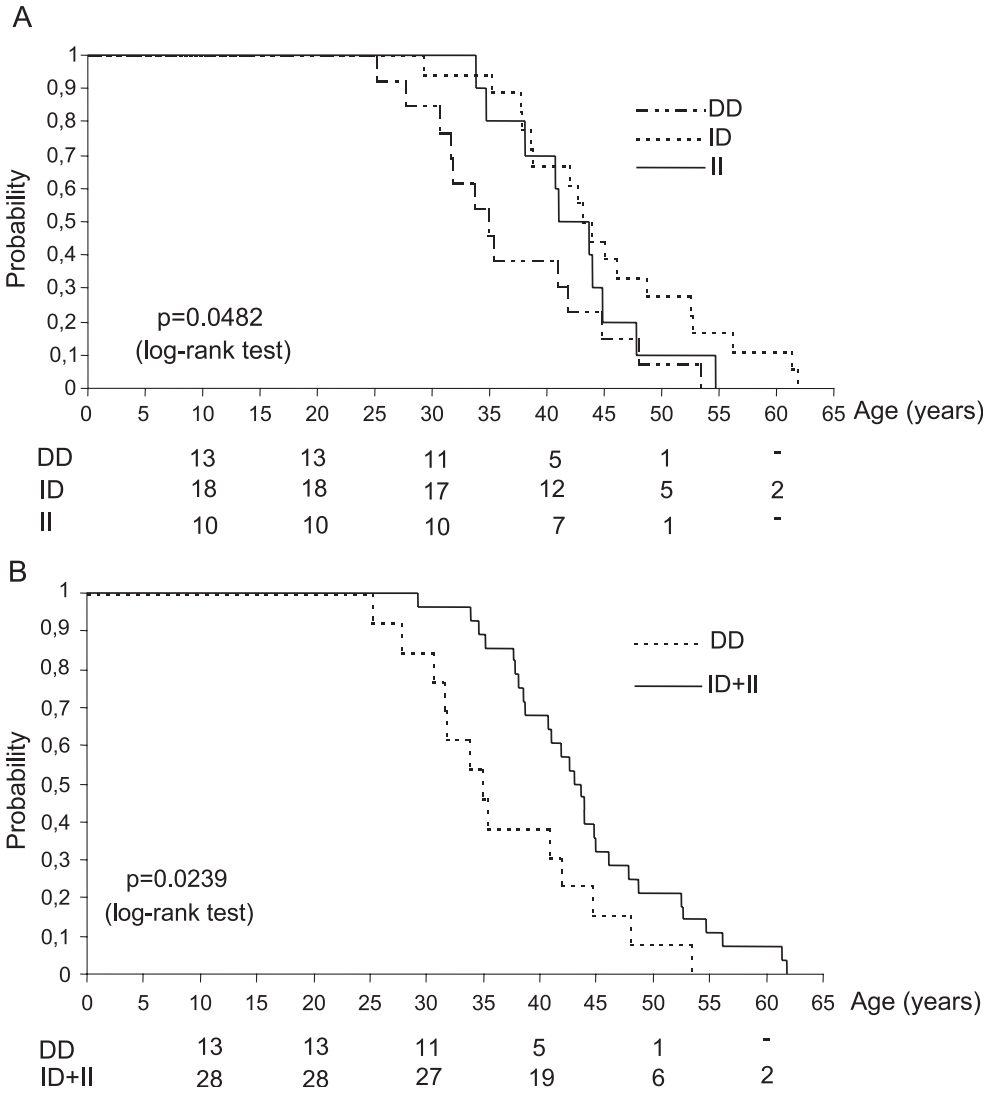

Fig. 2. (A) Onset of symptoms and hypertensive cardiomyopathy relative to I/D polymorphism (codominant D allele model). (B) Onset of symptoms and hypertensive cardiomyopathy relative to I/D polymorphism (recessive D allele model). The time in the abscissa refers to the time elapsed from birth to onset of symptoms. The numbers below the abscissa refer to the number of patients being followed up at the beginning of the subsequent interval.

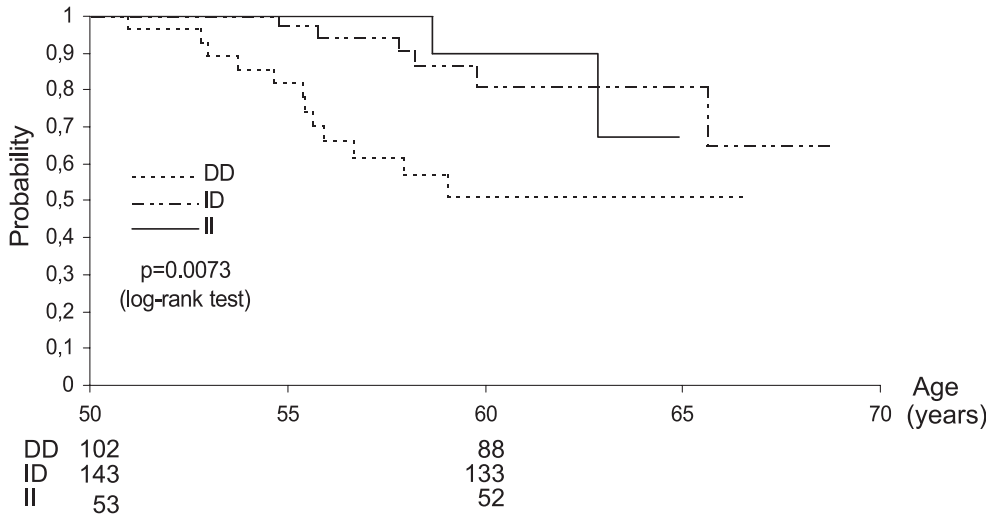

Fig. 3. Probability of survival of patients older than 50 years relative to I/D polymorphism (codominant D allele model). The numbers below the abscissa refer to the number of patients being followed up at the beginning of the subsequent interval.

In addition, the difference in the probability of survival relative to genotypes DD, ID and II in the whole study sample was not statistically significant. Neither was the difference in the probability of survival statistically significant when the three studied genotypes were compared within the group of patients with idiopathic dilated cardiomyopathy, nor in the group of patients with acquired causes of cardiomyopathy.

Out of the 333 patients, 36 (10.8%) were submitted to surgical treatment of heart failure during the follow-up: 22 (61%) were submitted to heart transplantation, 12 (33.3%) to partial left ventriculectomy, 1 (2.8%) to dynamic cardiomyoplasty and 1 (2.8%) to aneurismectomy associated with left ventricular reconstruction. There was no statistically significant difference in the distribution of the genotypes and the time elapsed from birth to surgery.

The analysis of the survival rate according to age strata (younger than 25 years, between 25 and 50 years and older than 50 years) showed higher mortality in patients with the DD genotype older than 50 years, assuming either a codominant ($p=0.007$) or a recessive ($p=0.002$) model of the D allele (Fig. 3).

Table 2
Variables independently related to survival rate in patients older than 50 years

Genotype	Independent variables	Relative risk (CI 95%)	p
DD vs. ID + II	age	0.613 (0.483–0.778)	0.0001
	diabetes mellitus	5.789 (1.800–18.623)	0.0032
	Chagas' disease	5.590 (1.698–18.399)	0.0046
	DD genotype	4.501 (1.656–12.235)	0.0032
DD vs. ID vs. II	age	0.627 (0.495–0.794)	0.0001
	diabetes mellitus	5.311 (1.672–16.876)	0.0046
	Chagas' disease	5.780 (1.768–18.897)	0.0037
	DD genotype	2.904 (1.227–6.873)	0.0153

CI: confidence interval.

Multivariate analysis revealed that the variables independently associated with higher mortality in patients older than 50 years were age, diabetes mellitus, Chagas' disease and the DD genotype (Table 2).

4. Discussion

The renin–angiotensin system has pleiotropic roles in cardiovascular homeostasis. Its actions over the heart, either systemically, or through paracrine regulation, influence architecture, growth and function. In this scenario, the ACE gene can be considered a candidate of involvement in development and progression of heart disease. [25] Our findings add information to this paradigm through the report of a particular subset of patients: severe heart failure of different etiologies.

The finding of increased left ventricular dimensions in patients with DD genotype is in accordance with previous reports [13,26], and may be associated with a presumably greater circulating and tissue concentration of angiotensin II associated with DD genotype [27], influencing ventricular remodeling.

In relation to alcoholic cardiomyopathy, the findings of an early onset of symptoms in patients homozygous for the D allele may be related to an increased vulnerability to alcoholic cardiomyopathy associated with the DD genotype, as recently demonstrated [10].

Regarding hypertensive cardiomyopathy, patients with the DD genotype showed a shorter onset of symptoms, when a recessive or codominant model of the D allele was tested. This finding is consistent with the association between the DD genotype and increased left ventricular mass and remodeling observed in hypertensive patients[28]. Hypertrophy may be associated with decreasing ventricular compliance and diastolic dysfunction, which may lead to an

earlier onset of symptoms of heart failure [29]. There was no significant association between the deletion polymorphism and valvular cardiomyopathy or peripartum cardiomyopathy. However, the small number of cases of patients with valvular cardiomyopathy ($n = 11$) or peripartum cardiomyopathy ($n = 11$) may have contributed to this finding.

Most interestingly, nevertheless, is the statistically significant association between the DD genotype and increased mortality in patients older than 50 years. Our data is in accordance with previous findings of higher mortality associated with DD genotype, both in patients with mean age 58 years and idiopathic dilated cardiomyopathy [11] and in patients with systolic dysfunction not treated with β-blockers [12].

Our findings were observed in the context of widespread therapy of patients with heart failure with ACE inhibitors. In fact, baseline drug therapy in this cohort showed that 95.5% of our patients were on ACE inhibitors therapy. This fact may be decreasing a possible association between the I/D polymorphism and mortality in patients younger than 50 years. It could be hypothesized that if the plasma and tissue levels of ACE are higher in the individuals with the DD genotype, the actions of ACE inhibitors could be more pronounced in these individuals. Corroborating this observation, it was demonstrated that hypertensive individuals with the DD genotype, treated with enalapril, showed increased regression of the left ventricular hypertrophy, as well as a better left venticular diastolic function, compared to hypertensive individuals with the ID and II genotypes, equally treated [30]. On the other hand, increased age per se carries an increased mortality risk. This situation of overall reduced reserve capacity may increase the influence of the DD genotype over an already fragile myocardium.

In addition to DD genotype, diabetes mellitus and Chagas' heart disease were also associated with higher mortality. In relation to diabetes, our finding is in accordance with a previously published study [31]. Further, Chagas' heart disease was also demonstrated to be an independent risk factor for mortality in a cohort of patients with heart failure of different etiologies [32].

4.1. Study limitations

Heterogeneity of the patients in this cohort may be a potential limitation. Such an heterogeneity is the cost of including patients with heart failure of different etiologies. Another potential limitation was the fact that we have not determined ACE plasmatic levels in our study sample. However, more than 90% of the patients were on therapy with ACE inhibitors limiting interpretation of plasma ACE activity levels. In addition, tissue specific renin–angiotensin systems may be operant despite plasma ACE activity [25]. Other potential limitation refers to the small number of patients that were on β-blockers therapy at the beginning of the study that hinders further analysis of the interaction of this therapy with genetic background and survival rate as recently demonstrated [12].

4.2. Clinical implications

Taken together, this study provides data that a functional variant of the ACE gene, namely the D allele, is associated with earlier onset of symptoms in patients with hear failure due to alcoholic or hypertensive heart disease and decreased survival rate.

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