Angiotensin II provokes cesium-induced ventricular tachyarrhythmias

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Abstract

Objective: The purpose of this study was to investigate whether angiotensin II provokes ventricular tachyarrhythmias and to clarify its mechanism using the cesium-induced arrhythmia model, which has been widely used as an afterdepolarization and triggered activity model.

Methods: Eighteen adult mongrel dogs of either sex weighing 9.6–23.0 kg were studied. The dogs were randomly divided into three groups. In the control group (n=6), the subjects received intravenous saline solution at a 0.45 ml/kg/h, and intravenous bolus injections of cesium (0.25, 0.5, 1.0 mmol/kg) were given at 20-min intervals. In the captopril-treated group (n=6), captopril was administered intravenously at 15 μg/kg/min, and cesium was injected as above. After the infusion of only captopril, in the captopril-treated group, angiotensin II was simultaneously infused at a dose of 0.1 ng/kg/min, and cesium was injected as above. When the dog survived, the dose of angiotensin II was increased to 1.0 ng/kg/min, and the same procedure was repeated. The remaining six dogs were simultaneously infused with captopril (15 μg/kg/min), angiotensin II (1.0 ng/kg/min), and U-73122 (10 μg/kg/min), a selective phospholipase C blocker, and injected with cesium (1.0 mmol/kg). Forty minutes after termination of U-73122 infusion, the dogs were injected with the same dose of cesium. Results: Sustained ventricular tachycardia or ventricular fibrillation was induced by cesium in all of the dogs in the control group. In the captopril-treated group, none of the dogs showed these arrhythmias when only captopril was infused. The treatment of captopril significantly reduced lethal arrhythmias (P<0.01 vs. control group). During the simultaneous infusion of captopril and angiotensin II (0.1 ng/kg/min), cesium produced sustained ventricular tachycardia in all six dogs and the arrhythmia developed into ventricular fibrillation in three dogs. By increasing the dose of angiotensin II (1.0 ng/kg/min), the surviving three dogs died following induced ventricular fibrillation. The additional infusion of angiotensin II (0.1 and 1.0 ng/kg/min) significantly increased fatal arrhythmias (P<0.01 vs. only captopril- infused period, respectively). None of the dogs in the third group exhibited ventricular tachycardia during the infusion of U-73122, and ventricular fibrillations were recorded in all six dogs in the absence of U-73122. The treatment of U-73122 significantly reduced lethal arrhythmias. (P<0.01 vs. control period). Conclusions: These results suggest that angiotensin II provokes cesium-induced ventricular tachyarrhythmias by increasing calcium release from sarcoplasmic reticulum in myocytes via activation of a phosphatidylinositol response. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: ACE inhibitors; Angiotensin; Impulse formation; Ventricular arrhythmias

1. Introduction

Severe congestive heart failure entails a heavy burden of symptoms and carries a grave prognosis. Patients who suffer from heart failure often show increased QT dispersion or a prolonged QT interval due to reduced potassium channel density [1], and subsequently show ventricular tachyarrhythmias. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, would be expected to offer all of the advantages of conventional vasodilators in heart failure or myocardial infarction. Several open studies have indicated that treatment with captopril is beneficial [2–6]. This agent has also been reported to have an anti-arrhythmic effect [7,8]. We previously demonstrated that losartan, an angiotensin II antagonist, had a beneficial effect on reperfusion arrhythmia [9]. It is supposed that a non-reentrant mechanism such as triggered activity due to afterdepolarizations is involved in the genesis of reperfusion arrhythmia [10]. Recently, the ELITE study [11] reported that losartan reduced sudden death in elderly heart failure patients. Brooksby et al. [12] explained that the mechanism

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of this protective effect might be related to a reduced QT dispersion, which is an important arrhythmogenic factor.

Angiotensin II seems to initiate ventricular arrhythmias by increasing intracellular calcium, however the underlying mechanism is unclear. To test the hypothesis that angiotensin II provokes ventricular tachyarrhythmias due to calcium overload, we investigated the effects of angiotensin II on ventricular arrhythmias using the cesium-induced arrhythmia model, which has been widely used as a model of afterdepolarization and triggered activity [13,14].

2. Methods

This investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Experimental preparation

Eighteen adult mongrel dogs of either sex weighing 9.6–23.0 kg were used. The animals were anesthetized with pentobarbital sodium (25 mg/kg). After endotracheal intubation, the dogs were ventilated with room air, oxygen, and halothan to maintain anesthesia by means of a Harvard respirator. The tidal volume and respiratory rate were adjusted to maintain the blood gases and pH within the physiologic range. Quadrupolar 6-Fr catheter electrodes with an interelectrode distance of 1 cm were advanced into the right atrial appendage through the right internal jugular vein. Stimulation of the right atrial appendage was performed with a distal pair of electrodes on the same catheter. A cardiac stimulator (Fukuda Denshi BC-02A) was used to deliver square-wave impulses of twice the diastolic threshold for atrial pacing. Bipolar recordings were obtained from the right atrial appendage with a proximal pair of electrodes. Another bipolar catheter electrode with an interelectrode distance of 5 mm was introduced through the left jugular vein and positioned within the right ventricular endocardium to record the monophasic action potential (MAP). Catheters were placed in the right femoral artery to monitor arterial blood pressure and in the right femoral vein to infuse drugs and normal saline (0.9%). The surface ECG of lead II, MAPs, and arterial blood pressure were recorded on a strip chart recorder (San Ei 8M14) at paper speeds of 25–100 mm/s. The operating room was maintained at 20–22°C throughout the experimental procedure.

2.2. Recording of MAPs

Action potentials were recorded by the contact electrode technique [15]. MAPs were recorded from the right ventricular endocardium with a bipolar contact catheter with a silver–silver chloride distal electrode and a reference lead 5-mm away. The surface ECG of lead II and MAPs were recorded simultaneously on a strip-chart recorder. Signals of MAPs were amplified and filtered at a frequency of 0.04–500 Hz. Baseline recordings were obtained 10 min after placement of all electrodes and only when the MAP recording appeared to be stable and over 10 mV with uniform morphology. The MAPD90 was measured as the interval between the beginning of depolarization and 90% repolarization of MAP. The MAPs were recorded before and after the injection of cesium in each state. We measured MAPD90 1 min after the injection of cesium when heart rate is controlled by atrial pacing (cycle length: CL = 500 ms). If ventricular tachyarrhythmias occurred at this point, the data were excluded.

2.3. Study protocol

The experimental protocol is shown in Fig. 1. The dogs were randomly divided into three groups of six dogs each. In the control group, dogs received intravenous saline solution at 0.45 ml/kg/h. After baseline recordings were obtained, the dogs received an initial intravenous injection of cesium (0.25 mmol/kg, dissolved in normal saline) over 15 s. Two additional injections were given at 20-min intervals. The doses of the second and third injections of cesium were 0.5 and 1.0 mmol/kg, respectively (Fig. 1A). In the captopril-treated group, captopril was administered intravenously at 15 µg/kg/min [16] 40 min before the first cesium injection and continuously throughout the entire study to block endogenous angiotensin II formation. Three injections of cesium were administered as in the control group. Following the infusion of only captopril, angiotensin II was infused simultaneously at a dose of 0.1 mg/kg/min for 40 min, and cesium injections were performed as above. When the dog survived after the injection of maximal dose (1.0 mmol/kg) of cesium, the dose of angiotensin II was increased to 1.0 mg/kg/min, and the same procedure was repeated (Fig. 1B).

In the protocol shown in Fig. 1C, the dogs were simultaneously infused with captopril (15 µg/kg/min), angiotensin II (1.0 ng/kg/min), and U-73122 (10 µg/kg/min), a selective phospholipase C blocker, and then received an intravenous injection of cesium (1.0 mmol/kg). Forty minutes after the termination of U-73122 infusion, the dogs were injected with the same dose of cesium.

The following definitions were used for ventricular tachyarrhythmias induced by cesium injections: ventricular tachycardia (VT), three or more consecutive premature ventricular beats; non-sustained VT (NSVT), VT terminating spontaneously within 30 s; sustained VT (SVT), VT persisting for >30 s; and ventricular fibrillation (VF), rapid and irregular ventricular activity (rate >300 beats/
min) and ineffective mechanical performance. We defined SVT and VF as fatal arrhythmias.

2.4. Statistical analysis

Data are expressed as the mean±S.D. unless specified otherwise. Hemodynamics, ECG variables and MAPD data were analyzed using a paired t-test and one-factor ANOVA (Table 1). The prolongation ratios of QT interval and MAPD90 were analyzed using unpaired t-test. The effects of treatments on ventricular tachyarrhythmias were estimated using Fisher’s exact test (Figs. 4–6). A P value of <0.05 was considered significant.

3. Results

3.1. Effects of captopril on hemodynamics, ECG variables and MAPD

Before the first cesium injection, none of the animals showed ventricular arrhythmia on ECG, and all MAPs showed smooth repolarization. The effects of saline and captopril on hemodynamics, ECG variables and MAPD are summarized in Table 1. The six dogs in the control group were infused with normal saline throughout the study. The sinus cycle length, systolic and diastolic arterial blood pressure, ECG variables including PQ, QRS and QT intervals and MAPD90 remained essentially unchanged by
Table 1
Hemodynamics, ECG variables and MAPD data, n=3 in A-II (1.0) period and n=6 in the other states

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Saline</th>
<th>Baseline</th>
<th>Captopril</th>
<th>A-II (0.1)</th>
<th>A-II (1.0)</th>
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<tbody>
<tr>
<td>SCL (ms)</td>
<td>535±26.6</td>
<td>532±31.3</td>
<td>575±42.3</td>
<td>578±33.7</td>
<td>675±49.7*</td>
<td>680±50.0*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>117±7.5</td>
<td>118±7.6</td>
<td>116±7.4</td>
<td>99±7.4*</td>
<td>108±6.9</td>
<td>123±2.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80±7.1</td>
<td>81±3.8</td>
<td>83±5.2</td>
<td>67±5.2*</td>
<td>75±9.5</td>
<td>83±2.9</td>
</tr>
<tr>
<td>PQ (ms)</td>
<td>121±8.6</td>
<td>120±12.2</td>
<td>119±11.1</td>
<td>122±10.8</td>
<td>123±8.2</td>
<td>122±7.6</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>95±9.5</td>
<td>95±6.3</td>
<td>93±6.9</td>
<td>93±15.4</td>
<td>94±11.6</td>
<td>97±5.8</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>247±9.3</td>
<td>247±6.1</td>
<td>246±7.4</td>
<td>247±5.2</td>
<td>255±8.9</td>
<td>257±12.6</td>
</tr>
<tr>
<td>MAPD90 (ms)</td>
<td>238±5.2</td>
<td>236±3.8</td>
<td>238±6.1</td>
<td>239±5.8</td>
<td>245±7.1</td>
<td>247±7.6</td>
</tr>
</tbody>
</table>

* Data are expressed as the mean±S.D., *P<0.01 vs. baseline state. Abbreviations: MAPD, monophasic action potential duration; A-II, angiotensin II; SCL, sinus cycle length; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAPD90, monophasic action potential duration at repolarization level of 90%.

saline infusion. In the captopril-treated group, there was no significant difference in the sinus cycle length, three ECG variables and MAPD90 between baseline and only captopril-infused period. In contrast, systolic blood pressure significantly decreased from 116±7.4 to 99±7.4 mmHg (P<0.01 vs. baseline), and diastolic blood pressure significantly decreased from 83±5.2 to 67±5.2 mmHg (P<0.01 vs. baseline).

3.2. Effects of cesium on QT interval, MAPD90 and ventricular tachyarrhythmias

Cesium blocks potassium channel currents, including inward rectifier potassium current [17,18], and prolongs the monophasic action potential duration. The records of subjects in the control and captopril-treated groups are shown in Fig. 2, in which atrial pacing was performed (cycle length: CL=500 ms). At baseline, both groups showed smooth repolarization. In the control group, the first injection of cesium (0.25 mmol/kg) slightly prolonged QT interval and MAPD, and the second injection (0.5 mmol/kg) produced longer QT interval and gentle repolarization in MAP. The similar findings were seen in the captopril-treated group. The QT interval and MAP data from all of the dogs are shown in Table 2. Cesium blocks diastolic inward depolarizing current [19]. It is activated by hyperpolarization, which may be responsible for initial phase of spontaneous depolarization in a sinus nodal pacemaker. Therefore, cesium decreased the heart rate in both groups. Atrial pacing (CL=500 ms) was performed to correct QT interval and MAPD90 by adjusting the cycle length, and the prolongation ratios of QT interval and MAPD90 by cesium injections (0.25 and 0.5 mmol/kg) were evaluated. There was no significant differ-

![Fig. 2](image-url)
ence in any variables among the four states. Therefore, we concluded that the inhibition of angiotensin II formation had no action on the potassium channel-blocking effect.

Fig. 3 shows the recordings illustrating the effect of maximal dose of cesium. About 20 s after the injection of cesium (1.0 mmol/kg), VF following VT occurred in the control group (Fig. 3B). In contrast, in the captopril-treated group the same dose of cesium produced only premature atrial and ventricular contractions, but not VT (Fig. 3A). The effects of angiotensin II on hemodynamics, ECG variables and MAPD90 are summarized in Table 1. There was no significant difference between baseline and each angiotensin-infused period. Accordingly, we considered

### Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>QT (ms)</th>
<th>MAPD90 (ms)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before 0.25 mmol/kg</td>
<td>0.5 mmol/kg</td>
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<tr>
<td>Saline</td>
<td>240</td>
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</tr>
<tr>
<td></td>
<td>265</td>
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<td></td>
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<tr>
<td></td>
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<td>305</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>305</td>
</tr>
<tr>
<td>PR (%)</td>
<td>119±3.9</td>
<td>139±13.4</td>
</tr>
<tr>
<td>Captopril</td>
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<td>275</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>280</td>
</tr>
<tr>
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<td>250</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>270</td>
</tr>
<tr>
<td>PR (%)</td>
<td>116±6.1</td>
<td>137±12.7</td>
</tr>
<tr>
<td>A-II (0.1)</td>
<td>245</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>245</td>
<td>285</td>
</tr>
<tr>
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<tr>
<td>PR (%)</td>
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<td>A-II (1.0)</td>
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<td>295</td>
</tr>
<tr>
<td>PR (%)</td>
<td>118±2.1</td>
<td>145±5.5</td>
</tr>
</tbody>
</table>

*PR (prolongation ratio) data are expressed as mean±S.D.; other abbreviations as in Table 1.*

3.3. Effects of angiotensin II on hemodynamics, ECG variables and MAPD

The effects of angiotensin II on hemodynamics, ECG variables and MAPD90 are summarized in Table 1. There was no significant difference in three ECG variables, MAPD90 between baseline and each angiotensin-infused (0.1 and 1.0 ng/kg/min) period. As stated above, systolic and diastolic arterial blood pressure significantly decreased in the only captopril-infused period compared with baseline, however, there was no significant difference between baseline and each angiotensin-infused period. The sinus cycle length significantly increased in each angiotensin-infused period compared with baseline. This is probably due to the remaining blocking of diastolic inward depolarizing current by cesium administered in the only captopril-infused period. In the same way as the only captopril-infused period, the prolongation ratios of QT interval and MAPD90 by cesium injections (0.25 and 0.5 mmol/kg) were evaluated (Table 2). There was no significant difference in any variables between baseline and each angiotensin-infused period. Accordingly, we considered
Fig. 3. Tracings of ECG (lead II) and MAP demonstrating arrhythmias induced by the third injection of cesium (1.0 mmol/kg) in the captopril-treated group (A) and the control group (B). In (A) premature atrial and ventricular contractions were induced by the maximal dose of cesium, but ventricular tachycardia was not recorded. In (B) ventricular fibrillation following ventricular tachycardia was induced by the same dose of cesium.

Fig. 4. Prevalence ventricular tachyarrhythmias during three repetitive injections of cesium in the control and the captopril-treated groups. The treatment of captopril had anti-arrhythmic effect on lower dose of cesium-induced arrhythmia, and significantly reduced the incidence of sustained ventricular tachycardia or a more severe grade of arrhythmia induced by the maximal dose of cesium ($P<0.01$ vs. control group).
that angiotensin II did not affect the potassium channel-blocking effect.

3.4. Infusion of angiotensin II provokes ventricular tachyarrhythmias

The prevalence of inducible ventricular tachyarrhythmias in the only captopril-infused, captopril and low dose of angiotensin II-infused and captopril and high dose of angiotensin II-infused periods is summarized in Fig. 5. When more than two types of tachyarrhythmias appeared in a single observation period, they were treated as in Fig. 4. NSVT was recorded in three of the six subjects with 1.0 mmol/kg cesium in the only captopril-infused period, and all of the subjects survived. During the infusion of angiotensin II (0.1 ng/kg/min), 0.5 mmol/kg cesium caused NSVT in two dogs and SVT in one. The third injection (1.0 mmol/kg cesium) produced SVT in all six dogs, and the arrhythmia developed into VF in three animals, which subsequently died. With an increased dose of angiotensin II (1.0 ng/kg/min), one and two dogs died following VF induced by 0.5 and 1.0 mmol/kg cesium, respectively. The additional infusion of angiotensin II (0.1 and 1.0 ng/kg/min) had proarrhythmic effect on the lower dose of cesium-induced arrhythmias, and significantly increased fatal arrhythmias induced by maximal dose of cesium (P<0.01 vs. only captopril-infused period).

3.5. Anti-arrhythmic effect of phospholipase C blocker

Although captopril did not improve the prolongation of MAPD90, it did have an anti-arrhythmic effect. Angiotensin II is known to bind to AT1 receptor and activate phospholipase C, which hydrolyzes phosphatidylinositol-4,5-biphosphate (PIP2) to form myoinositol-1,4,5-triphosphate (IP3) and diacylglycerol. The availability of IP3 leads to an increase in the cytosolic calcium concentration from the sarcoplasmic reticulum. Therefore, we hypothesized that the inhibition of endogenous angiotensin II formation by captopril would attenuate calcium release from sarcoplasmic reticulum, and subsequently suppress the genesis of malignant ventricular tachyarrhythmias. The purpose of this experiment was to examine whether U-73122, a selective phospholipase C blocker, can mimic captopril with respect to its anti-arrhythmic effect. The protocol is shown in Fig. 1C.

Infusion of U-73122 did not affect the sinus cycle length, ECG variables and MAPD90 (data not shown), whereas both the systolic and diastolic arterial blood pressure decreased significantly during the infusion of U-73122 compared with baseline (SBP; from 119±8.6 to

![Graph](image-url)
C blocker, had an anti-arrhythmic effect similar to that of captopril. Thus, these are the first findings to suggest that angiotensin II contributes to cesium-induced tachyarrhythmias by increasing calcium release from sarcoplasmic reticulum in myocytes via activation of a phosphatidylinositol response.

4.2. Previous studies on the anti-arrhythmic effect of an ACE inhibitor

Previous studies have shown that treatment with captopril has various beneficial effects on ventricular arrhythmias [7,8]. For example, Cleland et al. [7] observed that long-term treatment with captopril reduced ventricular arrhythmias in patients who suffered from congestive heart failure, and Kingma et al. [8] demonstrated that intravenous captopril suppressed inducible VT 1 week after experimental infarction in the anesthetized pig. They suggested that the inhibition of angiotensin II formation and the subsequent inhibition of noradrenaline release might be responsible for this anti-arrhythmic effect. The local release of catecholamine is an important arrhythmogenic factor. Indeed, the decrease in catecholamine may play a role in the mechanism of this improvement. In our experimental model, however, there may not be excessive local release of catecholamine as in reperfusion or post-infarct models. Therefore, we did not regard inhibition of the local release of catecholamine as the main mechanism of the anti-arrhythmic effect of captopril. Several investigators have reported that angiotensin II shortened the duration of monophasic action potential [20], and that enalapril, an ACE inhibitor, prolonged this duration [21].

As shown in Tables 1 and 2, however, our observations revealed that both captopril and angiotensin II did not significantly change QT interval and MAPD90. In addition, these agents had no effect on the prolongation of QT interval and MAPD90 by the injection of cesium. Accordingly, the effect on the action potential duration cannot account for the anti-arrhythmic action of an ACE inhibitor.

4.3. Contribution of phosphatidylinositol-phospholipase C pathways to ventricular tachyarrhythmias

Several investigators have reported that cesium-induced ventricular tachyarrhythmias are modulated by some drugs or the stimulation of autonomic nerves [22,23]. Takahashi et al. [22] observed that vagal stimulation suppressed the genesis of ventricular arrhythmias. Iwao et al. [23] demonstrated that sustained stimulation of the left ansae subclaviae for 5 h inhibited this arrhythmia. They suggested that this protective effect might be partially explained by desensitization to β-adrenergic stimulation. In addition, David and Zipes [24] showed that α1-adrenoceptor stimulation increased, and α-adrenoceptor blockade decreased, the incidence of cesium-induced VT in dogs. They proposed that the mechanism might be related, in part, to

Fig. 6. Prevalence of ventricular tachyarrhythmias by the injection of cesium (1.0 mmol/kg) in the U-73122-infused (10 μg/kg/min) period and the control period. The treatment of U-731122, a selective phospholipase C blocker, significantly reduced incidence of fatal ventricular arrhythmia induced by the injection of cesium (P<0.01 vs. control period).

98±8.2 mmHg, DBP; from 86±6.6 to 68±4.1 mmHg). Vasodilatation induced by the reduction of calcium release from sarcoplasmic reticulum in vascular smooth muscle cells might account for this decrease in arterial blood pressure.

The injection of cesium produced isolated premature ventricular contractions, but VT was never recorded during the infusion of U-73122. In the same dog, however, the same dose of cesium induced lethal ventricular arrhythmia 40 min after termination of the infusion of U-73122. Fig. 6 compares the incidence of ventricular tachyarrhythmias between the U-73122-infused period and the control period. None of the six dogs presented VT during the infusion of U-73122, whereas VF occurred in all of the six subjects in the control period. The treatment of U-731122 significantly reduced the incidence of fatal ventricular arrhythmia by the injection of cesium (1.0 mmol/kg) (P<0.01 vs. control period). Thus, a selective phospholipase C blocker had an anti-arrhythmic effect like an ACE inhibitor.

4. Discussion

4.1. Main findings

In this study, captopril, which blocks endogenous angiotensin II formation, attenuated the risk of developing ventricular tachyarrhythmias induced by the intravenous injection of cesium without improving the prolongation of QT interval and MAPD, and exogenous angiotensin II provoked fatal ventricular tachyarrhythmias. Additionally, we demonstrated that U-73122, a selective phospholipase C blocker, had an anti-arrhythmic effect similar to that of captopril. Thus, these are the first findings to suggest that angiotensin II contributes to cesium-induced tachyarrhythmias by increasing calcium release from sarcoplasmic reticulum in myocytes via activation of a phosphatidylinositol response.
an increase in the cytosolic calcium concentration. Activation of the α1-adrenoceptor is postulated to activate an enzyme, phospholipase C, which hydrolyzes PIP2 to form IP3 and diacylglycerol [25]. The availability of IP3 leads to an increase in the cytosolic calcium concentration [26,27], in some tissues directly from the sarcoplasmic reticulum [28]. Angiotensin II is known to activate phospholipase C like α1-adrenoceptor stimulation [29]. Accordingly, we suggest that the inhibition of angiotensin II formation may have an anti-arrhythmic effect by attenuating the increase in the cytosolic calcium concentration.

4.4. Study limitations and clinical implications

One of the limitations of the present study might be the manner in which captopril was administered. Although intravenous infusion was used in the present study, long-term oral treatment might be necessary to determine the efficacy of this drug on ventricular tachyarrhythmias in humans. Another concern is the failure to compare the prolongation ratios of QT interval and MAPD90 by the injection of maximal dose (1.0 mmol/kg) of cesium in the control and captopril-treated groups. Because most of the control animals showed VT just after injection of the maximal dose of cesium, we could not measure the QT interval and MAPD90 with atrial pacing. Therefore, the prolongation ratios of the QT interval and MAPD90 by lower doses of cesium (0.25 and 0.5 mmol/kg) were evaluated. Thirdly, since we did not measure MAPD of the M-cell, which seemed to be more sensitive to potassium channel blocker, we could not conclude that captopril and angiotensin II did not influence MAPD of myocardium. However, Shimizu and Antzelevitch [30] explained that the peak of the T wave in the ECG was coincident with the repolarization of epicardial action potential, the end of the T wave was coincident with the repolarization of the M cell action potential, and that repolarization of the endocardial action potential was intermediate between that of the M cell and epicardial cell. We illustrated that the QT interval, which was from the beginning of Q wave to the end of T wave, was unchanged by the infusion of captopril and angiotensin II. Therefore, it is suggested that these two agents do not affect MAPD of myocardium including the M-cell. Although we measured QT interval of only the lead II in the present study, several leads of surface ECG should be recorded to precisely evaluate QT intervals. Fourthly, it is not known whether U-73122 selectively inhibits phospholipase C in vivo in this study. However, Bleasdale et al. [31] proved that U-73122 selectively inhibited phospholipase C-dependent process in vitro. Therefore, we considered that U-73122 would selectively inhibit phospholipase C in vivo. Finally, recent studies provided evidence that the human heart contained high affinity angiotensin II receptors with both subtype populations and ACE. In addition to ACE, a novel cardiac angiotensin II forming enzyme (human chymase) has been identified in human hearts [32]. We used captopril, which was angiotensin-converting enzyme inhibitor, to inhibit endogenous angiotensin II formation. Therefore, angiotensin II production could not be completely blocked. During the infusion of captopril and angiotensin II, we observed the effect of endogenous angiotensin II via the renin–angiotensin system independent pathways plus infused angiotensin II from outside. To block endogenous angiotensin II completely, angiotensin II antagonist should also be administered in a future study.

The beneficial effects of ACE inhibitors on the long-term prognosis of patients after congestive heart failure have been clearly demonstrated [3,4]. Although the mechanisms of these effects may involve many factors, suppression of the cardiac renin–angiotensin system may make an important contribution to the cardiac effects of ACE inhibitors. We have shown that angiotensin II contributes to the genesis of lethal ventricular tachyarrhythmias. Therefore, an ACE inhibitor or angiotensin II antagonist may help protect against malignant ventricular tachyarrhythmias induced by triggered activity. Furthermore, it might be worthwhile to develop a selective cardiac phospholipase C blocker, which dose not affect vascular smooth muscle, to maintain an appropriate systemic arterial blood pressure and treat ventricular tachyarrhythmias.

References


