Transthoracic Cardiac Ultrasonic Stimulation Induces a Negative Chronotropic Effect


Abstract—The objective of this study is to investigate cardiac bioeffects resulting from ultrasonic stimulation using a specific set of acoustical parameters. Ten Sprague–Dawley rats were anesthetized and exposed to 1-MHz ultrasound pulses of 3-MPa peak rarefractional pressure and approximately 1% duty factor. The pulse repetition frequency started slightly above the heart rate and was decreased by 1 Hz every 10 s, for a total exposure duration of 30 s. The control group was composed of five rats. Two-way analysis of variance for repeated measures and Bonferroni post hoc tests were used to compare heart rate and ejection fraction, which was used as an index of myocardial contractility. It was demonstrated for the first time that transthoracic ultrasound has the potential to decrease the heart rate by ~20%. The negative chronotropic effect lasted for at least 15 min after ultrasound exposure and there was no apparent gross damage to the cardiac tissue.

I. INTRODUCTION

Although diagnostic ultrasound is well established in cardiology, there is an unexplored potential for therapeutic applications. The available literature indicates the possibility of using ultrasound for nonpharmacological treatment of heart failure [1], defibrillation [2], pacing [3], cardiac gene therapy [4], and ablation for treating arrhythmias [5].

Ultrasound is a mechanical wave and it is known that the heart can be affected by mechanical disturbances. Such disturbances are able to influence the origin and the spread of cardiac electrical excitation by intra- or extra-cardiac mechanisms. This process is called mechano-electric feedback and is involved in a variety of clinical manifestations. It affects the physiological heart rate modulation, and underlies the mechanical induction (e.g., commotio cordis) and termination (e.g., precordial thump) of heart rhythm disturbances. This feedback involves mechanosensitive ion channels and mechanisms that affect modulation of cellular Ca²⁺ handling [6], [7].

In a preliminary study [8], we tested how different operation modes of ultrasound application [i.e., continuous wave, pulsed wave at a single pulse repetition frequency (PRF), and pulsed wave at variable PRFs] could produce cardiac bioeffects. At that point, the variable PRF seemed to be quite interesting for further investigation. Thus, the objective of this study is to investigate cardiac chronotropic effects resulting from ultrasonic stimulation using a variable PRF. The experimental group was compared with a control group that went through the same experimental procedures, except for the application of ultrasound.

II. METHODOLOGY

A. Ultrasound Transducer

The 1-MHz ultrasound transducer was constructed using a 25-mm-diameter PZT-4 piezoceramic (Morgan Technical Ceramics, Windsor, UK). The transducer calibration was conducted in a tank containing distilled, degassed water at 22°C. A calibrated polyvinylidene fluoride (PVDF) membrane hydrophone (Y-34–3598 EW295, GEC Marconi, Chelmsford, UK), with a 0.5-mm-diameter active element was used. The custom-made transducer was held in a fixed position while the hydrophone was moved by a micro-positioning system. This system allows movement along the three translational axes (2-μm accuracy), and around two angular axes (0.02° accuracy). A signal generator (33250A, Agilent Technologies Inc., Santa Clara, CA) and an RF power amplifier (A150, Electronic Navigation Industries, Rochester, NY; 0.3 to 35 MHz; 55 dB) were used to drive the transducer with 50-cycle bursts and voltages ranging from 25 to 275 Vpp. In response to the applied voltage, the transducer output pressure behaves quite linearly, ranging from approximately 0.3 to 3 MPa peak rarefactive pressure, as shown in Fig. 1.

B. Animal Studies

The experimental protocols were approved by the University of Illinois Institutional Animal Care and Use Committee (protocol #10104). Ten Sprague–Dawley rats (Harlan Laboratories Inc., Indianapolis, IN) were exposed to the experimental sequence. Animals were anesthetized with 5% isoflurane for induction of anesthesia and then 1.5% to 2% isoflurane for maintenance of anesthesia via...
face mask. Although isoflurane does not impact cardiac contractility [9], it is a respiratory depressant and it affects the cardiac function, reducing the heart rhythm [10]. Therefore, five additional rats were used as a control group, exposed to the same study protocol, except for the application of ultrasound. Fig. 2 presents the block diagram of the experimental setup.

Rats were depilated and placed on a platform in dorsal recumbency for ultrasonic cardiac exposure. Four electrocardiography (ECG) electrodes on the platform were coated with gel to contact the paws. Temperature, respiratory rate, heart rate, and ECG were monitored. Ultrasound was applied to the thorax, and thus to the whole heart, including the sino-atrial node and the lower myocardium. Only one animal was euthanized (CO₂ for 5 min) for histological evaluation, which revealed no evidence of damage as determined by a board-certified pathologist. Because there were no signs of major problems via gross observations, all the other animals were allowed to recover.

Each ultrasound application lasted 30 s and consisted of 1-MHz bursts of 3-MPa peak rarefactual pressure, with a PRF starting slightly greater than the heart rate and decreasing by 1 Hz every 10 s. The duty factor was approximately 1%, which means that for a PRF sequence of 6, 5, and 4 Hz (i.e., 167, 200, and 250-ms pulse repetition periods, correspondingly), a 2-ms pulse duration was used.

A VisualSonics Vevo 2100 (VisualSonics Inc., Toronto, ON, Canada) high-frequency ultrasound imaging system was used to dynamically monitor the heart through B-mode and M-mode real-time ultrasound images [acquired by a registered diagnostic medical sonographer (RDMS)]. Ejection fraction and other cardiac parameters were calculated by the ventricular trace tool from the Vevo 2100 workstation. This tool is used to trace the position of the inner and outer ventricular walls over one or more heart cycles on a long-axis M-mode tracing of the left ventricle. The left ventricular internal diameter during systole and diastole are used to calculate the end systolic and the end diastolic volumes by the Teichholz method. The stroke volume is then obtained by subtracting the end systolic volume from the end diastolic volume, and the ratio of the stroke volume and the end diastolic volume represents the ejection fraction [11].

M-mode images were acquired three times: approximately 6 min before, 3 min after, and 15 min after the 30-s duration ultrasonic stimulation. The values obtained 3 min and 15 min after were normalized to the values obtained 6 min before ultrasound stimulation. The statistical analysis was performed in Matlab 7.0.1 (The MathWorks Inc., Natick, MA), using two-way analysis of variance (ANOVA) for repeated measures and Bonferroni post hoc tests. The significance level was set at 0.05.

III. Results

Heart rate decrease occurred for all the animals of the experimental group. Fig. 3 shows an example of the heart rate decrease during the 30-s duration ultrasonic stimulation. In some other cases, the negative chronotrophic response was only observed right after ultrasound application.

The physiological parameters initial absolute values and normalized values after ultrasound stimulation are presented in Tables I and II, respectively. All values in both tables are expressed as mean and standard error of the mean.

Two-way ANOVA for repeated measures (Table III) was performed to verify whether physiological parameters (heart rate, cardiac output, stroke volume, ejection fraction, and respiratory rate) were modified as a response to ultrasound, and whether the effects lasted. Bonferroni post hoc tests were applied to compare the results.

For heart rate, there was a significant difference between groups ($p < 0.0001$) and between times ($p = 0.046$). However, time did not influence each group differently, because the interaction is not significant ($p = 0.81$). Heart rate decreased with time for both the experimental group and the control group (see Table II). The Bonferroni test
buiochi et al. : transthoracic cardiac ultrasonic stimulation induces a negative chronotropic effect

(Fig. 4) showed significant differences between the experimental and control values, for both points in time, depicted by the absence of superposition of horizontal bars that correspond to a 95% confidence interval.

The cardiac output decreased considering the baseline values in the experimental group (both points in time) and in the control group after 15 min (Table II). In spite of that, there was neither significant difference between experimental and control groups \((p = 0.28)\) nor between points in time \((p = 0.1)\), as presented in Table III. The Bonferroni test also showed no difference between groups (superposition of the 95% confidence interval horizontal bars, Fig. 5).

Relative to the effect of ultrasound on stroke volume, there was a significant difference \((p = 0.005)\) between groups. The stroke volume increased in the experimental group and decreased in the control group, particularly after 15 min, as shown in Fig. 6.

The ejection fraction, defined as the ratio of the stroke volume and the end diastolic volume, was used to assess possible cardiac contractility alterations. The ANOVA showed a significant difference between experimental and control groups \((p = 0.026)\) when looking at the set of points in time. Nevertheless, the Bonferroni test showed no difference between groups, regardless of the point in time (superposition of the 95% confidence interval horizontal bars, Fig. 7), suggesting that major cardiac damage was unlikely.

The respiratory rate difference was only significant for time \((p = 0.03)\), but group \(\times\) time interaction was not significant \((p = 0.94)\), meaning that this change with time was not different between groups. Respiratory rate decreased in both groups (see Table II) and it was probably a result of isoflurane anesthesia.

IV. Discussion

Ultrasonic waves are known to interfere in the cardiac activity of turtle [12], dog [2], frog [13], mouse [14], pig [3], and guinea pig [1]. However, negative chronotropic effect has never been reported previously. In this study, transthoracic therapeutic ultrasound, delivered at a decreasingly variable PRF, has shown the capability to decrease the heart rate without apparent damage to the cardiac tissue. After removal of ultrasonic stimulation, the negative chronotropic effect lasted until the end of each experiment (at least 15 min). The delayed effect suggests that there might be a more subtle effect that yet needs to be better understood, and that will need to be evaluated in another more comprehensive ultrasound-induced bioeffect study.

For 3-MPa peak pressure and 1% duty factor, the spatial-peak temporal-average intensity (\(I_{\text{SPTA}}\)) applied was

### Table I. Initial Absolute Values of Physiological Parameters Expressed as Mean and Standard Error of the Mean (SEM) for the Experimental and Control Groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>bpm</td>
<td>344.92</td>
<td>353.17</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>mL/min</td>
<td>49.55</td>
<td>56.72</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>µL</td>
<td>143.80</td>
<td>160.56</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>%</td>
<td>83.71</td>
<td>78.10</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>µL</td>
<td>172.98</td>
<td>206.12</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>µL</td>
<td>29.81</td>
<td>45.56</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>%</td>
<td>54.15</td>
<td>47.96</td>
</tr>
<tr>
<td>End-diastolic diameter</td>
<td>mm</td>
<td>5.9</td>
<td>6.36</td>
</tr>
<tr>
<td>End-systolic diameter</td>
<td>mm</td>
<td>2.7</td>
<td>3.31</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>/min</td>
<td>42.10</td>
<td>44.00</td>
</tr>
<tr>
<td>Temperature</td>
<td>°C</td>
<td>33.22</td>
<td>33.82</td>
</tr>
</tbody>
</table>

Fig. 3. Heart rate response during 30-s duration ultrasonic stimulation: (a) ECG record of the first and last seconds; (b) heart rate as a function of time for the 30-s duration ultrasonic stimulation.
around 3 W/cm². The insonification scheme used in this study excludes bulk (temporal average) temperature effects (maximum temperature rise of 0.6°C ± 0.05°C), as previously reported [8]. One may also consider a maximum temperature increase from a single pulse, \( \Delta T_{\text{max}} = \frac{\dot{Q}\Delta t}{C_v} \), where \( \Delta t \) is the pulse duration (2 ms for a single pulse), \( C_v \) is the medium’s heat capacity per unit volume (4.18 J/cm³·°C for biological tissue), and \( \dot{Q} = 2\alpha I_A \) (the absorption coefficient \( \alpha \approx 0.05/cm \) at 1 MHz; \( I_A \approx 300 \text{ W/cm}^2 \)) is the rate of heat generation per unit volume \( [15]–[17] \). Therefore, \( \Delta T_{\text{max}} \approx 0.014°C \), and assumes no heat removal. Therefore, the observed effect results from a nonthermal mechanism, possibly a combination of tissue vibration, promoted by the propagating ultrasonic wave, and radiation force mechanism.

The radiation force has been associated with cardiac changes in frogs [13] and pigs [3]. It is a second-order effect of the propagating wave which is able to transiently push matter away from the source of ultrasound. In biological tissues, the radiation force is estimated to range from

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental 3 min after</th>
<th>15 min after</th>
<th>Control 3 min after</th>
<th>15 min after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.80 0.02</td>
<td>0.75 0.02</td>
<td>0.99 0.01</td>
<td>0.95 0.02</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.85 0.04</td>
<td>0.83 0.04</td>
<td>0.97 0.01</td>
<td>0.84 0.03</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>1.06 0.04</td>
<td>1.10 0.05</td>
<td>0.98 0.02</td>
<td>0.88 0.03</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.95 0.02</td>
<td>0.97 0.01</td>
<td>1.00 0.01</td>
<td>1.00 0.01</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>1.11 0.05</td>
<td>1.14 0.05</td>
<td>0.98 0.02</td>
<td>0.88 0.03</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>1.52 0.21</td>
<td>1.45 0.18</td>
<td>0.98 0.04</td>
<td>0.88 0.06</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>0.93 0.03</td>
<td>0.95 0.03</td>
<td>1.00 0.00</td>
<td>1.00 0.01</td>
</tr>
<tr>
<td>End-diastolic diameter</td>
<td>1.05 0.02</td>
<td>1.06 0.02</td>
<td>0.99 0.01</td>
<td>0.95 0.02</td>
</tr>
<tr>
<td>End-systolic diameter</td>
<td>1.16 0.06</td>
<td>1.14 0.06</td>
<td>0.99 0.00</td>
<td>0.95 0.03</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>0.85 0.04</td>
<td>0.75 0.04</td>
<td>0.93 0.02</td>
<td>0.82 0.04</td>
</tr>
<tr>
<td>Temperature</td>
<td>0.97 0.01</td>
<td>0.94 0.01</td>
<td>0.97 0.00</td>
<td>0.96 0.01</td>
</tr>
</tbody>
</table>

| TABLE III. Two-Way Analysis of Variance (ANOVA) for Repeated Measures of Heart Rate, Cardiac Output, Stroke Volume, Ejection Fraction, and Respiratory Rate. Factors: Group (Experimental/Control); Time (3 min/15 min). |
|-------------|-----------------|-------------|-----------------|-------------|
|             | Sum of squares (SS) | Degrees of freedom (DOF) | Mean squares (SS/DOF) | F | p |
| Heart rate  | Group (G)       | 0.24627     | 1              | 0.24627 | 73.88 | 0.045 e−7 |
|             | Time (T)        | 0.01466     | 1              | 0.01466 | 4.4   | 0.0458   |
|             | Interaction (G×T) | 0.00019     | 1              | 0.00019 | 0.06  | 0.8145   |
|             | Error           | 0.08667     | 26             | 0.00333 |       |          |
|             | Total           | 0.35089     | 29             |           |       |          |
| Cardiac output | Group (G)       | 0.02022     | 1              | 0.02022 | 1.53  | 0.28     |
|             | Time (T)        | 0.03878     | 1              | 0.03878 | 2.94  | 0.10     |
|             | Interaction (G×T) | 0.01968     | 1              | 0.01968 | 1.49  | 0.23     |
|             | Error           | 0.31063     | 24             | 0.01319 |       |          |
|             | Total           | 0.38332     | 27             |           |       |          |
| Stroke volume | Group (G)       | 0.14905     | 1              | 0.14905 | 9.43  | 0.005    |
|             | Time (T)        | 0.00471     | 1              | 0.00471 | 0.3   | 0.59     |
|             | Interaction (G×T) | 0.03216     | 1              | 0.03216 | 2.03  | 0.17     |
|             | Error           | 0.3794      | 24             | 0.01581 |       |          |
|             | Total           | 0.56094     | 27             |           |       |          |
| Ejection fraction | Group (G)       | 0.01082     | 1              | 0.01082 | 5.65  | 0.0258   |
|             | Time (T)        | 0.00097     | 1              | 0.00097 | 0.5   | 0.4845   |
|             | Interaction (G×T) | 0.00076     | 1              | 0.00076 | 0.4   | 0.5353   |
|             | Error           | 0.04596     | 24             | 0.00192 |       |          |
|             | Total           | 0.05919     | 27             |           |       |          |
| Respiratory rate | Group (G)       | 0.04035     | 1              | 0.04035 | 2.79  | 0.1069   |
|             | Time (T)        | 0.07661     | 1              | 0.07661 | 5.3   | 0.0297   |
|             | Interaction (G×T) | 0.00009     | 1              | 0.00009 | 0.01  | 0.939    |
|             | Error           | 0.37617     | 26             | 0.01447 |       |          |
|             | Total           | 0.50688     | 29             |           |       |          |
0.1% to 1% of the instantaneous pressure. High-intensity ultrasound pulses produce greater radiation force effects [18]. Considering the radiation pressure to be 1% of a 3-MPa wave, a transient pressure of 30 kPa (or 0.3 atm or 225 mmHg) would be created on the heart. This pressure rise is close to that described to occur during a precordial thump, which is a single blow that has potential to promote defibrillation. In this case, cell membranes are deformed, thus activating stretch-sensitive ion channels and increasing transmembrane current flow by means of mechano–electrical coupling [19].

The heart rate reduction probably involves the activation of mechanosensitive channels. These channels are able to change their open probability in response to a mechanical stimulus, and have been roughly divided into stretch-activated channels (SAC) and volume-activated channels (VAC). They can be further subdivided by their ion selectivity, such as cation-nonselective, potassium-selective, and chloride-selective channels (e.g., SACNS, SACK, VACCl) [20]. In the past, cell swelling was assumed to accelerate spontaneous pacemaking rate via activation of VACCl. Nevertheless, experiments demonstrated that
the opposite occurs: spontaneously active sino-atrial node cells reduce their pacemaking rate by approximately 24% during swelling [21]. In spite of its name, VAC\textsubscript{C1} is not only stimulated by osmotic and hydrostatic increases in cell volume, but also by direct mechanical stretch. VAC\textsubscript{C1} is largely distributed throughout the heart and plays a role in arrhythmogenesis, myocardial injury, preconditioning, and apoptosis of myocytes [22].

Because decreasing the heart rate through parasympathetic stimulation of the heart has been shown to protect against the development of some life-threatening arrhythmias [23], the ultrasound sequence proposed here might be protective as well. The cardiac chronotropic response to ultrasound may also include a reflex component, which has not been examined in the present study, and is under current investigation.

The cardiac output is the product of heart rate and stroke volume. The decrease in heart rate would directly lead to a decrease in cardiac output. However, this did not happen after ultrasound application, apparently because of the significant increase in stroke volume. The latter is likely to have occurred via Frank–Starling mechanism, as the negative chronotropic effect seems to have happened after ultrasound application, apparently because the latter was not observed in preliminary experiments with constant PRF.

Production of this effect requires, in addition to an ideal range of ultrasound parameters (frequency, rarefactive pressure, and duty cycle), a particular protocol of ultrasound application, with PRF close to the heart rate. Variation of PRF was a clear requisite for production of the negative chronotropic effect, as the latter was not observed in preliminary experiments with constant PRF.

V. Conclusion

This is the first study to demonstrate that a specific sequence of pulsed ultrasound delivered transthoracically has potential to induce a negative chronotropic effect without major impairment of myocardial contractile activity. Ultrasound was able to decrease the heart rate by 18.7% immediately after stimulation was discontinued. After removal of ultrasonic stimulation, the negative chronotropic effect lasted until the end of each experiment (15 to 45 min). The acoustic parameters used herein were frequency of 1 MHz, peak rarefactive pressure of 3 MPa, approximately 1% duty cycle (2- to 2.5-ms pulses), and variable PRF that ranged from slightly above the heart rate to 2 Hz less than the heart rate. The stimulation lasted 30 s, changing the PRF every 10 s.

Production of this effect requires, in addition to an ideal range of ultrasound parameters (frequency, rarefactive pressure, and duty cycle), a particular protocol of ultrasound application, with PRF close to the heart rate. Variation of PRF was a clear requisite for production of the negative chronotropic effect, as the latter was not observed in preliminary experiments with constant PRF.

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REFERENCES

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Emily L. Hartman completed a B.S. degree in radiologic sciences with a specialization in ultrasound from Southern Illinois University Carbondale in 2001. She became ARDMS registered in abdomen/small parts and OB/gynecology in 2002, and is certified by the NTQR for prenatal mchual transnscency and nasal bone screening. She began working for Carle Clinic Association/Carle Hospital in 2001 in the radiology and OB departments before training to perform targeted ultrasounds and fetal echocardiography on high-risk patients. While at Carle, she held the positions of lead sonographer and coordinator of radiology and OB ultrasound. Since coming to the University of Illinois at Urbana–Champaign in 2010, she assisted in the establishment of the Ultrasound Imaging Laboratory in the Beckman Institute Biomedical Imaging Center and works with a variety of investigators on a wide array of projects. She performs the imaging for studies including evaluation of ultrasound-tissue interaction, vascular remodeling of tumor growth, and cardiac function on species including rats, mice, and frogs. She is a member of the Society of Diagnostic Medical Sonographers.

Flávio Buiochi received the B.S., M.Sc., and doctoral degrees in mechanical engineering from the School of Engineering, University of São Paulo, Brazil, in 1990, 1994, and 2000, respectively. He started his teaching career in the Department of Mechatronics Engineering, University of São Paulo, São Paulo, Brazil, in 1992, where he is currently an Associate Professor. From September 2001 to March 2003, he was a postdoctoral Fellow with the Acoustics Institute, Spanish National Research Council, Madrid, Spain. In 2010, he was a visitor at the Bioacoustics Research Laboratory, University of Illinois at Urbana–Champaign. He is a member of the Brazilian Society of Mechanical Sciences and Engineering (ABCMC). His research interests include the applications of ultrasonic transducers in nondestructive evaluation, the characterization of liquids and solids by ultrasound, and the development of ultrasonic piezoelectric and piezocomposite transducers.

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William D. O’Brien, Jr. (S’64–M’70–SM’79–F’89–LF’08) received the B.S., M.S., and Ph.D. degrees from the University of Illinois at Urbana–Champaign, Urbana, IL, in 1971 and 1973, respectively. He has been at the University of Illinois, Urbana–Champaign, where he is currently a Professor in the Department of Electrical and Computer Engineering, Associate Director of the Beckman Institute for Advanced Science and Technology, and member of the Beckman Institute for Advanced Science and Technology, and member of the Beckman Institute for Advanced Science and Technology. He is the Director of the Beckman Institute for Advanced Science and Technology, and member of the Beckman Institute for Advanced Science and Technology. He is the Director of the Bioacoustics Research Laboratory. His current research interests involve the assessment of ultrasound-induced lung damage and attenuation coefficient determination of intercostal tissues. Her current research involves the assessment of the biological effects of ultrasound on tissue, including the heart, capillary beds, and large arteries, and the interaction of contrast agents with ultrasound.