Original Research

Frequent ventricular premature beats increase blood pressure variability in rats[1]

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KEY WORDS arrhythmia; blood pressure variability; heart period variability

ABSTRACT

AIM: The present study was designed to test a hypothesis that nonfatal ventricular arrhythmia such as ventricular premature beats (VPB) is a contributing factor in the elevation of blood pressure variability (BPV). **METHODS:** Blood pressure (BP) and electrocardiogram were continuously recorded. The relation between VPB and BPV was observed under conscious state in chronic myocardial infarction (MI) rats one month after ligation of the left coronary artery, and further verified under anesthetized state in rat model of ventricular arrhythmia produced by acute intravenous infusion of aconitine. **RESULTS:** MI rats exhibited a big difference in the count and pattern of VPB, and were divided into no VPB, occasional VPB, and frequent VPB groups. Among the three groups, there were no differences in BP, heart period (HP), and MI size. However, BPV was markedly higher in frequent not occasional VPB rats, and HP variability (HPV) was larger in both frequent and occasional VPB rats, when compared with no VPB rats. In the whole population of MI rats, BPV was positively correlated with VPB and HPV, not with BP, HP and MI size. Infusion of aconitine had no effect on BP, HP, BPV, and HPV during the period without VPB. Frequent VPB after several minutes of aconitine infusion induced significant increase in BPV and HPV with no change in BP and HP. BPV was also positively correlated with VPB and HPV, not with BP and HP. Hemodynamics in aconitine-evoked ventricular tachycardia was characterized as lower BP, higher BPV, and higher HPV. **CONCLUSION:** High BPV can be caused by frequent not occasional VPB in rats.

INTRODUCTION

Blood pressure variability (BPV) is increased in several conditions, including hypertension[1-3], aging[4], diabetes[5,6], spinal cord injury[7], and alcohol consumption[8], and linked with the severity of the underlying diseases, such as hypertension[1,2]. Causes for high BPV are manifold and varied in different conditions. It is well known that arterial baroreflex is important in the stabilization of blood pressure (BP), and interruption of arterial baroreflex by sinoaortic denervation or lesions of the nucleus tractus solitarii makes the BP very unstable[9,10]. Therefore, the impairment of baroreflex function is considered as one of the factors involved in the elevation of BPV in some diseases, at least in hypertension[11,12]. In a recent experiment, we unexpectedly found that BP was unstable in a chronic myocardial infarction (MI) rat with premature arrhythmia. This unexpected finding leads to our hypothesis that nonfatal ventricular arrhythmia such as ventricular prema-

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ture beats (VPB) may be a contributing factor in the elevation of BPV.

To test this hypothesis, the relation between VPB and BPV was investigated under conscious state in chronic MI rats, and further verified under anesthetized state in acute aconitine infused rats.

MATERIALS AND METHODS

Male Sprague-Dawley rats were purchased from the Sino-British SIPPR/BK Lab Animal Ltd. All surgical and experimental procedures were in accordance with institutional animal care guidelines. Rats were housed with controlled temperature (23-25 ºC) and lighting (8:00-20:00 light, 20:00-8:00 dark) and with free access to standard chow and tap water.

Arrhythmia and BPV in chronic MI rats under conscious state

Preparation of chronic MI rats Thirty rats, weighing (213±35) g, were used in the experiment. Myocardial infarction (MI) was prepared by ligation of the left anterior descending coronary artery[13]. Briefly, with rats under ether inhalation anesthesia, the heart was exteriorized via a left thoracotomy, and the left anterior descending artery was ligated between the pulmonary outflow tract and left atrium. The heart was returned to its normal position, the air was removed, the thorax was closed, and artificial respiration was performed until recovery of spontaneous respiration. The above procedures should be carried out as soon as possible. Rats were then injected intramuscularly with procaine benzylpenicillin (60 kU/rat), returned to cages (2 or 3 rats in each cage), and brought up for 1 month. In this experiment, 21 of 30 rats survived 1 month after operation. The mortality rate of the operation was 30 % (9/30). All deaths occurred within the day after operation, especially within the first several hours after operation.

BP and ECG recording in conscious rats One month after ligation of the left coronary artery, the rat was anaesthetized with a mixture of ketamine (50 mg/kg, ip) and diazepam (5 mg/kg, ip). A polyethylene catheter (PE-10 connected to PE-50) was chronically placed into the lower abdominal aorta via the left femoral artery for measurement of BP and heart period (HP). This catheter was then tunneled subcutaneously, exteriorized between the scapulae, and fixed on the saddle. After 2 days of recovery, the conscious rat was placed in a cylindrical cage, and the aortic catheter and electrocardiogram (ECG) leads were connected to the computerized BP and ECG monitoring systems (MPA 2000M, Alcott Biotech Co LTD, Shanghai), respectively[3,9,14]. BP and ECG (lead II) were continuously recorded for 1 h after a 1-h period of stabilization.

BPV and HPV estimation According to beat-to-beat pressure wave, the 1-h recording of BP signal was analyzed to determine BP and HP, and their variabilities. The mean of 1-h BP was used as an index of BP, and the standard deviation of 1-h BP as an index of BPV[3,9,15]. The same method was applied for calculation of HP and its variability (HPV).

Arrhythmia examination Ventricular arrhythmia was examined during 1-h period of ECG recording. Of total 21 MI rats, 8 rats exhibited normal sinus rhythm, 12 rats exhibited different extent of VPB, and 1 rat exhibited a mixture of VPB and ventricular tachycardia (VT). To avoid the interference of ventricular tachycardia, one MI rat with a mixture of VPB and VT was excluded in the analysis of the results. The remains (20 MI rats) were divided into three groups: no VPB (n=8), occasional VPB (n=8), and frequent VPB (n=4), since the count and pattern of VPB were obviously different in these rats. The criteria for division were modified from the method described by Curtis *et al*[16]: no VPB (0 VPB/h), occasional VPB (<250 VPB/h, demonstrated in single VPB), and frequent VPB (>>250 VPB/h, usually demonstrated in the manner of 1-3 normal beats followed by 1 premature beat, ie, bigemina, trigemina and quadrigemina).

Measurement of MI size At the end of experiment, MI size was measured according to the previously reported methods[13,14]. Briefly, the rat was killed by an overdose of pentobarbital. The left ventricle was isolated, and cut into four slices perpendicular to the cardiac long axis. The slices were stained for 6 min at 37 ºC in a 1% solution of triphenyltetrazolium chloride (TTC, Sigma Chemical Co) in phosphate buffer. TTC stained the normal tissue red, but necrotic tissue remained unstained. The stained and unstained tissues were isolated and weighed separately. MI size was expressed as a fraction of the total left ventricular weight[14].

Arrhythmia and BPV in aconitine infused rats under anesthetized state Fifteen rats, weighing (288±23) g, were used in the experiment. With rat under urethan (1.3 g/kg, ip) anesthesia, a polyethylene catheter (PE-10 connected to PE-50) was placed into the lower abdominal aorta via the left femoral artery for measurement of BP and HP, and another catheter (PE-

50) was inserted into the left femoral vein for drug administration. The aortic catheter, ECG leads, and venous catheter were connected to the BP recording system, ECG monitoring system, and infusion pump, respectively. After a 30-min period of stabilization, BP and ECG were continuously recorded throughout the designed protocol (Fig 1). BP and ECG were analyzed in four periods: before intravenous infusion of aconitine (Baseline, 10-min), during the first aconitine infusion without VPB (aconitine, about 6-min), during the occurrence of VPB without aconitine infusion (VPB, 10-min), and during the occurrence of ventricular tachycardia without aconitine infusion (VT, 10-min). Aconitine (Sigma Chemical Co) was intravenously infused at a concentration of 10 mg/L and a speed of 0.1 mL/min. The infusion was immediately stopped when the VPB or VT happened. In the experiment, some rats (3 of 10 rats) exhibited a mixture of VPB and VT following the first aconitine infusion. These rats were not included in the study. In addition, five rats were used for vehicle infusion with the same protocol described above. The first vehicle infusion persisted 6 min, and the second 3 min. This was to control for any potential effects of experimental conditions on hemodynamics and ECG.

Statistical analysis Statistical analysis was performed using statistical program SAS. Data are reported as mean±SD. For unpaired data, the differences among three groups were evaluated by using analysis of variance (ANOVA) followed by unpaired *t* test. For paired data, the differences were determined by paired *t* test. The relationship between two variables was assessed by linear regression analysis. Statistical significance was judged at $P<0.05$.

RESULTS

Data from chronic MI rats In chronic MI rats with no VPB, occasional VPB and frequent VPB, there existed big differences in the count and pattern of VPB as described in the Method; the actual beats of ventricular premature during 1-h recording were 0, 166±85 (60-249), and 4300±889 (3388-5400), respectively (Tab 1). Body weights at the initial time of MI operation and at the final time of the measurements, and weight gains were not significantly different among three groups. MI size expressed as a fraction of the total left ventricular weight was 27.0 %±9.1 % in the whole population of chronic MI rats. There were no significant differences in MI sizes of three groups.

In hemodynamics, BP and HP in two VPB groups were not different from those in no VPB group. However, the variability of HP was slightly increased in occasional VPB group, and the variabilities of both BP and HP were markedly elevated by more than 80 % in frequent VPB group, as compared with the no VPB group (Tab 1). Fig 2 demonstrates the hemodynamic tracings of chronic MI rats. In chronic MI rat without VBP, pulsatile pressure wave was relative regular, and

Tab 1. Body weight, MI size, VPB count, and hemodynamic parameters in chronic MI rats. $^{b}P<0.05$, $^{c}P<0.01$ *vs* No VPB; $^{f}P<0.01$ *vs* Occasional VPB.

	No VPB (n=8)	Occasional VPB (n=8)	Frequent VPB (n=4)
Body weight/g			
Initial	220±19	212±51	203±21
Final	368±32	354±21	372±30
Gain	148±24	142±42	169±25
MI size/%	27±10	31±9	22±4
VPB/h	0	166±85^{c}	4300±889^{cf}
Systolic BP/mmHg	135±7	135±14	137±9
Diastolic BP/mmHg	91±5	92±10	92±7
HP/ms	175±17	175±15	189±14
Systolic BPV/mmHg	5.4±1.2	5.1±1.2	9.8±0.7^{cf}
Diastolic BPV/mmHg	4.2±0.4	4.3±0.8	7.7±0.8^{cf}
HPV/ms	23.1±1.9	26.5±2.8^{b}	44±7^{cf}

MI: myocardial infarction; VPB: ventricular premature beats; BP and BPV: blood pressure and its variability; HP and HPV: heart period and its variability.

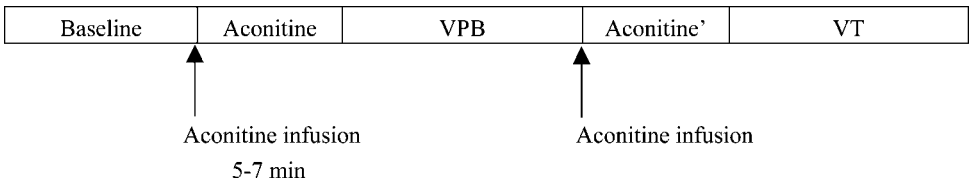

Fig 1. Schematic diagram of the experimental protocol. VPB: ventricular premature beats; VT: ventricular tachycardia.

the tracings of HP, systolic BP (SBP) and diastolic BP (DBP) were rather stable. However, in chronic MI rat with frequent VPB, pulsatile pressure wave was irregular, and the tracings of HP, SBP and DBP were much more variable. The beat-to-beat SBP, DBP and HP values during 15 s are illustrated in Fig 3, showing the BP and HP responses to a single ventricular premature beat with a complete compensatory period.

Linear regression analysis was performed in the whole population of MI rats (Tab 2). BPV was positively correlated with VPB and HPV, but not with BP, HP, and MI size. HPV was positively correlated with VPB, BPV, and HP, but not with BP and MI size.

Data from aconitine infused rats In vehicle infused rats, no arrhythmia was found, and there were no significant differences in all measured hemodynamic parameters during the four periods (data not shown). In aconitine infused rats, hemodynamic parameters during the first aconitine infusion without VPB were not different from the baselines (Fig 4). The intravenous infusion of aconitine was immediately stopped as soon as the VPB happened. The occurrence of VPB belonged to the frequent VPB and maintained more than 10 min. When compared with the baselines, BP and HP were not significantly changed, while their variabilities were significantly increased during the occurrence of VPB (Fig 4). Hemodynamic parameters were also observed during the occurrence of VT produced by the second aconitine infusion. They exhibited a lower BP, a higher BPV, and a larger HPV, with no significant change of HP, as compared with the baselines (Fig 4). Fig 5 is a typical original tracing of systolic BP from one aconitine infused rat. It is demonstrated that during aconitine infusion without VPB, both systolic BP and BPV remained unchanged; during the occurrence of VPB, the average level of systolic BP remained unchanged, while the variability of systolic BP was enlarged; and during the occurrence of VT, the average level of systolic BP was reduced, whereas the variability of systolic BP was still enlarged. Similar phenomena were also found in the original tracing of diastolic BP.

Linear regression analysis was performed in the combined data (Tab 3). BPV was positively correlated with VPB and HPV, but not with BP and HP. HPV was positively correlated with VPB, BPV and HP, but not with BP.

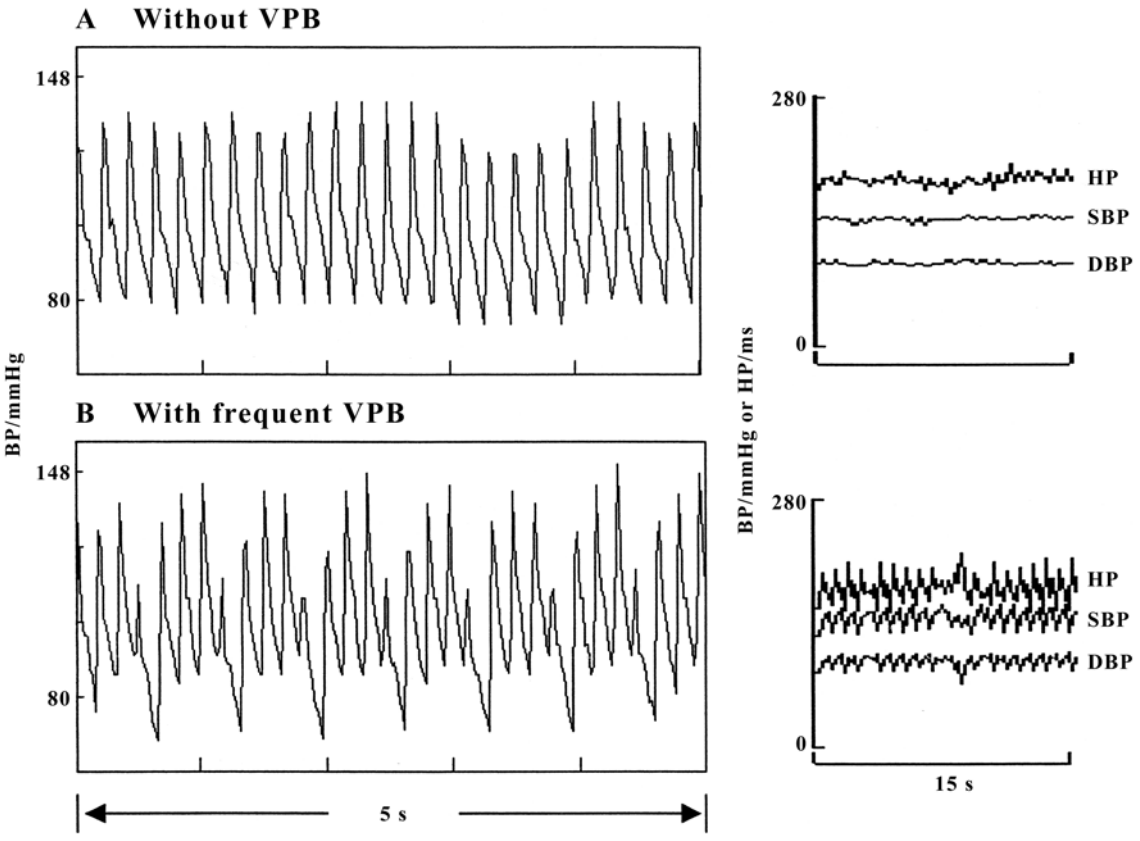

Fig 2. Hemodynamic tracings to demonstrate the increased variability of systolic BP (SBP), diastolic BP (DBP), and heart period (HP) in MI rat with frequent VPB.

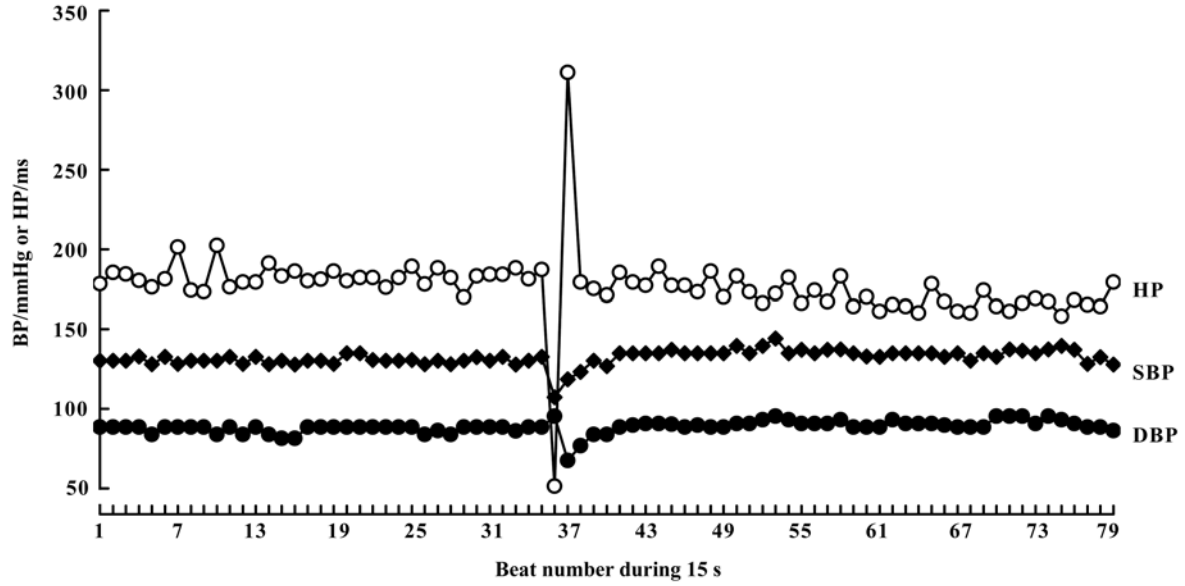

Fig 3. Beat-to-beat systolic BP (SBP), diastolic BP (DBP), and heart period (HP) during 15 s to show the BP and HP responses to a single ventricular premature beat with a complete compensatory period.

Tab 2. Linear regression coefficients for hemodynamic, VPB count and MI size data from chronic MI rats. $^{b}P<0.05$, $^{c}P<0.01$.

	Systolic BP	HP	Systolic BPV	HPV	VPB/h	MI size
Systolic BP		0.2484	0.2469	0.2154	0.1190	0.0880
HP	0.2484		0.3645	0.5133^{b}	0.4033	0.0998
Systolic BPV	0.2469	0.3645		0.8078^{c}	0.8399^{c}	-0.0869
HPV	0.2154	0.5133^{b}	0.8078^{c}		0.9471^{c}	-0.2518
VPB/h	0.1190	0.4033	0.8399^{c}	0.9471^{c}		-0.3009
MI size	0.0880	0.0998	-0.0869	-0.2518	-0.3009	

VPB: ventricular premature beats; MI: myocardial infarction; BP and BPV: blood pressure and its variability; HP and HPV: heart period and its variability. Linear regression analysis was performed in the whole population of chronic MI rats (No VPB+Occasional VPB+Frequent VPB).

DISCUSSION

Cardiovascular variabilities have been examined in both physiological and pathophysiological conditions. Under physiological conditions, it is unquestionable that the heart beats at normal sinus rhythm. However, under certain pathophysiological conditions, arrhythmia may occur. One can find from the literature that both HPV and BPV have been reported in different cardiovascular diseases accompanied by ventricular arrhythmia[1,17-25], even malignant ventricular arrhythmia such as bigemina and VT[22-25].

There were many publications regarding ventricular arrhythmia and HPV[17,20-25]. The present study demonstrated that HPV was significantly increased with the occurrence of VPB and positively correlated with VPB count in both ventricular arrhythmia models. It is easy to understand that larger HPV is a direct consequence of ventricular arrhythmias. The larger HPV is mainly due to the shortened HP at the premature beat and heart rate turbulence after the premature beat (Fig 2, 3). Also, HPV was positively correlated with HP, but not with BP or MI size. These results further confirm the previous report that heart rate is a major determinant of its variability[19]. In that report, a large population-based sample with 2722 eligible subjects was used for investigation. The stepwise multiple linear regression analysis demonstrated that heart rate and age selected from 16 candidate variables were the major determinants of heart rate variability (partial R^2 values 0.125 to

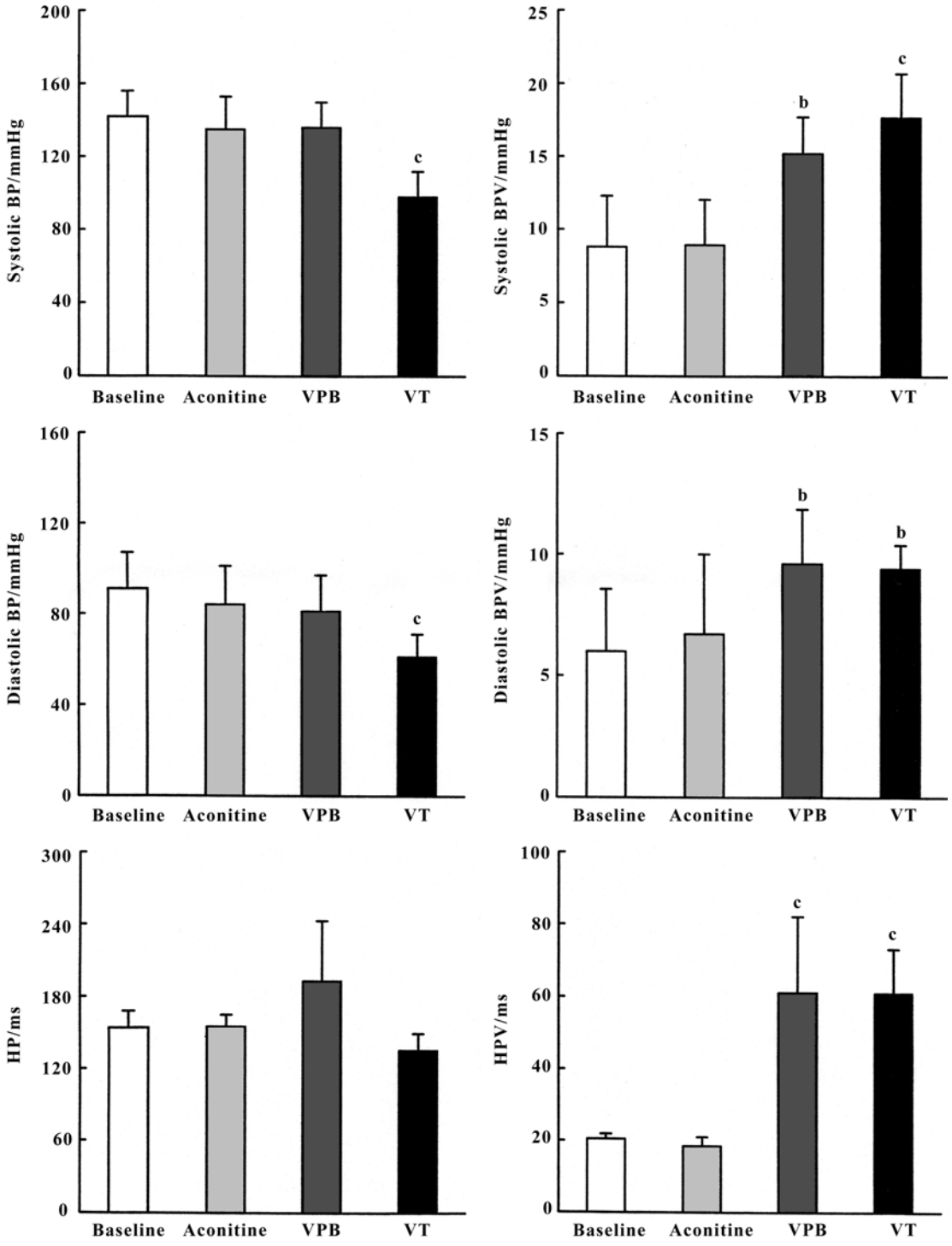

Fig 4. Hemodynamics in aconitine infused rats. *n*=7. Mean±SD. $^{b}P<0.05$, $^{c}P<0.01$ *vs* Baseline.

0.389). Heart rate variability decreased with increasing heart rate and advancing age.

The new contribution of the current study was to verify that nonfatal ventricular arrhythmia such as VPB may be a factor for increasing BPV. Our results certainly demonstrated that high BPV could be caused by frequent not occasional VPB. First, BPV was positively correlated with VPB count, indicating high BPV is associated with VPB. Second, in chronic MI rats, a substantial increase of BPV was found only in frequent VPB rats, not in occasional VPB rats. Finally, in acute aconitine infused rats, intravenous infusion of aconitine

Tab 3. Linear regression coefficients for hemodynamic and VPB count data from aconitine-infused rats. $^cP<0.01$.

	Systolic BP	HP	Systolic BPV	HPV	VPB/10 min
Systolic BP		-0.3232	0.1509	-0.1942	-0.1121
HP	-0.3232		0.3674	0.6899^c	0.6444^c
Systolic BPV	0.1509	0.3674		0.6781^c	0.7269^c
HPV	-0.1942	0.6899^c	0.6781^c		0.8900^c
VPB/10 min	-0.1121	0.6444^c	0.7269^c	0.8900^c	

VPB: ventricular premature beats; BP and BPV: blood pressure and its variability; HP and HPV: heart period and its variability. Linear regression analysis was performed in the combined data (Baseline+Aconitine+VPB).

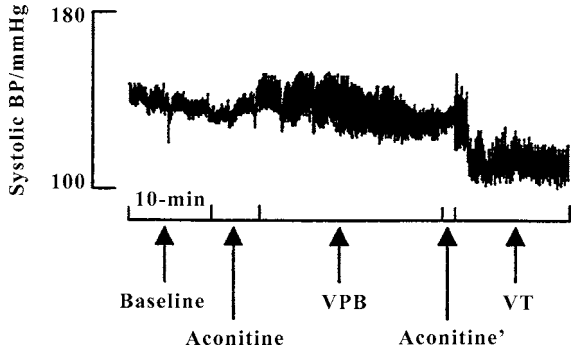

Fig 5. Systolic BP tracing from one aconitine-infused rat.

had no effect on BPV during the period without VPB, whereas the occurrence of frequent VPB following several minutes of aconitine infusion produced a significant increase in BPV. These are direct evidences for frequent VPB-induced high BPV. At least two components are involved in the VPB-induced high BPV. One is an immediate decrease in BP at the premature beat, and another is a gradual return during several beats following the premature beat (Fig 2, 3).

Another interesting finding is that high HPV existed in both occasional and frequent VPB rats, whereas high BPV only in frequent VPB rats. The result means that HPV is easier to be influenced by ventricular arrhythmia than BPV. In addition, there existed a close correlation between BPV and HPV, and the correlation coefficient was larger between HPV and VPB than between BPV and VPB, in both ventricular arrhythmia models. Taken together, these indicate that VPB-induced high BPV may be mediated at least partly by HPV. This notion is also supported by the literature data that heart rate fluctuations increased BPV in normal children[26].

BPV is increased in almost all hypertensive patients and animals[1-3]. This often leads to a confounded conception that alterations in BP and BPV are parallel. The present study showed that frequent VPB caused high BPV with unchanged BP level, ventricular tachycardia induced high BPV with the reduction of BP level, and there is no association between BPV and BP. These provide a good example to delineate that BPV is not necessarily dependent on the BP level. The facts were also demonstrated in other previous studies. Under physiological conditions, rabbits are known for their unstable BP, and when compared with rats, rabbits exhibited a higher BPV and a lower BP level[27]. In pathophysiological states of baroreflex interruption, BPV is markedly increased with no change in the average BP level after sinoaortic denervation or nucleus tractus solitarii lesions[9,10]. Finally, in pharmacological studies, BPV was significantly reduced by simultaneous infusion of phenylephrine and adenosine when the BP level maintained unchanged[28]. All above results confirm that BPV may be dissociated with the BP level.

In the present study, standard deviations of beat-to-beat systolic BP, diastolic BP, and HP values were used as the measures of systolic BPV, diastolic BPV, and HPV, respectively. They are conceptually simpler measures compared with those derived from power spectral analysis[19,25], and widely applied in the experimental and clinical studies[1-3,9,10,12,15,17,19,20]. Moreover, their clinical significance has been extensively explored[1,2,9,29]. MI operation in our study produced an average MI size of 27 % with an operation mortality of 30 %, similar to the previous reported results[13,14]. Since chronic MI rats exhibited a big difference in the occurrence of VPB, we divided them into three groups of no VPB, occasional VPB, and frequent VPB, and analyzed the data not only in divided groups but also in the whole population. Aconitine is a commonly used arrhythmo-

genic agent to produce various forms of ventricular arrhythmias (in order of occurrence: VPB, VT, ventricular flutter and ventricular fibrillation) with intravenous infusion at the certain concentration and speed[30]. Doses are very difficult to adjust for occasional VPB. Therefore, we did not observe the effects of occasional VPB in aconitine-induced ventricular arrhythmias. In addition, the effects of VT were studied without difficulty, to provide the informative hemodynamic data during the occurrence of VT.

Nonfatal ventricular arrhythmias were found in certain cardiovascular diseases, including hypertension[20], myocardial infarction[29], and chronic heart failure[18]. These ventricular arrhythmias such as VPB and VT may lead to cardiovascular instability. Lower heart rate variability has been as one of predictors for poor prognosis of MI patients[29]. However, the importance of higher heart rate variability is still unclear, although it was reported that heart rate fluctuations increased BPV in normal children[26]. Regarding high BPV, many studies have shown that high BPV is a risk factor involved in the hypertensive organ damage[1,2,9,15]. Both ventricular arrhythmias and high BPV were associated with left ventricular hypertrophy or target organ damage in hypertension[20]. We hypothesize that frequent ventricular arrhythmias may be secondary to the left ventricular hypertrophy, and may play additional contribution to high BPV, aggravating cardiac and extracardiac organ damage in hypertension. The clinical significance of arrhythmias related higher BPV in myocardial infarction and chronic heart failure remains unknown. Higher BPV may be a deteriorating factor in these diseases. Increased BPV can produce a greater variation in tissue perfusion. This may be harmful to ventricular tissue, especially to the ischemic ventricular tissue after MI. Cellular metabolism may be disturbed by such a variation. These may deteriorate cardiac damage. In chronic heart failure, either disease itself or digoxin-induced frequent ventricular arrhythmias may produce a potential increase in BPV, which may be extremely harmful to heart perfusion under cardiac dysfunction.

In conclusion, the current work presented a new factor influencing BPV; that is nonfatal ventricular arrhythmia of frequent VPB can lead to pressure lability. The provided data are valuable for further studying the clinical importance of ventricular arrhythmia-induced high BPV in certain cardiovascular diseases, and helpful for creating a new model of high BPV without sustained hypertension.

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Correction

Acta Pharmacol Sin. 2004 Apr; 25 (4): 458-61. Title: Thermal preconditioning protected cerebellar granule neurons of mice by modulating HSP70 expression. The animals should be rats not mice. The authors felt sorry to readers.