EFFECTS OF WEAK EXTERNAL MECHANICAL FORCE STIMULATION ON THE HEART RATE VARIABILITY OF RATS

HSIN HSIU^{1,3}, PIN-TSUN CHAO^{2,3}, TSE-LIN HSU³, WEI-CHEN HSU^{3,4}, WEI-KUNG WANG^{2,3}

¹Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan

²Department of Electrical Engineering, National Taiwan University, Taipei, Taiwan

³Biophysics Lab., Institute of Physics, Academia Sinica, Taipei, Taiwan

⁴Zhongxiao Municipal Hospital, Taipei, Taiwan

ABSTRACT

Motivation: The heartbeat is driven by electric signals generated inside the heart, the cardiac conducting system plays an important role. Although there are pharmacological and electrical methods working on this conducting system, effect of mechanical stimulation has rarely been discussed. **Methods:** We used waterbed (size 60×40×10 cm) as a media to study the heart rate variability (HRV) affected by beating the bed with weak mechanical force with 0.5-mm-Hg amplitude. The waterbed is specially designed to raise the transmission efficiency for sound wave. **Results:** Among 7 studies on 5 rats, there were almost no changes in diastolic pressure, systolic pressure and heart rate, but average of CV (coefficient of variance) of 15-minute heart rate sequences increased from the control value 0.0098 ± 0.0023 (mean $\pm$ SD) to 0.0119 ± 0.0032 (mean $\pm$ SD) during the stimulation and decreased to 0.0078 ± 0.0020 (mean $\pm$ SD) in 15 minutes after the stimulation [*p* values (paired *t*-test, both compared with the control) < 0.006 and < 0.0007 respectively]. **Discussion:** Here we show that such a weak mechanical stimulation was sufficient to affect the circulatory system. Since the effect is not directly acting on the conducting system, this small power may influence the arterial system through resonance mechanism.

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1. INTRODUCTION

The beating of the heart can be affected by many factors in the body, such as body size, aging, or exercise. It can also be changed by external environment such as temperature. Since the heartbeat is driven by electric signals generated inside the heart, the cardiac electric conducting system (including SA

node, AV node and conducting fibers) plays an important role [1]. The two clinical methods to change the heart rate: pharmacological and non-pharmacological methods, both work on this conducting system [2].

Pharmacologically, drugs are used to tune the activities of ANS (autonomic nerve system) to alter the heart rate [3]. Non-pharmacological methods are referred to electric methods [2], such as pacemakers and electric shock in first-aid procedure to recover patients from fibrillation. Some researchers had attempted to analyze the heartbeat sequence in order to control it. For example, A. Garfinkel [4] took heartbeat interval sequence as chaotic, extracted the characteristic parameters, and tried to convert the arrhythmia to periodic beating with electric stimulation. All these methods exploit their influences

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Correspondence: Hsin Hsiu, Professor

Department of Electrical Engineering, Yuan Ze University, 135 Yuan-Tung Rd., Chung-Li, 320, Taoyuan, Taiwan

E-mail: hhsiu@saturn.yzu.edu.tw

through the conducting system.

1.1 Heart Rate Variability

The heartbeat time sequence is approximately periodic with quite a number of irregularities [5-6]. These irregularities were found to be chaotic, and the magnitude of variation τ HRV (heart rate variability) was shown to correlate with the ANS activity [7]. Following this concept, many indexes were deduced: in time domain, differences of SD (standard deviation) and CV (coefficient of variance) were shown to be correlated with pathology or aging [7]. In frequency domain, HF (high-frequency) component and LF (low-frequency) component of interbeat interval spectrum correspond to sympathetic and vagal tones respectively [8-10]; LF/HF ratio assesses the state of sympathetic-vagal balance [11]. Influences of age, exercise, electric beating or different drugs were also discussed widely, however, effect of mechanical stimulation has rarely been discussed.

Loss of normal variability in heart rate sequence often means unhealthy, therefore we can observe changes of HRV to monitor effect of weak sound wave on hemodynamics. For example, HRV is decreased in aged people as well as in patients with high risk of sudden cardiac death [12]. The effect of applying 100-dB ultrasound is also defined "chronic" by similar concept [13].

1.2 Hemodynamic Point of View

The total mechanical work of the left ventricle for man is only 1.7 Watt [14], which is about the power of a small toy car's motor. It impresses us with its extremely high efficiency to distribute the blood to such a large body (≈ 70 kgw). Most hemodynamic theories nowadays will introduce large impedance and will inevitably lower the arterial transmission efficiency. For example, the Poiseuille equation describes the ratio of pressure gradient to flow as "vascular resistance", a measure of the opposing property to flow of this system [15-16]. In electric analog, the blood pressure corresponds to the electric voltage, the blood flow to the electric current, and therefore the vascular resistance is analogous to a pure electric resistance (See Fig.1a and Theory Part 1).

Take Womersley model as another example, its derivation starts from Navier-Stokes equations, in which the involving forces are viscous and inertial ones. In electric analog for a segment of artery, these two forces can be analogous to a resistance and an inductance in series [15-16] (See Fig.1b and Theory Part 2). The Windkessel model describes the exponential elastic recoil of the vessel wall as a RC-discharging-like procedure. Therefore its electric analog composes of a resistance and a capacitance in

series [15-16] (See Fig.1c and Theory Part 3). All these models have large impedance and therefore cannot explain this high transmission efficiency of the arterial system.

According to the electric circuit theory, the only solutions to decrease the impedance in the Womersley model are to add capacitances to the circuit to achieve resonance, either in series or in parallel form (See Fig.1d). This resonance frequency further synchronized with the cardiac beating frequency will significantly enhance the transmission efficiency and let the small energy generated by the left ventricular distribute blood to the whole body.

Unlike other hemodynamic theories that treat the artery as flow pathways, in our conjecture, the artery works as a pressure wave delivering system, same as the transmission line in the alternating current system which transmits electric power through high-voltage-low-current design. Based on the radial dilatation of the arterial wall, the capacitance in series spontaneously shows up in the electric analog; while coupling of organs contribute additional capacitances in parallel (See Fig.1d and Theory 4, 5), the optimal resonance was thus achieved. The heart is as an ultra-low-power impulse generator, the artery with the organs is a well-designed high-efficiency transmission line, and the whole arterial system resonates with the heartbeat to keep the transmission efficient [17-24].

1.3 Arterial System as a Mechanical Antenna

If we send an external sound wave synchronized to the heartbeat into the arterial system through an impedance-matched media τ water, the energy may easily be absorbed by the resonant system τ the arterial system. As stated above, the arterial system is like a broadcast-receiving antenna, but in mechanical form. It can receive mechanical signal with frequency synchronizing the heart rate, just like it is driven by the heartbeat. This illustrates that we may affect the hemodynamics with very small mechanical stimulation, under the situation that interface between wave source and the tissue achieves impedance-match for sound wave transmission. Here we designed this experiment to verify it.

(1) choice of transmitting media

The effect of sound wave on the circulatory system has been discussed, but most are focused on those with large energy. For example, many researches used 100-dB ultrasonic wave as a non-contact stimulus and observed decrease of HRV (usually viewed as chronic effect) [13].

In these previous studies, the sound wave is transmitted through the air. The air-body interface will dramatically reduce the transmission efficiency of the sound wave and thus the effective received energy for

the experiment animals. It may be the reason why large amplitude stimulation must be used to induce significant hemodynamic changes.

In the ultrasound image, the gel is widely used to reduce the air gap and achieve impedance match so that the ultrasound wave can penetrate into the body with high efficiency. Here we use similar concept by applying the sound wave through the waterbed as a media to raise the transmission efficiency of the sound wave. Since the waterbed is filled with water, which is the main composition of the body, the physical properties (such as density) for the waterbed and the animal body are alike. It will help the impedance match for the sound wave. In this way, sound wave with small amplitude (0.5 mm-Hg in our experiment) may go into the body and be sufficient to affect the cardiac rhythm.

(2) synchronized beating frequency

Also in these previous studies, the frequency of the stimulation is irrelevant with the heart rate. Since the heart has a very small output power of 1.7 Watt, the applying sound wave may disturb the small energy that distributes the blood to the whole body. That may partly account for the observed chronic effects.

From the resonance theory, the aorta owns a resonance frequency according to the elastic properties of the aortic wall. The heart beats this rhythm to utilize the resonance phenomenon so that the blood pressure wave can reach the terminals with high transmission efficiency. Similarly, in order to raise the transmission efficiency of the external sound wave, the best strategy is to tune its frequency to be close to the heart rate of the recipient animal.

Besides, the heart rate of the rat is outside its auditory range, the small amplitude of our sound wave can also help to exclude the interference of the sensory perception, and thus prevent participation of psychological effects.

2. THEORY

2.1. Electric Analog of Poiseuille Equation

In Poiseuille equation, the relation between the pressure gradient and the flow along a tube can be described by:

$$Q = \frac{\pi^4 \Delta P}{8\eta L}$$

Q: volume rate of flow, ΔP : pressure gradient,
r: inner radius ; L: length of the tube;
 η : fluid viscosity

To derive the electric analog model, if we replace

ΔP by V (electric voltage), Q by i (electric current), we can define R (vascular resistance) by:

$$R = \frac{\Delta P}{Q} = \frac{8\eta L}{\pi^4}$$

Therefore, the electric analog of Poiseuille equation can be represented by a pure resistance (See Fig. 1A).

2.2 Electric Analog of Womersley Model

The Womersley model was derived from the Navier-Stokes equation. In its derivation, radial velocity and nonlinear terms are discarded, and only the longitudinal pressure gradient is considered. Consequently, the Navier-Stokes can be reduced to:

$$-\frac{dP}{dx} = \rho \left(\frac{dw}{dt} \right) - \eta \left(\frac{d^2 w}{dr^2} + \frac{1}{r} \frac{dw}{dr} \right) \quad (E2.1)$$

ρ : fluid density, η : fluid viscosity,
w: longitudinal velocity ;
x: longitudinal, r: radial;

From the definition in electric analog:

$$V = L \frac{di}{dt} \quad (E2.2)$$

$$\Rightarrow \Delta P = -\frac{dP}{dx} = L \frac{dQ}{dt}$$

From $Q = \omega A$ (A: cross section area), the first right term can be turned to:

$$\Delta P = \frac{\rho}{A} \left(\frac{dQ}{dt} \right) \quad (E2.3)$$

When we compare (E2.2) and (E2.3), if we define $L = (\rho / A)$, these two equations are identical. Therefore the first right term can be corresponding to an inductance in electric analog, which represents the inertial force of a small piece of fluid.

As for the second right term, from the definition of resistance (R) in electric analog:

$$V = Ri \Rightarrow \Delta P = -\frac{dP}{dx} = RQ$$

Since η in the second right term is the fluid viscosity, if the two sub-terms are equivalent to a hydraulic resistance R multiplied by Q [13], it represents the viscous force to this small piece of fluid. The second right term thus corresponds to a resistance in electric analog.

Therefore, the electric analog for the Womersley model is an inductance and a resistance in series (See

Fig. 1B).

2.3: Electric Analog of Windkessel Model

The heart and the arterial system are treated as: "flow from a pump (the heart) enters a one-way valve distending the elastic wall of the Windkessel (the artery). When inflow stops, the elastic wall recoils, and fluid leaves the chamber through narrow outflow tube" [13]. The whole process is like iterative charging and discharging of a volume compliance of arterial wall.

Considering the discharging process, the flow is pushed by the recoil force of Windkessel compliance (C) and leaves the chamber through a narrow tube with resistance R. From the definition of R and C, we can get the governing equation for P:

$$\frac{1}{RC} = -\frac{1}{\frac{\Delta P}{Q} \cdot \frac{dv}{dP}} = -\frac{1}{\frac{P}{\frac{dv}{dP}} \cdot \frac{dv}{dP}} = -\frac{dP}{P dt}$$

P: pressure in the elastic windkessel (the artery); since the pressure is assumed thoroughly dissipated by R, $\Delta P = P$.

v: volume of the elastic windkessel, Q is equal to dv/dt

R: resistance of the outflow tube, defined by $R = \Delta P / Q$

C: compliance of the windkessel, defined by $C = dv/dP$

The pressure (P) can be solved to get:

$$P(t) = P_0 \exp[-t / RC]$$

It is just like the charging and discharging process in electric RC (resistance & capacitance) circuit, therefore the electric analog can be analogous to a resistance and a capacitance in series (See Fig. 1C).

2.4. A Segment of Aorta in the Resonance Theory

In the conjecture of the resonance theory, the blood is "pumped from the heart, then the blood pressure is generated by the momentum of the injecting blood colliding on the vessel wall and travels along the aorta in the form of transverse wave" [17-21]. The wave propagation equation based on the radial movement for a small piece of wall was:

$$\frac{\partial^2 P}{\partial t^2} + b \frac{\partial P}{\partial t} + v_0^2 P = v_\infty^2 \frac{\partial^2 P}{\partial x^2}$$

v_0 : natural frequency of the tube

b: resistance coefficient of the vessel wall

v_∞ : wave velocity at high frequency

$\mu = \rho_w h + \rho_f h_f$, ρ_w : the density of the tube material, ρ_f : the density of the adherent fluid which moves together with the wall, h_f , h: the tube thickness

At some particular position ($x=x_0$), we will have:

$$\mu \frac{d^2 P}{dt^2} + b \mu \frac{dP}{dt} + \mu v_0^2 P = -\mu V_\infty^2 k^2 P, \quad (E4.1)$$

$$(k = \frac{2\pi}{\lambda}, \lambda = \text{wavelength})$$

The last term ($\mu V_\infty^2 k^2 P$) represents the external force (denoted by F_{ext}) passing along the artery (either coming from the heart pumping or all other effects from the vascular bed).

In electric circuit, relation between voltage and current for series of a resistance (R), an inductance (L) and a capacitance (C) is:

$$L \frac{di}{dt} + iR + \frac{1}{C} \int i dt = V$$

After differentiation for both sides, we get:

$$L \frac{d^2 i}{dt^2} + R \frac{di}{dt} + \frac{i}{C} = \frac{dV}{dt} \quad (E4.2)$$

Comparing (E4.1) and (E4.2), let the parameters in (E4.1) substituted by electric parameters in (E4.2):

$L \rightarrow \mu$, equivalent inductance for a segment of aorta

$R \rightarrow b\mu$, equivalent resistance for a segment of aorta

$1/C \rightarrow \mu v_0^2$, equivalent compliance for a segment of aorta

$i \rightarrow P$

$dV/dt \rightarrow F_{ext}$

Then these two equations become identical. Therefore the electric analog for a segment of the artery in resonance theory can be represented by series of an L (inductance), an R (resistance), and a C (capacitance). Another very small R' parallel to C is necessary to serve as a DC current pathway for C. (See Fig. 1D)

This model uses the electric current i to correspond to pressure. It means that the artery is treated mainly as a transmission system for the pressure wave, while the flow is derived from equation of continuity [17-21]. This is different from other hemodynamic models stated above that deal flow directly.

2.5. Electric Analog for the Whole Circulatory System in the Resonance Theory

We can divide the whole circulatory system as 3 parts: the artery, the vein and the vascular beds as pathways between the main artery and the vein. (1)

The electric analog of the artery has been shown above. (2) Since the blood pressure drop in the vein is very small, we can treat it as a pure return line with no voltage drop. (3) A vascular bed, such as an organ, is composed of branch arteries and capillaries. The electric analog of branch artery is just like the main artery, while the capillaries is like a pure resistance for the wall's elasticity is much smaller than that of the arteries. An organ (or a vascular bed) can thus be treated as series of another set of RLC (the branch artery) and a pure resistance (the capillary). There are two resistances in series, they can be combined to one. Therefore the electric analog can be further reduced to a set of RLC.

Putting these 3 parts together, we can get the electric analog model of the whole circulatory system. As shown in Fig.1D, the above RLC series represents the main artery, the below return line is the vein, and the middle RLC represents one organ (or a vascular bed).

3. MATERIALS AND METHODS

3.1. Animal Preparation

Rats were chosen by two criteria to keep uniformity: the body weight between 200 and 250 gw, and the heart rate between 6.2 and 7.5 Hz. 5 male normal Wistar rats weighted 231.05 ± 11.92 gw were anesthetized with urethane (1.2 mg gw^{-1} body weight). Abdominal aortic pressure was measured through a PE tube (2F, outer diameter 0.6mm; filled with liquids: 0.9 % NaCl and 0.3 % heparin) inserted from the caudate artery. The pressure pulses were recorded by a catheter-tip pressure transducer (P10EZ transducer, RP-1500 Narco-Bio-System) and converted to digital data with sampling frequency 500 Hz. [22-24] The heartbeat was picked by the peak of R-enhanced ECG signal. We can get same results from relatively lowest points in blood pressure waveform.

3.2. Mechanical Stimulation and Choice of Waterbed Mattress

We used waterbed mattress (size: $60 \times 40 \times 10$ cm; surface: 0.5 mm PVC; filled with water) as media and weak single-frequency mechanical vibration generated by a stepping motor beating under the bed as a stimulus to study the effect on HRV. The generated wave inside the waterbed was measured by the same pressure transducer as in the blood pressure measurement of the rat

The beating of the motor was set following the heartbeat by synchronized the beat with the appearance of the R, the largest signal in ECG (electrocardiogram). The pressure amplitude that travelled in the waterbed

during beating was only 0.5 mm-Hg ($\approx 0.7 \text{ gw cm}^{-2}$, 0.7 gw is about the weight for a grain of peanut). It is so small that we can hardly feel it, and it won't joggle the rat (the movement distance is $< 1 \text{ mm}$).

3.2.1 Wavelength match

Since we use very weak force stimulation, the waterbed needs special design to enhance the

(a)

(b)

(c)

(d)

Fig 1. Electric analog of important hemodynamic theories. (a) Poiseuille's equation: a pure resistance. (b) Womersley model: a resistance and an inductance in series. (c) Windkessel model: a resistance and a capacitance in series. (d) Resonance theory: The arterial wall can be represented by series of a resistance, an inductance and a capacitance (R_1, L_1, C_1). One attached organ can be represented by another set of RLC₂. Each set of RLC will introduce a resonance frequency respectively. When these resonance frequencies match each other, the transmission efficiency of blood pressure wave will increase dramatically. R' parallel to the capacitance is a small bypass resistance to avoid DC open circuit.

transmission efficiency for the sound wave. The size of the waterbed was so chosen that the wave excited and travelled inside the waterbed had a wavelength close to that of the blood pressure wave in the rat to ensure the mechanical energy can be transmitted into the body efficiently. The waterbed can be approximated as a closed square with the longest dimension about 0.6 m. When standing wave takes place inside the waterbed, 0.6 m can be treated as the half wavelength of the wave generated inside, hence the wavelength is about 1.2 m.

The blood pressure wave velocity in the aorta of the rats is about 9 m/s [16, 20]. From c (wave velocity) = f (wave frequency) $\times \lambda$ (wavelength) and $f \approx 7$ (the heart rate of rats), the wavelength inside the artery of rats can be estimated by $9/7 \approx 1.3$ m, these two wavelengths are thus shown to be very close to each other.

3.2.2 Wave generation efficiency

We also need high efficiency wave generation from the waterbed. We tested the impulse response of the generated wave by knocking the waterbed with a stick, and then measure by a pressure transducer to find the natural frequency of this waterbed from peak frequency of the FFT spectrum. We calibrated the waterbed to have a natural frequency of 6.8 Hz (see Fig. 2). Since this natural frequency is very close to the heart rate of the rats (also our beating rate), owing to the resonance effect inside the waterbed, the beating of the motor can achieve highest efficiency and generate waves with enough amplitude.

3.3. Experimental Procedure

After the surgical operation, the rat was grovelled on the bed and rested 1 hour for the blood pressure to return to steady. We first recorded for 1st 15-minute data sequence as a "control". The ECG of the rat was monitored and the motor speed was set to synchronize the beat with the appearance of the R, the largest signal in ECG. The motor was turned on for 15 minutes to apply mechanical stimulation. At the same time, the 2nd 15-minute data was recorded as the "effect during the stimulation". After this process, we removed the stimulation and recorded for the 3rd 15-minute data as the "effect after the stimulation". At least 20 more minutes were waited before another experiment to avoid interference.

The sampling interval was 1 minute, CV for each 15-minute heartbeat sequence was calculated. In control experiment without mechanical stimulation, we can maintain the rats for more than 2 hours with variation (deviation from mean value) of HRV always smaller than 0.0021 (averaged 0.0013).

The average of 15-minute SD for the 7 CVs of the data sequences (before, during and after the stimulation) were 0.0016 ± 0.0005 , 0.0018 ± 0.0008

Fig 2. Impulse response of our waterbed.

Upper: time-domain response: Ordinate, pressure amplitude (cm-H₂O); Abscissa, time (second).

Lower: frequency-domain response by FFT: Ordinate, pressure amplitude (cm-H₂O); Abscissa, frequency (Hz). The peak frequency is about 6.8 Hz.

and 0.0010 ± 0.0003 (mean $\pm$ SD), respectively. Between each experiment, the exposed tissues were kept moist with physiological saline and the waterbed was kept at 32°C by a lamp and a heat radiator.

4. RESULTS

The change of HRV in each study is shown in Table 1. Among 7 studies on 5 rats, the 15-minute average of CV of the heart rate sequence changed from the control value, 0.0098 ± 0.0023 (mean $\pm$ SD) to 0.0119 ± 0.0032 (mean $\pm$ SD) during the stimulation and decreased to 0.0078 ± 0.0020 (mean $\pm$ SD) after removing the stimulation. The p values for paired t-test (by Microsoft EXCEL, both compared with the control) were <0.006 and <0.0007 respectively. All effects are much larger than deviation of HRV in control experiment (as stated in Method section).

The time-domain result with 2 typical processes is shown in Figure 3. The CV rose when mechanical stimulation was on, and dropped below the control

Fig 3: Alteration of HRV with mechanical stimulation. Here we show 2 processes on 4th rat in Table 1.

value right after the stimulation was off. After 15-minute recording, the CV would return to its control value within another 10 minutes.

The diastolic pressure were 76.57 ± 7.64 , 77.40 ± 7.32 and 76.77 ± 8.40 mm-Hg (mean $\pm$ SD) before, during and after the stimulation, the systolic pressure were 116.22 ± 10.37 , 115.83 ± 10.58 and 115.03 ± 9.62 mm-Hg (mean $\pm$ SD), and the heart rate 6.86 ± 0.30 , 6.85 ± 0.28 and 6.85 ± 0.29 Hz (mean $\pm$ SD) respectively. No significant changes in them.

5. DISCUSSION

From the results we can see that all runs follow the same trends, and the effects are statistically significant. It indicates that this weak sound wave through impedance-match media indeed affected the cardiac rhythms.

HRV implies the complexity of heartbeat sequence [12]. This variation may reflect the ANS activity for the heart to find its optimal working condition when facing the arterial load or other environmental parameters. This optimization is necessary since the human left ventricle uses a very small output power [14](only 1.7 Watt) to distribute the blood to such a large body (human " 70 kgw).

In healthy human body, the heart keeps adjusting its beating to find an optimal mode. That may explain why normal heartbeat shows variability. When aging, chronic stress, or circulatory dysfunction occurs, the heart has to pay more effort to overcome the increasing work loading. Therefore the choice becomes narrower for the heartbeat adjustment, and the HRV thus decreases.

In our experiment, the increasing HRV during the stimulation suggests that heart can feel the external sound wave. The heart gets assistance from the energy of the external sound wave and thus has more freedom to adjust its beating to explore better working condition. When the stimulation was removed, the HRV become slightly smaller than the control value for a while and then returned to control value. It implies that the heart did not feel the external energy any longer, therefore the heart lost the external stimulation to lead its exploration. The heart hesitated for a while and then adjusted its beating as it used to be in control period.

By this conjecture, we can also explain the opposite outcomes in HRV alteration between our and previous experiments. Large irregular mechanical stimulation will bring psychological panic or direct force impact on the rats, thus increase the cardiac work loading and lead to the decrease of HRV. However in our experiment, on one hand, our small stimulation energy is sufficient to be felt by the heart, but is a less menace to the small output power of the heart. On the other hand, synchronized frequency to the heart rate keeps us from disturbing the cardiac rhythm and

Table 1: Changes of HRV before, during, and after applying sound wave in each study. HRV were calculated from CV of 15-minute heartbeat interval sequence. Body weight is in the unit of gw. In all studies the HRV followed the same trends: increased during the stimulation and decreased after.

rat	Body weight	HRV(control)	HRV(ON-effect)	HRV(OFF-effect)
1	220	0.0088	0.0119	0.0072
		0.0085	0.0090	0.0070
2	220	0.0147	0.0172	0.0126
3	225	0.0071	0.0077	0.0059
4	240	0.0106	0.0147	0.0067
		0.0101	0.0135	0.0075
5	250	0.0089	0.0093	0.0076

increasing the cardiac work loading, thus gives the heart an assistance to adjust its beating towards optimization. Consequently, it won't harm the delicate optimization of the heart beating, and it made us observe the increasing HRV rather than the chronic effect (decreasing HRV) in previous studies [12-13].

The blood pressure showed no significant changes, which also implied there were no chronic effects by our stimulation.

CONCLUSION

Here we show that the circulatory system has interaction with this weak synchronized sound wave. The impedance-match waterbed can raise the transmission efficiency of the sound wave, and the HRV alteration indicates that this stimulation can affect the cardiac rhythm. Since we cannot directly stimulate the ANS or the cardiac conducting system by mechanical force, the resonance theory provides a possible clue to this phenomenon.

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