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# Quercetin decreased heart rate and cardiomyocyte $Ca^{2+}$ oscillation frequency in rats and prevented cardiac hypertrophy in mice[1]

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**KEY WORDS** quercetin; bradycardia; myocardium; cultured cells; calcium; left ventricular hypertrophy; isoproterenol; ouabain; aortic coarctation; angiotensin II

## ABSTRACT

**AIM**: To study the effects of quercetin (Que) on myocardial excitation-contraction coupling and cardiac remodeling. **METHODS**: Left ventricles and femoral arteries of rats were cannulated for hemodynamic recording. Mouse cardiac hypertrophy was induced by abdominal aortic coarctation (AAC). Cultured myocardial cells in neonatal rats were loaded with Fura 2-AM. The intracellular calcium ($[Ca^{2+}]_i$) and spontaneous $[Ca^{2+}]_i$ oscillations ($[Ca^{2+}]_i$-SO) were tested by AR-CM-MIC cation measurement system. **RESULTS**: Que 3 or 25 mg·kg$^{-1}$ iv in rats decreased heart rate from (420 ± 19) to (390 ± 15) and (314 ± 18) beat·min$^{-1}$, respectively, companied with very modest changes in both left ventricular pressures (LVP) and its differential $dp_{LV}/dt_{max}$. Que 10, 50, 250 μmol·L$^{-1}$ concentration-dependently slowed the frequency of $[Ca^{2+}]_i$-SO in cultured myocardial cells from (26 ± 4) to (25 ± 3), (18 ± 4), and (12 ± 3) time·min$^{-1}$, respectively, but did not change their resting $[Ca^{2+}]_i$ or amplitudes of $[Ca^{2+}]_i$-SO. Similarly, the increases in frequency of $[Ca^{2+}]_i$-SO caused by either isoproterenol (Iso) or ouabain (Oua) were prevented by Que 100 μmol·L$^{-1}$, while the simultaneous increases in amplitude of $[Ca^{2+}]_i$-SO remained. Besides, $[Ca^{2+}]_i$ rises excited by angiotensin II (Ang II) but not high $[K^+]_o$ were prevented by Que 100 μmol·L$^{-1}$. Daily administration of Que 120 mg·kg$^{-1}$ ig for 5 d markedly prevented the cardiac hypertrophy in AAC mice, without effects on the ventricular mass to body weight ratio (VM/BW) in sham-operated mice. **CONCLUSION**: Que decreased myocardial $[Ca^{2+}]_i$-oscillation frequency and prevented cardiac remodeling, but had no direct effect on cardiac excitation-contraction coupling.

## INTRODUCTION

Quercetin (Que) was regarded as a nonselective $Ca^{2+}$-antagonist, but now researchers know its actions were more intricate than previous estimates. It was found that Que modulated a number of intracellular biochemical transduction signals or cytokines[1,2] and inhibited many functional proteins in pathway of intracellular $Ca^{2+}$ regulation such as myocardial $Na^+$-$K^+$-ATPase[3] and protein kinase C[4]. However, so far there was no any direct evidence showing if these effects influenced the myocardial excitation-contraction coupling or remodeling, this ignorance, in turn, brings much uncertainty about cardiovascular effects of Que. The present study attempted to determine if Que could influence hemodynamic processes or cardiac hypertrophy *via* modulating myocardial intracellular calcium movements.

## MATERIALS AND METHODS

**Chemicals and rodents** Fura 2-AM was from Shanghai Institute of Physiology, Chinese Academy of Sciences. Captopril (Cap) was supplied by the Changzhou Pharmaceutical Factory of China. Ouabain (Oua), angiotensin II (Ang II). Dulbecco's modified Eagle's medium (DMEM) and inomycin were

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purchased from Sigma. Que was purchased from Fluka AG. All animals used in this study were provided by the Experimental Animal Center of Jiangsu Province (Nanjing, China) and conformed for experimental research (Grade Ⅱ, Certificate № 93008).

**Cardiovascular responses to Que** SD rats, ♂, weighing (280 ± 35) g, were anesthetized with pentobarbitone sodium 40 mg·kg$^{-1}$ ip. Their right femoral arteries were cannulated for measuring blood pressure (BP). A $PE_{50}$ tube was introduced into left ventricle via exposed right carotid for recording left ventricular pressure (LVP) along with its differential $dp_{LV}/dt_{max}$. All hemodynamic signals and ECG were simultaneously measured by computerized physiograph recorder.

**Abdominal aorta coarctation (AAC)** Mice of both sexes, weighing (27 ± 4) g, were anesthetized with pentobarbitone sodium 60 mg·kg$^{-1}$ ip. The abdominal aorta was isolated to expose the fork of left renal artery as previously described[5], where a nylon fiber (ø 0.3 mm) was tied along with the aorta. The AAC was achieved immediately following withdrawing the nylon fiber. The surgery protocol for sham-operated mice was similar only without ligating their abdominal aortae.

**Drug treatment and histological examination** Twenty-four hours after surgery AAC mice were divided into 4 groups and received different treatments for 5 d as follows: Que 60 or 120 mg·kg$^{-1}$, dissolved by 100 % ethanol and diluted with distilled water, was daily given ig to two groups of AAC mice; Cap 60 mg·kg$^{-1}$ was injected ip to the third group; AAC control mice daily received ig saline containing 5 % ethanol. To assess the effect of Que on the growth in normal mice, Que 120 mg·kg$^{-1}$·d$^{-1}$ or solvent soultion was given to two sham-operated groups of mice for 5 d. After therapeutic treatment, animals were returned to standard living condition and daily weighed for a week. All animals were decapitated on d 12 and the body weights (BW) before decapitation and ventricular masses (VM) were weighed to calculate the VM/BM. The heart and kidney samples from each group were fixed with 10% formalin. Paraffin-embedded blocks were sectioned; HE staining was carried out; the thickness of ventricular septal myocardia was measured under light microscopy.

**Myocardial culture** Monolayer myocardial cells with spontaneous contraction were cultured[6]. Briefly, ventricular fragments from 3 – 4-d-old neonatal SD rats were digested with 0.06 % trypsin at 37 ℃ for 10 min, serial digestion solutions were collected and centrifugalized at 1500 × g for 5 min. Cell pellets were rinsed and resuspended with Hanks' solution: NaCl 137, KCl 5, $KH_2PO_4$ 0.44, $Na_2HPO_4$ 0.38, $NaHCO_3$ 2.62, $MgSO_4$ 0.5, $CaCl_2$ 1.3, glucose 5.6 mmol·L$^{-1}$, pH = 7.2. Washed cells were harvested and resuspended in DMEM supplemented with 15 % bovine serum and both benzylpenicillin and streptomycin 100 mg·L$^{-1}$. After preplating for 1 h the upper portion of cell suspention enriched myocardial cells was diluted to 1 × 10$^9$ cells·L$^{-1}$. Myocardial cells were seeded on a 24-well plate. After incubation in humidified 5 % $CO_2$ and 95 % air at 37 ℃ for 36 – 48 h, they were used for $[Ca^{2+}]_i$ measurement.

**$[Ca^{2+}]_i$ and $[Ca^{2+}]_i$-SO measurement** Fura 2-AM loading and $[Ca^{2+}]_i$ measurement were carried out[7]. Fluorescence intensities excited at 340 and 380 nm were simutaneously measured by AR-CM-MIC cation measurement system. $[Ca^{2+}]_i$ was calculated according to the 340/380 nm fluorescence intensity ratio using the software in the system. Cultured myocardial cells were incubated in Hanks' solution which contained $Ca^{2+}$ 1.3 mmol·L$^{-1}$. The frequency of $[Ca^{2+}]_i$-SO was determined through dividing the number of spike-like $Ca^{2+}$-signal by related scanning time. Those $[Ca^{2+}]_i$-SO arisen from resting myocardial cells or irregularly inserted $[Ca^{2+}]_i$-SO after Iso or Oua stimulation was defined to the extra $[Ca^{2+}]_i$-SO. Both frequency and amplitude of $[Ca^{2+}]_i$-SO were simultaneously observed and compared with their basal values.

**Statistical methods** Data were presented as $x \pm s$ and compared with paired $t$ test (Tab 1) and one-way ANOVA. (Tab 2, 3).

## RESULTS

**Effect on hemodynamics** Intravenous administrtion of Que caused only a dose-related bradycardia with very slight changes in BP, LVP, and $dp_{LV}/dt_{max}$, these responses were obviously different from the effects of calcium channel blocker verapamil (Tab 1).

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**Tab 1. Effects of Que and verapamil on hemodynamics of anesthetized rats. $n = 7$, $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control.**

| Hemodynamic parameters | Control | Que/mg·kg$^{-1}$ 3 | Que/mg·kg$^{-1}$ 25 | Ver/mg·kg$^{-1}$ 1 |
|---|---|---|---|---|
| HR/beat·min$^{-1}$ | 420 ± 19 | 390 ± 15$^b$ | 314 ± 18$^c$ | 334 ± 20$^c$ |
| SBP/kPa | 14.2 ± 0.7 | 13.9 ± 0.8 | 13.7 ± 0.8 | 10.0 ± 1.4$^c$ |
| DBP/kPa | 10.1 ± 0.6 | 9.8 ± 0.7 | 9.7 ± 0.7 | 5.3 ± 0.4$^c$ |
| LVSP/kPa | 16.7 ± 0.9 | 16.2 ± 0.8 | 16.0 ± 0.5 | 12.6 ± 0.5$^c$ |
| LVDP/kPa | -2.0 ± 0.9 | -1.9 ± 0.9 | -1.8 ± 0.9 | -0.6 ± 0.7$^c$ |
| $dp_{LV}/dt_{max}$, kPa·s$^{-1}$ | 1995 ± 190 | 1870 ± 167 | 1839 ± 161 | 1474 ± 156$^b$ |

### Effect on spontaneous $[Ca^{2+}]_i$ transients

Before exposure to Que, two types of $[Ca^{2+}]_i$ transients were observed in cultured myocardial cells. The cells without spontaneous contraction exhibited a rather stable resting $[Ca^{2+}]_i$ that equated to (102 ± 18) nmol·L$^{-1}$ ($n = 17$). Que had no effect on this value. In contrast, regularly contracting myocardial cells often showed their $[Ca^{2+}]_i$-SO in a fixed frequency and nearly equal amplitude. Directly adding Que 10 – 250 μmol·L$^{-1}$ in extracellular solution decreased the frequency of myocardial $[Ca^{2+}]_i$-SO in a concentration-dependent manner. However, the amplitudes of $[Ca^{2+}]_i$-SO remained unchanged (Fig 1). Spike-like extra $[Ca^{2+}]_i$-SO could be occasionally triggered by Que 250 μmol·L$^{-1}$, but disappeared immediately after some bursts.

### Effect on excitatory $[Ca^{2+}]_i$ transients

KCl 50 mmol·L$^{-1}$ abruptly increased the amplitudes of $[Ca^{2+}]_i$-SO in both contracting and resting myocardial cells accompanied with irregular frequency changes. The administration of Que 0.1 mmol·L$^{-1}$ decreased the frequency of $[Ca^{2+}]_i$-SO but negligibly affected high $[K^+]_o$-induced $[Ca^{2+}]_i$ rise. The cells exposed to Ang Ⅱ resulted in a moderate amplitude increase of $[Ca^{2+}]_i$-SO, this reaction was completely prevented by Que 0.1 mmol·L$^{-1}$ along with a decreased frequency in $[Ca^{2+}]_i$-SO. In the presence of Iso 10 μmol·L$^{-1}$ or Oua 50 μmol·L$^{-1}$, both amplitude and frequency of myocardial $[Ca^{2+}]_i$-SO were increased. Moreover, Oua-elicited $[Ca^{2+}]_i$ elevation resulted in occurrence of extra $[Ca^{2+}]_i$-SO within 5 cells from 12 tested cells whithout spontaneous contractions. Pre-adding Que

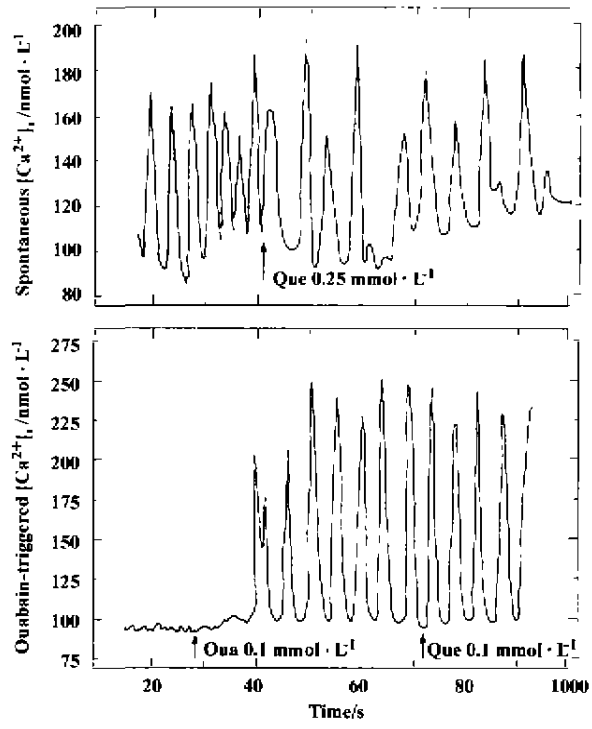


**Fig 1. Effect of Que on the spontaneous and Oua-triggered $[Ca^{2+}]_i$ oscillation of a single cultured myocardial cell from neonatal rats.**

0.1 mmol·L$^{-1}$ remarkably prevented Oua or Iso-caused frequency acceleration of $[Ca^{2+}]_i$-SO, whereas only slightly inhibited the change in their amplitudes (Tab 2). The extra $[Ca^{2+}]_i$-SO was triggered only in 1

**Tab 2. Effects of Que on spontaneous $[Ca^{2+}]_i$-SO in myocardial cells of neonatal rats. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control. $^eP < 0.05$ *vs* Ang Ⅱ group. $^iP < 0.01$ *vs* Iso group. $^lP < 0.01$ *vs* Oua group.**

| Drugs/mmol·L$^{-1}$ | $n$ | Frequency/time·min$^{-1}$ | $[Ca^{2+}]_i$/nmol·L$^{-1}$ Minimal | Maximal |
|---|---|---|---|---|
| Control | 9 | 26 ± 4 | 105 ± 18 | 158 ± 24 |
| Que 0.01 | 7 | 25 ± 3 | 104 ± 21 | 166 ± 27 |
| Que 0.05 | 8 | 18 ± 4$^b$ | 107 ± 14 | 156 ± 23 |
| Que 0.25 | 8 | 12 ± 3$^c$ | 109 ± 17 | 148 ± 18 |
| KCl 50 | 10 | 28 ± 4 | 115 ± 18 | 275 ± 38$^c$ |
| Que 0.1 + KCl 50 | 10 | 19 ± 3$^b$ | 109 ± 19 | 247 ± 36$^c$ |
| Ang Ⅱ 0.003 | 12 | 27 ± 3 | 116 ± 14 | 178 ± 32$^b$ |
| Que 0.1 + Ang Ⅱ 0.003 | 12 | 19 ± 3$^b$ | 106 ± 15 | 150 ± 21$^e$ |
| Iso 0.01 | 9 | 38 ± 4$^c$ | 105 ± 17 | 196 ± 24$^c$ |
| Que 0.1 + Iso 0.01 | 10 | 26 ± 3$^i$ | 111 ± 15 | 181 ± 26$^b$ |
| Oua 0.05 | 10 | 34 ± 4$^c$ | 109 ± 12 | 193 ± 23$^b$ |
| Que 0.1 + Oua 0.05 | 11 | 26 ± 4$^l$ | 105 ± 17 | 182 ± 20$^b$ |

from 14 tested cells in the coincubation with both Oua μmol·L$^{-1}$ and Que 0.1 mmol·L$^{-1}$. However, once Oua-induced extra $[Ca^{2+}]_i$-SO occurred, it could not be reversed by Que.

**Effect on cardiac hypertrophy** Compared with sham-operated control, coarctating abdominal aorta for 12 d induced the increases in VM and VM/BW ratio with hypertrophic left ventricular walls; the thickness of ventricular septal was increased from (0.76 ± 0.05) mm in sham mice to (1.04 ± 0.17) mm in AAC mice ($n=6$, $P<0.05$ *vs* sham). The atrophied glomeruli in left renal cortex were only seen in AAC mice. Que 120 mg·kg$^{-1}$ ig for 5 d inhibited the growth of BW in both sham and AAC mice but maintained the ratio of VM/BW in normal, whereas Que 60 mg·kg$^{-1}$ for 5 d neither retarded the BW growth nor much affected VM/BW increases in AAC mice. The thickness of ventricular septal after AAC for 12 d was normalized from (1.04 ± 0.17) to (0.72 ± 0.08) mm by Que 120 mg·kg$^{-1}$·d$^{-1}$ ($n=6$, $P<0.05$ *vs* AAC group). But renal cortical atrophy was unchanged. Cap 60 mg·kg$^{-1}$·d$^{-1}$ ip for 5 d completely prevented cardiac hypertrophy in AAC mice without any inhibition in BW (Tab 3).

**Tab 3. Effects of Que and Cap on the increases in body weight after AAC for 12 d (ΔBW) and AAC-induced the elevation of ventricular mass to body weight ratio (VM/BW) in mice.** $n=10$. $\bar{x} \pm s$. $^bP<0.05$, $^cP<0.01$ *vs* **sham control.** $^fP<0.01$ *vs* **AAC control.**

| Treatment/ mg·kg$^{-1}$ | BW/g | ΔBW/g | VM/mg | VM/BW (mg·g$^{-1}$) |
|---|---|---|---|---|
| Sham control | 31 ± 4 | 2.9 ± 2.0 | 109 ± 20 | 3.5 ± 0.2 |
| Sham + Que 120 | 28 ± 3 | −1.2 ± 1.3$^b$ | 98 ± 19 | 3.6 ± 0.2 |
| AAC control | 31 ± 6 | 2.7 ± 2.5 | 127 ± 25$^c$ | 4.1 ± 0.4$^c$ |
| AAC + Cap 60 | 29 ± 4 | 2.2 ± 1.1 | 101 ± 12 | 3.5 ± 0.2$^f$ |
| AAC + Que 60 | 27 ± 4 | 1.4 ± 1.7 | 105 ± 24 | 3.9 ± 0.4 |
| AAC + Que 120 | 26 ± 4 | −0.9 ± 2.1$^b$ | 88 ± 13 | 3.4 ± 0.2$^f$ |

## DISCUSSION

Many reports showed that the cardiovascular effects of Que were similar to those of calcium channel blockers[8-10], but the present study demonstrated that Que did not act like typical $Ca^{2+}$ channel blocker in some aspects. Que dose-dependently decreased the heart rate with negligible effects on arterial blood pressure and left ventricular pressure as well as myocardial contractile parameter $dp_{LV}/dt_{max}$, these effects indicated that the drug was not analogous to any of known L-type $Ca^{2+}$ channel blockers.

The effects of Que on myocardial $[Ca^{2+}]_i$ transient were different from typical $Ca^{2+}$ channel blockers too. Que concentration-dependently decreased the frequency of $[Ca^{2+}]_i$-SO, but neither significantly affected the innate amplitude of $[Ca^{2+}]_i$-SO nor the amplitude increases in $[Ca^{2+}]_i$-SO elicited by Iso, Oua, and high $[K^+]_o$. These results indicate that Que seems unable to directly intervene the myocardial excitation-contraction coupling process, but somewhat interfere with calcium-related cardiac impulse generation.

The present study also found that Que 0.25 mmol·L$^{-1}$ only occasionally initiated some arrhythmia-like extra $[Ca^{2+}]_i$-SO. However, it actually exerted preventive effects on Oua-induced occurrences of extra $[Ca^{2+}]_i$-SO. These results may reveal that Que is possessed of less proarrhythmic toxication than Oua through the delayed afterdepolarization, which ofter results from $Na^+$-$K^+$-ATPase inhibition in myocardial cellular membrane[3].

By inhibiting the activities of protein kinase C, tyrosine protein kinase and some cytokines[2,4], Que may be a potential inhibitor for cardiac remodeling[1,11]. This estimate was confirmed by the results that Que significantly prevented the increase in VM/BW ratio and alleviated thickening of ventricular walls in AAC mice. It is consistent with the results that Ang II-induced $[Ca^{2+}]_i$ rise was prevented by administration of Que. Considering that Que had no hypotensive actions, the effect of Que on cardiac hypertrophy could not be attributed to any sequential hemodynamic consequences. On the other hand, daily administration of Que 120 mg·kg$^{-1}$ obviously inhibited the body growth in mice, therefore, it is reasonable that Que-inhibited cardiac hypertrophy bore some relation to its antimetabolic effects[1,12].

In summary, the effects of Que on myocardial cells were substantially different from that of any known L-type calcium channel blockers in hemodynamics and $[Ca^{2+}]_i$-transcients. It rarely induced extra $[Ca^{2+}]_i$-SO, but concentration-dependently decreased the frequency of $[Ca^{2+}]_i$-SO and inhibited cardiac

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hypertrophy in AAC mice. Therefore, Que exerting its cardiovascular effects is probably not so much through the excitation-contraction coupling as through its antimetabolic actions.

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## 槲皮素降低大鼠心率和心肌钙振荡频率和抑制小鼠心肌肥厚[1]

R972 R965.2

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**关键词** 槲皮素; 心动过缓; 心肌; 培养的细胞; 钙; 左心室肥大; 异丙肾上腺素; 哇巴因; 主动脉缩窄; 血管紧张素 II

**目的**: 研究槲皮素对心肌兴奋收缩耦联及构型重建的影响. **方法**: 经动脉插管记录大鼠血流动力学; 缩窄小鼠腹主动脉致心肌肥厚; 检测 Fura 2-AM 负载的培养大鼠心肌细胞内游离钙($[Ca^{2+}]_i$)及钙振荡. **结果**: 槲皮素剂量相关地降低大鼠窦性心率, 而动脉血压、左室压及其微分改变轻微; 10 – 250 $\mu mol \cdot L^{-1}$时浓度依赖性降低培养心肌自发钙振荡频率, 100 $\mu mol \cdot L^{-1}$时预防异丙肾上腺素及哇巴因加速钙振荡频率, 但不抑制静息$[Ca^{2+}]_i$和自发钙振荡及二药增高的振荡幅度. 槲皮素还抑制血管紧张素 II 而非高钾的升$[Ca^{2+}]_i$作用. 槲皮素 120 $mg \cdot kg^{-1} \cdot d^{-1}$ 5 d 灌胃不改变假手术鼠的心室与体重之比, 但显著抑制腹主动脉结扎小鼠的心室肥大. **结论**: 槲皮素降低心肌钙振荡频率和心肌肥厚但不直接影响心脏兴奋收缩耦联.

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