

Chronic converting enzyme inhibition normalizes QT interval in aging rats

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Abstract

The aim of the present study was to investigate the effects of converting enzyme inhibition by captopril on ECG parameters in aged rats. Four-month-old male rats received captopril dissolved in tap water (0.5 mg/l) or tap water for 2 or 20 months. At the end of treatment, under anesthesia, RR and PR interval, P wave and QRS duration, QT and corrected QT interval were measured in all animals. On the following day, chronic ECG (lead II) recordings were performed to quantify supraventricular (SVPB) or ventricular premature beats (VPB). After sacrifice, the hearts were removed and weighed. RR interval was similar in young and untreated aged rats, but significantly larger in aged rats treated with captopril. P wave and QRS length did not differ among groups. PR interval was significantly larger in old than in young rats and was not affected by captopril. Corrected QT interval was larger in aged than in young rats (117 ± 4 vs 64 ± 6 ms, $P < 0.05$) and was reduced by captopril (71 ± 6 ms, $P < 0.05$). VPB were absent in young rats and highly frequent in untreated old animals ($8.4 \pm 3.0/30$ min). Captopril significantly reduced VPB in old rats ($0.3 \pm 0.1/30$ min, $P < 0.05$). The cardiac hypertrophy found in untreated aged rats was prevented by captopril (3.44 ± 0.14 vs 3.07 ± 0.10 mg/g, $P < 0.05$). The beneficial effects of angiotensin converting enzyme inhibition on the rat heart during the aging process are remarkable.

Key words

- Aging
- Electrocardiogram
- Captopril
- Rats

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Presented at the IV International
Symposium on Vasoactive Peptides,
Belo Horizonte, MG, Brazil,
October 19-21, 2001.

Research supported by PRONEX-
CNPq, FAPESP and FUNEPU.
E. Ferreira Neto was supported
by a scientific training grant from
PIBIC program of CNPq.

Received November 22, 2001
Accepted May 3, 2002

Introduction

Several electrocardiographic (ECG) indices have been proposed to identify patients at risk of sudden death, including the QT interval length and/or dispersion (1-3). Clinical trials have demonstrated that QT interval is particularly altered in situations such as cardiac hypertrophy (4) or myocardial ischemia (5), but is normalized by appropriate therapy (6). The myocardial alterations that occur with aging (7,8) alter ECG parameters

such as QT interval (9,10).

Aging is associated with electrical and morphological changes of the myocardium (7,8), increasing significantly the incidence of life-threatening cardiac arrhythmias and sudden death in aged subjects (9-11).

A number of studies have demonstrated a beneficial action of angiotensin converting enzyme (ACE) inhibitors in the treatment of several cardiovascular diseases (12,13). These drugs act by inhibiting the conversion of angiotensin I to angiotensin II, blocking

the renin-angiotensin system (RAS). In addition, other vasoactive peptides can be also modified by ACE inhibitors, especially bradykinin, which is potentiated by ACE blockage (12,13). These effects elicit a decrease in arterial pressure in several experimental models of hypertension and clinical forms of human hypertension as well (12,13). In addition, these drugs improve cardiac performance in patients with congestive heart failure, reducing cardiovascular risk and mortality (12,13).

Studies performed on experimental models, particularly rats, have evaluated the effects of ACE inhibitors on aging. Concerning the cardiovascular system, these studies have demonstrated that ACE inhibitors reduce renal intravascular resistance (14) and thickness of the media and intima layers of large arteries (15). Moreover, ACE inhibitors improve the endothelial function of resistance vessels (16), and partially restore the impaired autoregulatory mechanism of cerebral blood flow due to aging (17).

Nevertheless, to our knowledge, the effect of ACE inhibitors on the alterations of ECG found in aging has not been previously examined in rats. Therefore, the aim of the present study was to evaluate ECG alterations in aged rats, as well as the effect of the ACE inhibitor captopril in this experimental model.

Material and Methods

Four-month-old male Wistar rats were divided into four groups. One group was treated with captopril dissolved in tap water (0.5 mg/ml) for 2 months (N = 10), a second group was treated with captopril dissolved in tap water (0.5 mg/ml) for 20 months (N = 7), a third age-matched time control group (N = 10) drank only tap water for 2 months, and a fourth age-matched time control group (N = 5) drank only tap water for 20 months. The rats drank about 20-30 ml/day of captopril solution which provided approximately

30 mg/kg of captopril a day. The efficacy of this dosage of captopril has been demonstrated in a number of pharmacokinetic and pharmacodynamic studies in rats (18). All surgical procedures and protocols were in accordance with the Guidelines for Ethical Care of Experimental Animals and were approved by the Institutional Animal Care and Use Committee.

At the end of a 2- or 20-month period of treatment, the animals were submitted to acute ECG studies under tribromoethanol anesthesia (250 mg/kg, *ip*). Electrodes were placed under the skin for recording the conventional bipolar limb leads (I, II, III), the unipolar limb leads (aVR, aVL and aVF), and the unipolar precordial (chest) leads (VA is immediately to the right of the sternum in the 4th intercostal space, VB is just to the left of the sternum in the 4th intercostal space, and VC is in the 5th intercostal space at the midaxillary line). In order to avoid errors in the position of the leads, the electrodes were always placed by the same person. The ECG was recorded using a three-channel digital ECG recorder (ER-65, Medikor, Budapest, Hungary) with a paper speed of 50 mm/s and sensitivity of 0.5 mV/cm. Each lead was recorded for 20 s.

At the end of the acute ECG recordings, the animals were implanted with a pair of stainless-steel electrodes positioned inside the subcutaneous tissue for chronic recording of conventional bipolar limb lead II without the effect of anesthesia. The animals were also cannulated with polyethylene tubing placed into the femoral artery and vein for direct measurement of arterial pressure and drug administration, respectively. After the surgical procedures the animals were left to recover in individual cages for at least 24 h.

On the following day, without the effect of anesthesia, the electrodes were connected to a bioelectric amplifier (model 8811A, Hewlett Packard, Waltham, MA, USA), and the ECG was continuously sampled (1000

Hz) with a personal computer (IBM/PC) equipped with a 12-bit analog to digital interface (CAD12/36 Lynx Tecnologia Eletrônica, São Paulo, SP, Brazil) for a period of 30 min. At the end of the ECG recording, the arterial catheter was connected to a pressure transducer (model P23Gb Statham, Hato Rey, Puerto Rico) attached to a pressure amplifier (model 8805D, Hewlett Packard) which fed the arterial pressure signal to a personal computer. The efficacy of ACE blockade was evaluated by the attenuation of the hypertensive response elicited by angiotensin I (100 ng/kg) given through the femoral vein. Only rats showing an attenuation of at least 85% of the hypertensive response elicited by angiotensin I were considered to have the RAS blockade. After the test of ACE efficacy the rats were killed with excess anesthesia and had their hearts removed and weighed on a precision scale (Micronal B160, São Paulo, SP, Brazil).

The ECG tracings were analyzed visually always by the same person, who was not aware of the protocol. The following ECG parameters were examined: 1) RR interval, defined as the interval between the apex of adjacent R waves; 2) P wave duration; 3) PR interval, defined as the interval between the apex of the P wave and the Q wave (beginning of the QRS complex); 4) QRS duration; 5) QT interval (defined as the interval between Q wave and T wave apex), and 6) corrected QT interval [QTc, defined as the QT interval corrected for the heart rate by means of Bazett's equation: corrected QTc = QT (in s)/RR (in s)^{1/2}]. In small rodents, in contrast to humans, the T wave is not well characterized and appears as a shoulder of the QRS complex (Figure 1). Accordingly, in order to measure the QT interval we used the apex of the T wave which can be determined with high accuracy. ECG recordings were carried out for 20 s for each lead, and the ECG parameters described above were determined from each lead and averaged.

The 30-min ECG recordings were care-

fully examined on the screen of the computer to identify premature heart beats. The total number of supraventricular (SVPB) and ventricular premature beats (VPB) were counted over the 30-min period. The classic definition of arrhythmias in humans, adapted to the high heart rate of the rat, has been described elsewhere (19,20) and was used to define the severity of ventricular arrhythmias. Briefly: class 0 - no VPB, class 1 - infrequent isolated unifocal VPB (<30/h), class 2 - frequent unifocal VPB (>30/h), class 3 - multifocal ectopic beats, class 4 - couplets of VPB, class 5 - triplets of VPB and non-sustained ventricular tachycardia (<6 ectopic beats), and class 6 - ventricular tachycardia.

Data are reported as means ± SEM. For ECG parameters and arterial pressure data, two-way ANOVA followed by Tukey's multiple comparison test was performed to evaluate the effects of treatment (captopril vs tap water) and age (young vs aged). The arrhythmia data, i.e., incidence of premature beats, were analyzed by the Kruskal-Wallis

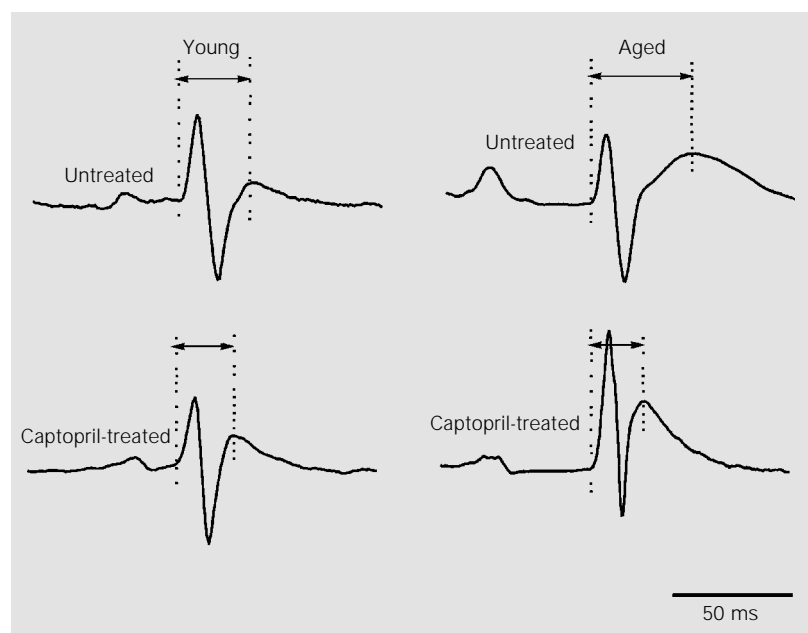


Figure 1. ECG tracings of representative rats of each experimental group. The arrows indicate the length of the QT interval. Notice the enlargement of the QT interval in untreated aged rats and the reduction of the QT interval in captopril treated aged rats.

ANOVA test. The differences were considered significant when $P < 0.05$.

Results

Untreated aged rats were significantly heavier than untreated young rats (512 ± 22 vs 460 ± 15 g, $P < 0.05$). In contrast, young

rats (treated or not) and aged rats treated with captopril presented similar body weights (434 ± 26 , 460 ± 24 and 460 ± 15 g, respectively).

The basal mean arterial pressure and heart rate of conscious rats are shown in Table 1. Arterial pressure and heart rate were significantly lower in old rats treated with captopril compared to other groups.

The pressor response to angiotensin I was 35 ± 3 mmHg in young untreated rats and 4 ± 2 mmHg in young rats treated with captopril ($P < 0.001$). Comparison of these values indicates a blockade of ACE by captopril of approximately 89%. In aged rats, the pressor response to angiotensin I was 68 ± 18 mmHg in untreated rats, and 1 ± 2 mmHg in rats treated with captopril ($P < 0.0001$), indicating an ACE blockade of approximately 98%.

The ECG parameters are presented in Table 2. The RR interval was similar in young (treated or not) and old untreated rats, but significantly larger in aged subjects treated with captopril. P wave length did not differ among groups. The PR interval was significantly larger in old than in young rats, but was not affected by captopril in either old or young rats. QRS length did not differ among groups. The QT and QTc intervals were significantly larger in old than in young rats, but were significantly reduced by captopril in old, but not in young rats (Table 2).

The incidence of SVPB was low in young rats, but high in old rats (Table 3). Captopril did not change the incidence of SVPB. VPB were absent in young rats (treated or not), but highly frequent in untreated old subjects (Table 3). Nevertheless, captopril significantly reduced VPB in old rats. Ventricular arrhythmias was 30 times less frequent than in untreated old rats (Table 3). According to the classification of ventricular arrhythmia adopted in the present study (20), all young rats belonged to class 0, whereas 80% of the untreated old rats belonged to class 1, 2 or 3. As a result of treatment with captopril, the

Table 1. Baseline values (mean \pm SEM) of mean arterial pressure (MAP) and heart rate (HR) in conscious male young and aged rats treated (Cap) or not (control, Con) with captopril.

| | Young | | Aged | |
|------------|--------------|--------------|--------------|----------------|
| | Con (N = 10) | Cap (N = 10) | Con (N = 5) | Cap (N = 7) |
| MAP (mmHg) | 89 ± 2 | 93 ± 4 | 97 ± 2 | $85 \pm 2^*$ |
| HR (bpm) | 381 ± 11 | 374 ± 15 | 405 ± 11 | $311 \pm 25^*$ |

* $P < 0.05$ vs untreated aged rats (Tukey's multiple comparison test).

Table 2. Mean values (\pm SEM) of ECG parameters measured in anesthetized young and aged rats treated (Cap) or not (control, Con) with captopril.

| | Young | | Aged | |
|--------------------|--------------|--------------|---------------|-------------------|
| | Con (N = 10) | Cap (N = 10) | Con (N = 5) | Cap (N = 7) |
| RR interval (ms) | 166 ± 8 | 172 ± 5 | 152 ± 6 | $218 \pm 22^{*+}$ |
| P wave length (ms) | 23 ± 2 | 23 ± 2 | 19 ± 1 | 18 ± 2 |
| PR interval (ms) | 50 ± 3 | 43 ± 4 | $64 \pm 2^+$ | $63 \pm 3^+$ |
| QRS length (ms) | 22 ± 1 | 21 ± 1 | 18 ± 1 | 16 ± 2 |
| QT interval (ms) | 26 ± 3 | 24 ± 2 | $46 \pm 2^+$ | $33 \pm 4^*$ |
| Corrected QT (ms) | 64 ± 6 | 58 ± 6 | $117 \pm 4^+$ | $71 \pm 6^*$ |

* $P < 0.05$ vs untreated aged rats (Tukey's multiple comparison test).

+ $P < 0.05$ vs young rats (Tukey's multiple comparison test).

Table 3. Number (mean \pm SEM) of supraventricular (SVPB) and ventricular premature beats (VPB) in conscious male young and aged rats treated (Cap) or not (control, Con) with captopril.

| | Young | | Aged | |
|-------|---------------|---------------|------------------|-----------------|
| | Con (N = 10) | Cap (N = 10) | Con (N = 5) | Cap (N = 7) |
| SVPB | 0.5 ± 0.1 | 0.3 ± 0.1 | $5.2 \pm 1.0^+$ | $3.0 \pm 0.5^+$ |
| VPB | 0.0 ± 0.0 | 0.0 ± 0.0 | $8.4 \pm 3.0^+$ | $0.3 \pm 0.1^*$ |
| Total | 0.5 ± 0.1 | 0.3 ± 0.1 | $13.6 \pm 3.3^+$ | $3.3 \pm 0.5^*$ |

* $P < 0.05$ vs untreated aged rats (Kruskal-Wallis ANOVA test).

+ $P < 0.05$ vs young rats (Kruskal-Wallis ANOVA test).

percentage of old rats in class 1 was 29%. No old rat treated with captopril was found in class 2 or 3, and no rat was found in classes 4, 5 or 6.

Relative heart weight (mg/g of body weight) was found to be similar in young rats treated (2.62 ± 0.08 mg/g) or not (2.70 ± 0.05 mg/g) with captopril. Aged rats without any treatment presented an increase in relative heart weight (3.44 ± 0.14 mg/g, $P < 0.05$) as compared to young rats, but captopril brought the relative heart weight of aged rats (3.07 ± 0.10 mg/g, $P < 0.05$) within the range of young rats.

Discussion

The remarkable attenuation of the pressor response produced by angiotensin I demonstrated the efficacy of ACE blockade by captopril.

Heart rate did not change with aging, in agreement with previous reports in the literature (21-23). Berg (24) also found no heart rate changes in rats aged 219 days (~7 months) or 557 days (~18 months), whereas they detected bradycardia in older rats aged 851 days (~28 months) and 951 days (~31 months). In the present study, chronic (20 months) captopril treatment of aged rats reduced the basal heart rate compared to age-matched control rats.

The bradycardia observed in aged rats treated with captopril may be associated with an increase in the vagal reflex controlling the heart rate caused by ACE inhibition (25), even though further studies are required to better understand this mechanism.

Concerning the other ECG parameters, the results of the present study have shown some differences in cardiac electrical activity with major alterations of PR and QT interval with aging. The PR interval is an index that correlates well with atrioventricular conduction, and an increase in this parameter indicates an impairment in atrioventricular conduction. The present finding that

aging decreases electrical conduction in the atrioventricular node is in accordance with previous findings in experimental animals (24) and humans (26).

The QT interval, i.e., the time elapsed for ventricular repolarization (ventricular refractory period), was also increased in aged rats, corroborating ECG (24) and electrophysiological data (27) obtained for aged rats. A prolonged QT interval has been associated with cardiac arrhythmia and sudden death in humans (1,2,5). At the cellular level, ventricular repolarization is prolonged in a number of cardiac disturbances such as myocardial hypertrophy, ischemia or congestive heart failure (1,2,5). Changes of the QT interval have also been described in experimental models of hypertension (28). The other parameters examined in the present study were found to be unchanged by aging.

SVPB and VPB were the most frequent cardiac arrhythmias found in aged rats in the present study. Despite the short period of ECG monitoring (30 min), this finding substantiates previous literature reports describing a higher incidence of this kind of arrhythmia, linked to aging, in rats submitted to 24-h Holter monitoring (20).

The impaired atrioventricular conduction (larger PR interval), the prolonged ventricular repolarization (larger QT interval), and the higher incidence of cardiac arrhythmias could be produced by degenerative lesions due to myocardial fibrosis and/or ischemia, as well as alterations in gene expression associated with the aging process (7,8,29).

Treatment of rats with the ACE inhibitor, captopril, prevented the increase in the QT interval, but did not blunt the increase in the PR interval due to aging. Thollon et al. (30) have shown that electrophysiological changes induced by cardiac hypertrophy in infarcted rat hearts were considerably attenuated by ACE inhibitors. Gonzalez-Juanatey et al. (31) also reported a beneficial effect of ACE inhibitors on ECG alterations in humans. There is evidence that ACE inhibitors have a

direct anti-trophic effect on cardiac myocyte proliferation, preventing myocardial fibrosis by means of the attenuation of the effect of angiotensin II, as well as inhibition of bradykinin degradation (12,13). The development of apoptosis in heart tissue is also associated with the hyperactivity of local ACE (13). ACE inhibitors also improve the coronary blood flow (12,13) which is impaired with aging (7,8).

The prolonged PR interval observed in aged rats is probably related to the same structural and functional changes due to aging (7,8). A possible explanation for the failure of captopril to normalize the PR interval is that ACE inhibition increases vagal control of the heart in aged rats (25), and it has been well documented that augmented vagal nerve activity increases the delay of atrioventricular conduction under physiological conditions (32). Therefore, the larger PR interval found in aged rats treated with captopril could be associated with a shift in the sympathovagal balance toward an increased parasympathetic activity. However, further studies are necessary to clarify this issue.

Chronic treatment with captopril almost eliminated the ventricular arrhythmias but did not affect SVPB in aged rats. This effect of ACE inhibitors seems not to be restricted to aging. In fact, a significant reduction in the incidence of ectopic beats has been observed in experimental (33,34) and clinical (35) arterial hypertension, acute myocardial infarction (36) and congestive heart failure (37) after chronic ACE inhibition. There are a number of hypotheses to explain this anti-arrhythmic effect. For instance, structural

changes in fibrosis and/or cardiac hypertrophy and remodeling (12,13), functional changes in coronary blood flow (12,13), autonomic imbalance (25), ion channel dysfunction (20) and intracellular gene expression (38).

In the present study a cardiac hypertrophy evaluated by relative cardiac weight was reported in untreated aged rats. Cardiac hypertrophy in aged male rats is a common feature reported by many investigators (7,8, 28,38). The heart undergoes myocardial cell enlargement associated with myocardial fibrosis (7,8). It is well accepted that this increase in heart weight is caused by the reduced diastolic stiffness of the left ventricle, and by changes in the properties of large arteries during the aging process (7,8,28). At the cellular level, excitation-contraction coupling is prolonged by aging (7,8,28).

Captopril was able to prevent cardiac hypertrophy in aged rats. This effect could be ascribed to the hemodynamic effects of captopril, which reduced the mean arterial pressure of aged rats. However, a direct effect of captopril inhibiting the trophic effect of angiotensin II on myocardial cells or fibrosis should be considered as well.

Rat aging is characterized by the development of ECG alterations associated with cardiac hypertrophy, typical of myocardial disorders. Chronic treatment with the ACE inhibitor, captopril, prevents some of these ECG alterations, as well as cardiac hypertrophy in rats. Therefore, ACE inhibitors have a remarkable beneficial effect on the heart during the aging process in rats.

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