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## Effects of whole-body mechanical stimulation at double the heart rate on the blood pressure waveform in rats

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### Abstract

The effects of mechanical stimulation on hemodynamics, such as due to mechanotransduction in vascular endothelial cells, have been widely discussed recently. We previously proposed a resonance model in which the arterial system is treated as a pressure-transmitting system, and suggested that the application of external mechanical stimulation with frequencies near the heart rate (HR) or harmonics thereof can be sensed by the arterial system and induce hemodynamic changes. In this study, we monitored the effects of external mechanical stimulation at a frequency of double the HR on BPW (blood pressure waveform), HRV (HR variability) and BPHV (blood-pressure-harmonics variability) in rats. A motor beating a waterbed mattress was used to generate pressure variations of 0.5 mmHg to apply onto the rats. The experiments were performed on three groups of rats with different beating frequencies: (A) double the HR, (B) 5% deviation from double the HR and (C) 1.5 times the HR. The experimental procedure was a 15 min control period followed by application of the mechanical stimulation for 15 min and further recording for 15 min (OFF period). During the OFF period, the amplitude of the second harmonic in the BPW significantly increased by >5% in group A with decreased HRV and BPHV. The second harmonic increased less in group B, and decreased in group C. The increase in the second-harmonic amplitude in group A may be due to the filtering properties of the renal arterial structure. This mechanism could be used to improve the local blood supply into the kidneys, and hence provide a new treatment modality for some important diseases, such as renal hypertension or nephrosis.

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Keywords: blood pressure, regional blood flow, heart rate variability, blood pressure variability

(Some figures in this article are in colour only in the electronic version)

## 1. Introduction

### 1.1. Effects of mechanical stimulation on hemodynamics

The effects of mechanical stimulation on hemodynamics have been discussed widely from a microscopic view, and are attributable to mechanotransduction in endothelial cells of the arterial walls. Specific patterns of mechanical stimulation can modulate the gene and protein expression of various cells as well as the performance of different tissues, as can the administration of certain drugs, such as hormones or growth factors. This mechanism may involve a multitude of sensors, signaling molecules and genes (Shyy and Chien 1997, 2002), so many studies have focused on the cell and tissue levels (Davies 1995, Shyy *et al* 1994).

From a macroscopic view, a few studies have examined the effects on the entire body by applying non-contact mechanical stimulation with extremely large amplitudes (for example, 100 dB SPL ultrasonic waves) (Andren *et al* 1982, Danielsson and Landstrom 1985). Such large powers may have harmful effects, as monitored by increased heart rate (HR) variability (HRV) (Andren *et al* 1982), although it is difficult to determine whether this effect is attributable to mechanosensing or a psychological pathway. Some studies have found that BPV (blood pressure variation) can be changed by ventilation in an intense care unit (Pinsky 2003, Gunn and Pinsky 2001) and in neonates with respiratory disease (Amitay *et al* 1993), and it has been suggested that BPV can be used to monitor changes in preload responsiveness. Other studies have investigated the response to ventilation with synchronized external chest compression in the presence of acute ventricular failure (Pizov *et al* 1989). Exercise can be viewed as another form of mechanical stimulation, and O'Rourke *et al* (1993) found that the HR and stride rate were correlated in marathon runners who exhibited very large vertical movements.

### 1.2. BPW analysis and the resonance theory

Frequency information of different arterial beds within BPW has been reported previously. Wiener *et al* (1966) reported that the pulmonary circulation system had the strongest effect on the fourth harmonic within BPW. Our previous studies reported that ligating the renal, gastric, splenic or the superior mesenteric artery caused different harmonic variation profiles of BPW specifically (Young *et al* 1989, 1992).

Treating the arteries as a pressure–wave transmitting system, Lin Wang *et al* suggested that the arterial system has a resonant frequency around the HR. Due to radial oscillation of the elastic vessel wall, the arterial system resonates with the heartbeat to keep the transmission highly efficient due to the maximal efficiency of the arterial hydraulic impedance at resonance (Lin Wang *et al* 1991, 1997). In this conjecture, the resonant frequency of an artery can be represented as a combination of the physical parameters of the vessel wall (Lin Wang *et al* 2000). For example, an increase in the elastic modulus of the arterial wall will decrease the resonant frequency for the arterial system.

Dealing with the peripheral vascular beds in this conjecture, each arterial bed (such as an internal organ) is regarded as a linking unit to the main artery. This arterial bed–artery coupled system is forced to oscillate with the pressure pulse in the resonance frequencies which are related to the natural frequencies of the arterial bed and the main artery (Lin Wang *et al* 1991, Yu *et al* 1994). Pulse spectrum is the combined result of the influences from all the arterial

beds. The major resonance frequencies of the main artery and of the kidney's arterial system are suggested to be equal to and double the HR, respectively (Young *et al* 1989, 1992, Lin Wang *et al* 2000).

We hypothesized that the resonant frequencies dramatically influence the transmission efficiency of the arterial pressure wave, and hence the BPW. Destroying the resonance between the wave source and the load may lead to a lowered transmission efficiency for the BP wave transmission. For example, destroying the resonance between the heart beating and the main artery may increase the transmission impedance for the first harmonic within BPW from the heart into the main artery, and that between the heart beating and the renal arterial structure may increase the impedance for the second harmonic within BPW from the heart into the renal arterial structure (Young *et al* 1992, Lin Wang *et al* 2004, Yu *et al* 1994).

### 1.3. Effects of single-frequency mechanical stimulation on the arterial system

The assumption of the resonant frequency of the main artery equaling the HR is based on maximizing the propelling force of the heartbeat. It was suggested that this brings hemodynamic benefits such as minimal input impedance (for the heart looking into the main artery) and thus maximal blood supply to the terminals (Lin Wang *et al* 2004). Similarly, an external power applied at a frequency close to the HR may also be received maximally by the main artery due to similarities of wave-transmission properties between the external power and propelling force of the heartbeat. The arterial system can therefore be treated as a mechanical antenna for receiving external mechanical power (Hsiu *et al* 2003).

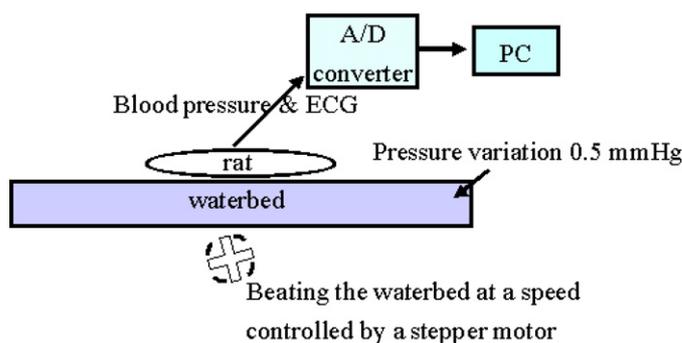
Based on this conjecture, we performed several experiments on rats to observe the effects of mechanical stimulation on several important hemodynamic parameters. By adjusting the external frequency, we forced the HR (and BP) to become faster (higher) or slower (lower) according to whether the external frequency was a little higher or lower than the rat's HR, respectively. We observed changes in HRV and the correlation between the HR and BP, and suggested that these changes represent optimal adaptation attempt by the cardiovascular system (Lin Wang *et al* 2004, Hsiu *et al* 2003).

Our previous studies were focused on the frequencies around the HR (Hsiu *et al* 2003). Based on the above conjecture, as well as the kidneys having a resonant frequency of double the HR, its amplitude is the second largest in the BPW *in vivo* (smaller only than the amplitude of the fundamental) (McDonald 1998, Milnor 1989). Moreover, among all organs, the kidneys receive the largest proportion of blood supply (Milnor 1989). Therefore, in this study we focused on the receiving ability of the kidneys and performed experiments on rats to observe the effects of external mechanical stimulation at different frequencies on hemodynamics.

## 2. Materials and methods

In this study, we applied mechanical stimulation at three frequencies in the following groups of rats to elucidate the specific effects of mechanical stimulation at a frequency of double the HR on hemodynamics: (1) in group A, the stimulus frequency was double each rat's control HR; (2) in group B, the stimulus frequency was either 5% higher or lower than double each rat's control HR and (3) in group C, the stimulus frequency was 1.5 times each rat's control HR. This protocol avoided interference on the BPW when applying external mechanical stimulation, such as due to variation in cardiac ejection or cardiac filling.

Experiments were performed on 14 male Wistar rats for group A (19 runs), 7 for group B (9 runs) and 7 for group C (9 runs), which weighed  $223.6 \pm 20.7$ ,  $238.6 \pm 22.1$  and  $222.9 \pm 20.2$  g (mean  $\pm$  SD), respectively. The rats were chosen by applying the following three



**Figure 1.** Experimental setup. Rats were laid on a waterbed in the prone position. The mechanical stimulation was generated by a stepper motor beating the waterbed so as to produce pressure variations of about 0.5 mmHg. The beating was performed at three frequencies in the following three groups of animals: (A) twice the control HR, (B) 5% deviation from twice the control HR and (C) 1.5 times the control HR. BP and ECG signals were recorded and sent to a PC for sampling and analysis.

criteria to ensure consistency: (1) body weight between 190 and 270 g, (2) control HR between 5.90 and 7.65 Hz and (3) SBP and DBP during the whole control periods between 65 and 135 mmHg.

### 2.1. Experimental application of mechanical stimulation

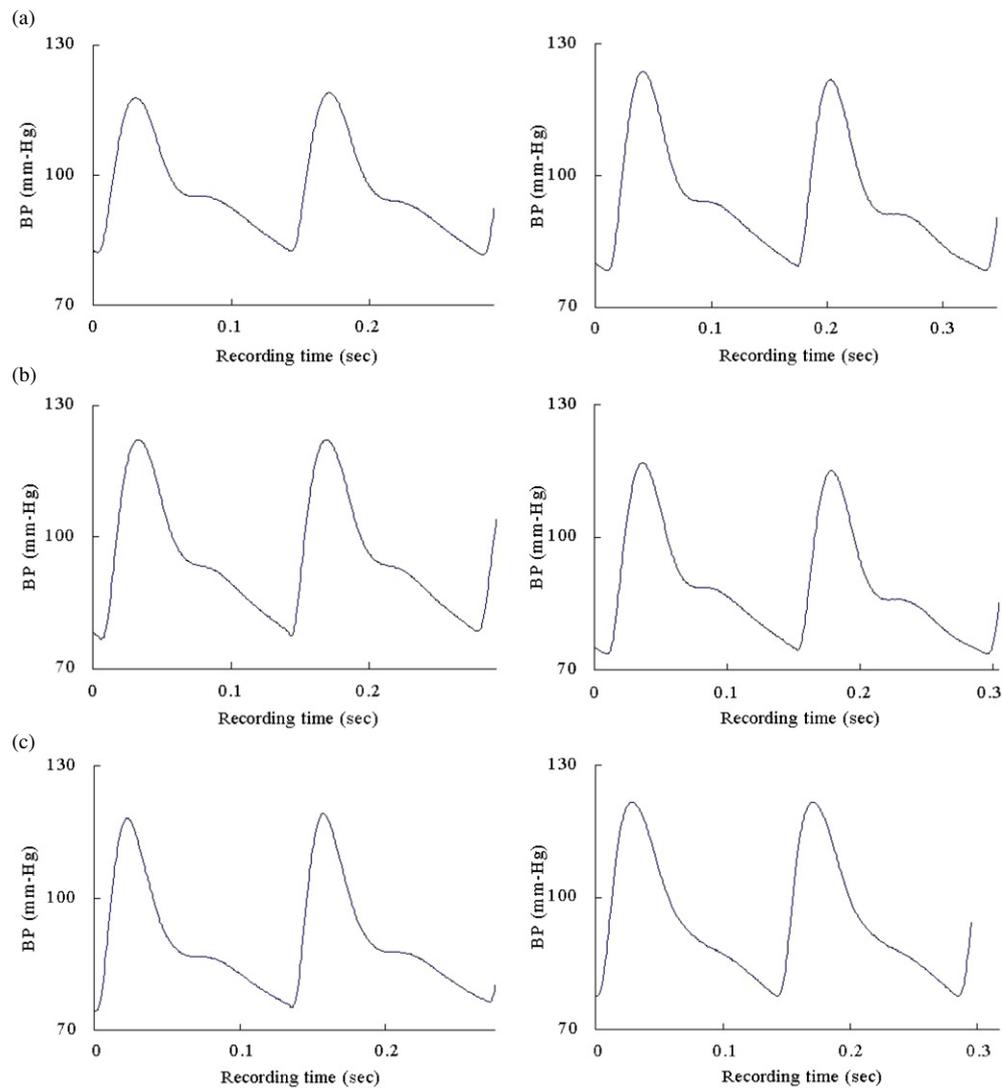
In our experiments, the rats were placed in a prone position on a waterbed (60 × 40 × 10 cm) that was mechanically stimulated by a stepper motor under the bed generating 0.5 mmHg single-frequency pressure variations. This pressure variation was transmitted to the rat lying on the waterbed by producing a 0.5 mm vertical displacement of the upper surface of the waterbed. The applied stimulation was so weak (0.5 mmHg) that we may exclude direct sensation and psychological effects (Hsiu *et al* 2003). A schematic of the experimental setup is shown in figure 1.

Rats were anesthetized with urethane (1.2 mg g<sup>-1</sup> body weight), and their abdominal aortic BP was measured through a polyethylene tube (2F, outer diameter 0.6 mm, filled with 0.9% NaCl and 0.3% heparin in water) inserted into the caudate artery. The pressure pulses were recorded by a catheter-tip pressure transducer (P10EZ transducer, RP-1500 Narco-Bio-System) and sampled at 500 Hz (Hsiu *et al* 2003). The heartbeat was monitored by the peak of the R-enhanced ECG signal (measured by wire electrodes penetrating the rats' palms; lead II, RA-LL, Cardisuny 501A, Fokoda). The ECG signal was tested to ensure that its measurement was not affected by mechanical vibration (Hsiu *et al* 2003).

After the surgery was completed, the following procedure was performed: resting for 1 h for the blood pressure to return to the steady state, recording a 15 min sequence of control data, applying mechanical stimuli (ON period) and recording for 15 min, and stopping mechanical stimuli (OFF period) and recording for 15 min.

Each rat could receive mechanical stimulation more than once. Between two experiments on the same rat, at least 40 min was allowed to ensure that the rat's physiological condition had returned to its control state, as evaluated by the HR and BP. During the control period (no mechanical stimulation), the rats could be maintained for >2 h with variations (deviations from the mean values) in the HR of <0.2 Hz (mean 0.09 Hz) and in the BP of <8 mmHg (mean 4.4 mmHg).

During the overall experimental process, the exposed tissues were kept moist with physiological saline. The waterbed and surrounding environment were maintained at 32 °C



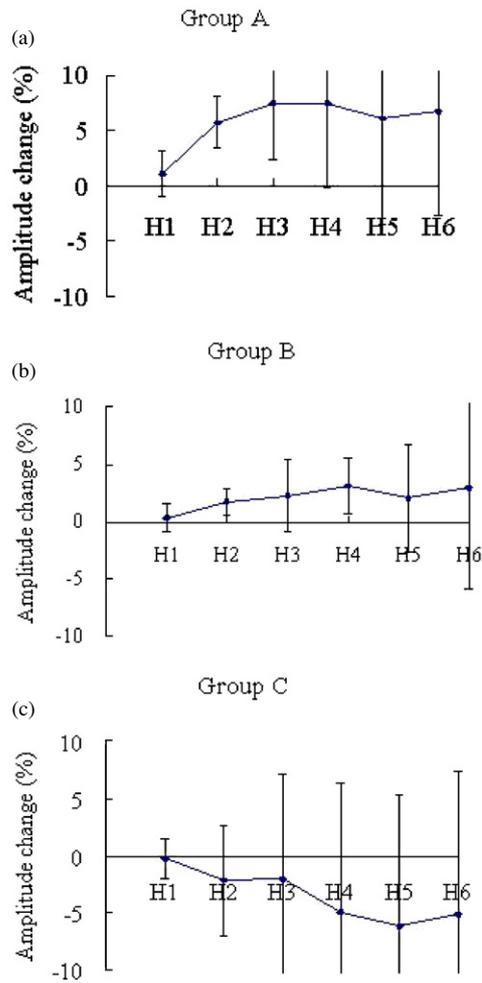
**Figure 2.** Typical time-domain BPW in three groups: (a) first run in rat 4 of group A, (b) first run in rat 3 of group B, and (c) first run in rat 2 of group C. Abscissa, recording time (seconds). Ordinate, BP (mmHg). Left and right are BPW in control and OFF periods, respectively.

using a lamp and a heat radiator. The investigation conformed to the *Guide for the Care and Use of Laboratory Animals* by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

## 2.2. Data analysis

HR and BP data were calculated as mean values over 1 min periods, and HRV data were calculated as the CV (coefficient of variance  $\equiv$  standard deviation (SD)/mean) of HR series in 1 min periods.

We calculated the variation of BPW spectra as the difference in the amplitude proportions of the harmonics between before- and after-force application (Hsu *et al* 2003) (shown in



**Figure 3.** Changes in the amplitudes of the harmonics in BPW: (a) group A ( $n = 19$ ), (b) group B ( $n = 9$ ) and (c) group C ( $n = 9$ ). Abscissa,  $H_n$ :  $n$ th harmonic. Ordinate, percentage changes in the proportions of the harmonics. Bars are SDs. Group A shows the most prominent increase ( $>5\%$ ) in the amplitude of the second harmonic ( $p < 0.0001$  by paired  $t$ -tests). Although still significant, group B exhibited a lower increase in the amplitude of the second harmonic. In contrast, the amplitude of the second harmonic decreased in group C.

figure 3), defined as

$$[C_n(T_1) - C_n(T_0)] / (C_n(T_0))$$

where  $T_1$  is the ON period,  $T_2$  is the OFF period and  $T_0$  is the control period before applying mechanical stimulation, and  $C_n$  is the average value during the whole period for the amplitude proportion of the  $n$ th harmonic =  $A_n/A_0$  for  $n = 1$  to 6, where  $A_n$  is the amplitude of the  $n$ th harmonic of BPW and  $A_0$  is the dc component of the pulse spectrum. For example,  $C_2(T_1)$  is the average amplitude proportion of the second harmonic in the ON period.

BPHV data were calculated as the SD of the proportions of the first to the sixth harmonics in BP in 1 min periods. For all statistics, the effects were considered significant when  $p < 0.05$ .

**Table 1.** Detailed data for group A with the frequency of the external mechanical stimulus located at exactly double the control HR, for 19 experiments on 14 rats. Body weight (BW) is in grams, HR and Diff\_HR are in hertz and BP (DP and SP) is in millimeters of mercury. '0', '1' and '2' indicate the values during the control, ON and OFF periods, respectively. Diff\_HR $x$  is defined as the absolute value of (HR $x$ -HR0).

Rat	BW	HR0	HR1	HR2	Diff_HR1	Diff_HR2	DP0	SP0	DP1	SP1	DP2	SP2
1	220	6.18	6.14	6.19	0.04	0.02	76.0	121.2	79.7	127.9	76.5	120.2
		6.29	6.34	6.37	0.05	0.07	80.3	123.7	74.7	123.8	76.1	127.0
2	195	6.89	6.79	6.77	0.11	0.12	68.4	123.8	68.8	118.9	68.7	116.8
		6.67	6.55	6.65	0.12	0.02	71.0	120.7	70.9	123.8	72.4	116.7
3	195	7.40	7.29	7.34	0.11	0.05	67.5	117.5	66.3	110.2	70.2	109.1
4	230	7.10	7.02	7.06	0.08	0.04	81.7	117.9	75.6	119.6	79.3	122.0
		7.17	7.19	7.20	0.02	0.04	84.0	123.8	76.9	120.3	79.2	120.8
5	205	6.45	6.59	6.48	0.14	0.03	73.2	116.8	74.2	120.8	71.6	117.2
		7.06	7.06	6.98	0.00	0.08	70.9	111.0	74.6	115.2	70.4	106.8
7	210	6.46	6.50	6.38	0.04	0.08	68.4	112.6	66.2	112.2	69.8	108.2
8	230	6.51	6.59	6.48	0.08	0.02	70.2	115.5	71.9	116.7	72.0	110.8
9	215	7.35	7.42	7.29	0.07	0.06	75.7	122.6	75.9	121.7	77.6	119.1
10	230	6.14	6.10	6.21	0.03	0.07	80.1	126.0	80.4	126.1	80.2	125.5
11	240	7.23	7.12	7.17	0.11	0.06	73.7	122.2	74.1	123.6	75.4	120.0
12	205	6.77	6.89	6.86	0.12	0.09	75.5	120.6	73.6	122.9	71.8	122.0
		6.55	6.62	6.53	0.08	0.02	81.3	122.6	77.5	121.0	75.1	125.6
13	250	7.13	7.15	7.15	0.02	0.01	71.6	114.2	69.4	117.8	67.3	116.8
		7.01	7.04	6.93	0.02	0.09	74.1	117.3	73.2	123.7	71.7	117.0
14	270	6.96	7.01	7.03	0.04	0.06	73.9	130.1	72.3	126.4	75.0	124.7

**Table 2.** Detailed data for group B with the frequency of the external stimulus deviating by 5% from double the control HR, for nine experiments on seven rats. BW is in grams, HR and Diff\_HR are in hertz and BP is in millimeters of mercury. '0', '1' and '2' indicate the values during the control, ON and OFF periods, respectively. Diff\_HR $x$  is defined as the absolute value of (HR $x$ -HR0).

Rat	BW	HR0	HR1	HR2	Diff_HR1	Diff_HR2	DP0	SP0	DP1	SP1	DP2	SP2
1	265	6.19	6.34	6.37	0.15	0.17	78.1	125.7	76.7	125.8	79.3	128.4
2	250	6.67	6.95	7.05	0.28	0.38	74.4	119.7	72.9	122.8	72.0	117.1
3	210	7.30	7.19	7.04	0.11	0.25	77.2	122.5	73.3	115.2	73.5	115.5
		7.20	7.26	7.01	0.06	0.20	71.1	113.6	72.0	114.4	71.6	112.2
4	235	6.95	6.96	6.70	0.02	0.24	78.0	120.2	77.6	120.6	78.2	120.6
		7.07	7.19	7.20	0.12	0.14	79.2	123.8	76.9	120.3	83.0	122.2
5	215	7.36	7.22	7.09	0.15	0.27	81.6	122.6	79.9	121.7	78.7	120.5
6	225	6.77	6.89	6.96	0.12	0.19	76.8	120.6	78.6	122.9	79.5	123.4
7	270	6.96	7.11	7.23	0.14	0.26	80.0	125.1	77.3	126.4	77.9	126.1

### 3. Results

#### 3.1. HR and BP

The HR and BP data for each rat in groups A–C are listed in tables 1–3. The HRs in group A ( $n = 19$ ) were  $6.81 \pm 0.38$ ,  $6.81 \pm 0.37$  and  $6.79 \pm 0.36$  Hz (mean  $\pm$  SD) before, during and after the mechanical stimulation, respectively; in group B ( $n = 9$ ), they were  $6.94 \pm 0.34$ ,  $7.01 \pm 0.27$  and  $6.96 \pm 0.25$  Hz; and in group C ( $n = 9$ ), they were  $7.05 \pm 0.38$ ,  $6.89 \pm 0.26$  and  $6.88 \pm 0.25$  Hz.

In tables 1–3, we define Diff\_HR1 (ON-control HR difference) as the absolute value of {ON HR (during the stimulation) – control HR} and Diff\_HR2 (OFF-control HR difference)

**Table 3.** Detailed data for group C with the frequency of the external stimulus equal to 1.5 times the control HR, for nine experiments on seven rats. BW is in grams, HR and Diff\_HR are in hertz and BP is in millimeters of mercury. '0', '1' and '2' indicate the values during the control, ON and OFF periods, respectively. Diff\_HR $x$  is defined as the absolute value of (HR $x$ –HR0).

Rat	BW	HR0	HR1	HR2	Diff_HR1	Diff_HR2	DP0	SP0	DP1	SP1	DP2	SP2
1	200	7.09	6.59	6.77	0.51	0.32	71.7	117.8	75.8	122.9	72.4	119.2
		7.11	7.04	7.35	0.07	0.24	69.6	118.3	69.3	117.1	71.5	120.2
2	215	7.32	7.03	6.87	0.29	0.44	73.7	116.4	75.2	118.2	77.0	120.6
		7.36	7.06	6.68	0.30	0.68	70.4	111.0	74.6	115.2	71.9	112.2
3	220	7.09	7.39	6.69	0.30	0.40	76.5	120.4	78.3	121.7	76.6	117.9
4	235	6.70	6.94	6.60	0.24	0.10	69.1	121.1	72.7	123.5	74.5	124.6
5	240	7.23	6.82	6.97	0.41	0.26	79.4	123.2	78.1	124.6	78.7	126.4
6	195	7.45	6.52	7.28	0.92	0.17	77.1	124.6	80.5	127.0	80.3	131.0
7	255	6.13	6.65	6.75	0.52	0.61	69.3	117.2	73.4	122.8	72.6	122.2

as the absolute value of {OFF HR (after turning off the stimulation) – control HR}. Diff\_HR1 was  $0.07 \pm 0.04$ ,  $0.13 \pm 0.07$  and  $0.39 \pm 0.23$  in groups A–C, respectively, and Diff\_HR2 was  $0.05 \pm 0.03$ ,  $0.23 \pm 0.07$  and  $0.36 \pm 0.18$ . Both Diff\_HR1 and Diff\_HR2 were larger in group B than in group A, and significantly larger in group C than in groups A and B (all  $p < 0.0001$  by  $t$ -test). In some cases of group C, the HR differences were larger than 0.5 Hz.

The systolic BPs (SBPs) in group A ( $n = 19$ ) were  $120.0 \pm 4.7$ ,  $120.7 \pm 4.6$  and  $118.2 \pm 5.8$  mmHg before, during and after the mechanical stimulation, respectively; in group B ( $n = 9$ ), they were  $121.5 \pm 3.4$ ,  $121.1 \pm 3.9$  and  $120.7 \pm 4.8$  mmHg; and in group C ( $n = 9$ ), they were  $118.9 \pm 3.8$ ,  $121.4 \pm 3.6$  and  $121.6 \pm 5.1$  mmHg. The diastolic BPs (DBPs) in group A ( $n = 19$ ) were  $74.6 \pm 4.8$ ,  $73.5 \pm 3.9$  and  $73.7 \pm 3.7$  mmHg before, during and after the mechanical stimulation, respectively; in group B ( $n = 9$ ), they were  $77.4 \pm 3.0$ ,  $76.1 \pm 2.6$  and  $77.1 \pm 3.6$  mmHg; and in group C ( $n = 9$ ), they were  $73.0 \pm 3.6$ ,  $75.3 \pm 3.2$  and  $75.1 \pm 3.0$  mmHg.

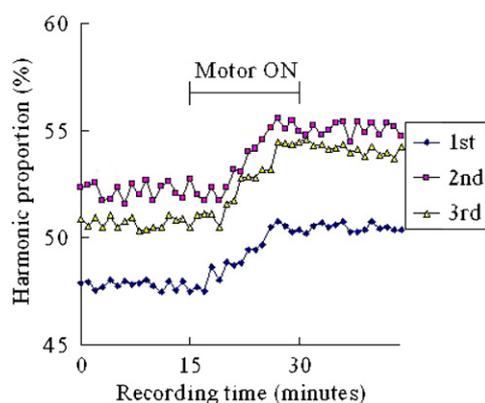
The BP changed only slightly with mechanical stimulation, but in the following situations the change was significant. In group A, the OFF SBP (mean SBP after turning off the stimulation) was significantly lower than the control SBP ( $p < 0.05$ ). In group C, the ON DBP, ON SBP and OFF SBP were all significantly higher than their control values (all  $p < 0.015$ ).

### 3.2. Variation of BPW spectra

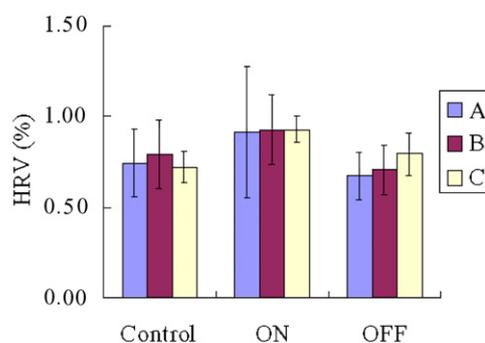
In figure 3(a), it is evident that the amplitude proportions of all the harmonics (H1–H6) increased significantly in group A (all  $p < 0.04$ ). The amplitude proportion of the second harmonic is at least twice that of higher harmonics. The amplitude variation in group B is shown in figure 3(b). Similar to figure 3(a), the amplitude proportions of all harmonics increased, but only the changes in H2 and H4 were significant ( $p < 0.01$ ).

The amplitude variation in group C is shown in figure 3(c). In contrast to figures 3(a) and 3(b), the amplitude proportions of all harmonics except H1 decreased with mechanical stimulation. The SDs of the amplitude changes (see figure 6) were all larger than those in groups A and B, and the amplitude changes were all non-significant ( $p > 0.15$ ).

Comparing results between the three groups, the spectra alterations were similar in groups A and B, but the changes were smaller and less significant in the latter. Spectrum alterations in group C were opposite to those in groups A and B, with larger SDs for H2–H6 (see also figure 6).



**Figure 4.** Typical time-domain amplitude proportion for the second harmonic in three typical cases in group A. The first line is the second run in rat 2, the second line is the run in rat 7 and the third line is the run in rat 10. Abscissa, recording time (seconds). Ordinate, amplitude proportion of the second harmonic (%). The mechanical stimulation was applied for 15 min, and the amplitude proportion of the second harmonic showed gradual increase in the ON period.

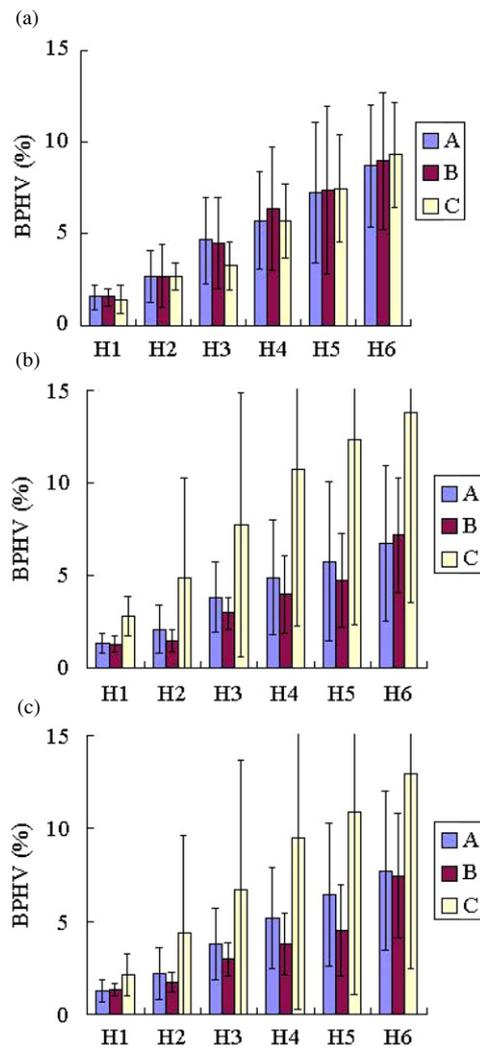


**Figure 5.** Changes in HRV values in the three groups. Abscissa, HRV values during the control, ON and OFF periods, respectively. Ordinate, HRV values (%)  $\equiv$  SD/mean of HR series in each 1 min period. All three groups exhibited similar HRV values during the control period. During the ON period, the HRV increased in all three groups, with group C exhibiting the largest increase. Compared to the HRV values during the control period, the HRV in groups A and B were lower during the OFF period, while group C exhibited a higher HRV. All changes were significant by paired *t*-tests ( $p < 0.02$ ).

### 3.3. HRV and BPHV

The 15 min HRV and BPHV values during the control, ON and OFF periods in all rats in each group are shown in figures 5 and 6. The HRVs were  $0.75 \pm 0.19$ ,  $0.91 \pm 0.36$  and  $0.67 \pm 0.13$  (%) before, during and after the mechanical stimulation, respectively, in group A ( $n = 19$ );  $0.79 \pm 0.19$ ,  $0.93 \pm 0.19$  and  $0.70 \pm 0.14$  (%) in group B ( $n = 9$ ) and  $0.72 \pm 0.09$ ,  $0.93 \pm 0.07$  and  $0.79 \pm 0.12$  (%) in group C ( $n = 9$ ).

Comparing HRV between the three periods (see figure 5), all three groups showed increased HRV during the ON period (compared to the control period), with this being the largest in group C. In the OFF period, groups A and B showed decreased HRV compared to the control value, while group C exhibited a lower increase in HRV than during the ON period. All HRV alterations stated above were significant by paired *t*-test ( $p < 0.02$ ).



**Figure 6.** Changes in BPHV values in the three groups during the (a) control, (b) ON and (c) OFF periods. Abscissa,  $H_n$ :  $n$ th harmonic. Ordinate, BPHV values  $\equiv$  SD of BP amplitude for the first-to-sixth harmonics in each 1 min period. All three groups exhibited similar BPHV values during the control period. During both the ON and OFF periods, the BPHV decreased in groups A and B and increased in group C.

During the control period, the rats were selected by a mean second-harmonic BPHV of  $<5\%$  and a sixth-harmonic BPV of  $<15\%$ . In figure 6, the mean second-harmonic BPHV values were 2.68%, 2.70% and 2.37% during the control period; 2.06%, 1.47% and 4.19% during the ON period and 2.24%, 1.74% and 3.78% during the OFF period for groups A–C, respectively. The mean sixth-harmonic BPHV values were 8.71%, 8.97% and 9.13% during the control period; 6.71%, 7.18% and 13.01% during the ON period and 7.72%, 7.48% and 11.81% during the OFF period for groups A–C, respectively. The mean second- and sixth-harmonic BPV values for the control period were all  $<3\%$  and  $<10\%$ , respectively.

In groups A and B, BPHV decreased during both the ON and OFF periods (compared to the control period), with a smaller decrease during the latter. However, in group C, the

BPHV increased during both the ON and OFF periods, with a larger increase during the former.

## 4. Discussion

### 4.1. Changes in BP spectra and HR in group A

The results for HR, BP, HRV, BPHV and BPW spectra indicate that the physiological control conditions for the three groups were quite similar, but the effects of mechanical stimulation differed significantly. For variations in BPW spectra, group A exhibited the largest relative increase in the second harmonic. The largest relative increase for group B was also in the second harmonic, but the increase was smaller than in group A. In group C, the amplitude of the second harmonic decreased. Since the second harmonic has the largest amplitude among the second to the sixth harmonics (McDonald 1998, Milnor 1989), its absolute changes were also the largest in groups A and B.

Here we suggest a possible mechanism for the different changes of BPW between these three groups. As conjectured in the introduction, the renal arterial structure acts as an antenna for mechanical stimulation at a frequency of double the HR. Therefore, we suggest that when we applied external mechanical stimulation at a frequency of exactly double the rat's HR in group A, the renal arterial system might have received this external power with high efficiency since its resonant frequency is near to that of the external stimulus. This may account for the largest amplitude increase in the second harmonic in group A.

In our previous report (Hsiu *et al* 2003), we suggested some possible prerequisites to ensure that the amplitude of mechanical stimulation was sufficient to allow the sensing of the external power and the induction of the changes of the hemodynamic parameters, including (1) sufficient external power, (2) the reception and sensing of the external power by the arterial system and (3) the heart adjusting when it senses external power. The output power of the human left ventricle is only 1.7 W (Milnor 1989), and after distribution to all organs and vascular beds for the entire body, each vascular bed receives only a tiny fraction of this. Although we stimulated with a pressure of only 0.5 mmHg in our experiments, the external power received at each vascular bed can still be substantial compared to the power from a heartbeat if appropriate media are used to reduce transmission loss (for example, a waterbed in Hsiu *et al* (2003)), and therefore the first prerequisite may still be achieved. With regard to the mechanotransduction mechanism in the endothelial cells of the arterial wall, it is widely known that the changes in shear stress or other methods of mechanical stimulation can alter the biochemical response in the vascular wall endothelial cells. An applied shear stress as small as around 12 dynes  $\text{cm}^{-2}$ , which is much smaller than (about one-fiftieth of) the 0.5 mmHg (667 dynes  $\text{cm}^{-2}$ ) pressure variation used here, is sufficient to induce a significant biochemical response (Shyy *et al* 1994).

The second prerequisite may be achieved by treating the arterial system as a mechanical antenna with a resonant frequency, as stated in the introduction. After the power enters the arterial system, this may be sensed by mechanotransduction in the endothelial cells (Shyy and Chien 1997, 2002) or baro-receptors.

The third prerequisite may also be achieved since the cardiovascular system may respond to external power by ventricular–arterial adaptation so as to find its optimal working condition. The optimization strategy of the heart is often considered to ensure sufficient blood supply and minimal cardiac energy expenditure (Milnor 1989). Under this constant mechanical stimulation with sufficient power based on the resonance equation stated in the introduction, it was suggested that the renal arterial system may modify its vascular elastic properties (such

as elasticity and radius) to adjust its resonant frequency to match the frequency of the external mechanical stimulation, so as to maximize the power received by the renal arterial system (we called this condition ‘frequency matching’ in our previous work (Lin Wang *et al* 2004)).

In the resonance phenomenon in fundamental physics, if the stimulating frequency from the wave source approaches the resonance frequency, the receiving efficiency for the receiver (such as a antenna) will be increased dramatically. It implies that in group A with external frequency nearly double the HR, the HR and the arterial elasticity only have to be changed a little around their original states to achieve the frequency-matching condition stated above. Since the adjustment is made near the original physiological state, the cardiovascular system only needs to pay a little effort to find a new beating mode. It may be what the cardiovascular system does to adapt to external mechanical stimulation. Through resonance phenomenon, we suggest that this adaptation may enhance the receiving efficiency not only for the pulse wave from the heart to the arterial system (including the main artery and renal arterial structure), but also the external mechanical power into the arterial system (Lin Wang *et al* 2004).

In summary, when applying the external mechanical stimulation at a frequency of double the HR, a possible way for the heart to adjust its rate is by beating it closer to half of the external frequency so that the propelling power from the heart and the external stimulus may work together to enlarge the PP arriving at the renal microcirculation.

By this conjecture, we also suggest an explanation why the effect can last after the removal of external mechanical stimulation. After turning off the stimulating motor, we suggest that the overall cardiovascular system (including the heart and the arterial system) may still keep working in this ‘frequency-match’ mode for a while so that the renal arterial structure may retain a high transmission efficiency for external mechanical stimulation at double the HR, also improving the receiving efficiency of components with the same frequency within the BPW (that is, the second harmonic) generated from the heart. This would result in increasing of the amplitude of the second harmonic, which lasted for about 15 min even after the removal of external mechanical stimulation, similar to the effects on HR seen in our previous work (Hsiu *et al* 2003).

Changes of HRV and BPHV in the ON and OFF periods illustrated that the cardiovascular system responded to the external stimulus. Besides, more evidence for the participation of cardiovascular adaptation is that the changes in the harmonics were gradual rather than abrupt (as shown in figure 4). It took several minutes for a vessel to adjust its elasticity or radius such that each harmonic within BPW reached a steady state (2–13 min for the second harmonic in all trials of our experiments). If there was no participation of such an adaptation after switching on (or switching off) the motor, the change in the harmonic should be abrupt due to the sudden reception (or loss) of the external power, and this was not observed in our experiments.

#### *4.2. Changes in the BP spectra in groups B and C*

Comparing the different effects on BPW between these three groups, we may get more support about the conjecture in the resonance concept. For group B, the applied external frequency deviated slightly (by around 5%) from the rat’s HR. By the resonance concept, this will lower the efficiency at which the external power is received by the renal arterial system. When applying external mechanical stimulation in group B, we suggest that the cardiovascular system had to expend more part of its effort than in group A to adjust the HR to catch up with the external frequency. Only after that can the cardiovascular system start to do the adaptation to achieve the frequency matching as in group A, and therefore less attention can be paid to utilize the external power. This reduced the receiving efficiency of the arterial system for

stimulation at double the HR, so the increase in the amplitude of the second harmonic was less in group B than in group A.

For group C, the external frequency was 1.5 times the HR. Most of the power in the BPW spectrum was at harmonics of the stimulus frequency (i.e. integer multiples of the HR) (Milnor 1989). Since the main artery and the renal arterial system have resonant frequencies of the HR and double the HR, respectively, we suggest that the application of a constant external mechanical stimulation at a frequency of 1.5 times the HR presents the cardiovascular system with two choices: (1) speed up the HR toward the stimulus frequency to enhance the receiving efficiency of the fundamental, which is considered to be correlated with minimal input impedance of the main artery (Lin Wang *et al* 1997, 2000) or (2) slow down the HR to improve the receiving efficiency of its second harmonic, which is considered to be correlated with the renal arterial structure (Young *et al* 1989, 1992, 1994).

When the external mechanical stimulation was applied on rats in group C, we suggested that these two conflicting choices make the cardiovascular system keep trying to achieve frequency matching, but were not able to find a new beating mode as in groups A and B. This meant that the cardiovascular system was unable to improve the efficiency of receiving the external power at double the HR. Therefore, after turning off the stimulating motor, the renal arterial system received the second-harmonic component in the propelling force generated from the heart at a lower efficiency, so the BP spectra showed a decrease in the amplitude of this harmonic.

#### 4.3. Conclusions and future work

Here we have shown that the application of weak external mechanical stimulation with a frequency of double the HR significantly increases the amplitude of the second harmonic within the BPW of rats. Earlier we hypothesized that the kidney exhibits a filtering property in the frequency domain by having a resonant frequency near to double the HR, which may improve the transmission efficiency for the second harmonic within BPW into the kidney (Young *et al* 1989). In our previous work, we suggest that the enlarged second harmonic within BPW may bring a larger PP into the renal microcirculatory region, resulting in larger openings on the arteriole's wall, and hence more blood pass through to provide a greater blood supply (Jan *et al* 2000). Therefore, an understanding of the underlying mechanism may help in the development of techniques to improve local blood supply into the kidneys, and hence provide new treatments for some important diseases, such as renal hypertension or nephrosis.

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