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Acoustic Analysis of a Mechanical Circulatory Support

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Abstract: Mechanical circulatory support technology is continually improving. However, adverse complications do occur with devastating consequences, for example, pump thrombosis that may develop in several parts of the pump system. The aim of this study was to design an experimental clot/thrombosis model to register and analyze acoustic signals from the left ventricular assist device (LVAD) HeartMate II (HMII) (Thoratec Corporation, Inc., Pleasanton, CA, USA) and detect changes in sound signals correlating to clots in the inflow, outflow, and pump housing. Using modern telecom techniques, it was possible to register and analyze the HMII pump-specific acoustic fingerprint in an experimental model of LVAD support using a mock loop. Increase in pump speed significantly ($P < 0.005$) changed the acoustic fingerprint at certain frequency (0–23 000 Hz) intervals (regions: R1–3 and peaks: P1,3–4). When the ball valves connected to the tubing were narrowed sequentially by ~50% of the inner diameter (to mimic clot in the out- and inflow tubing), the frequency spectrum changed significantly ($P < 0.005$) in P1 and P2 and R1 when the outflow tubing was narrowed. This change was not seen to the same extent when the lumen of the ball valve connected to the inflow tube was narrowed by ~50%. More significant ($P < 0.005$) acoustic changes were detected in P1 and P2 and R1 and R3, with the largest dB figs. in the lower frequency ranges in R1 and P2, when artificial clots and blood clots passed through the pump system. At higher frequencies, a significant change in dB figs. in R3 and P4 was detected when clots passed through the pump system. Acoustic monitoring

of pump sounds may become a valuable tool in LVAD surveillance. **Key Words:** Mechanical circulatory support—Frequency analysis—Thrombosis.

The worldwide use of mechanical circulatory support (MCS) has grown rapidly (1). Outcome continues to improve, but complications such as embolic events related to treatment with MCS are feared (2,3). Pump thrombosis formation can occur even if the patient apparently has adequate anticoagulation. The development of a pump thrombosis is difficult to detect, and an embolic event may be the first symptom suffered by the patient. Our clinical finding of an altering sound from the left ventricular assist device (LVAD) HeartMate II (Thoratec Corporation, Inc., Pleasanton, CA, USA) (HMII), heard through a regular stethoscope in recipients before the occurrence of a thromboembolic event, has resulted in the ongoing SoundMate study, where patients with an HMII perform daily acoustic recordings at home and transmit them to the study center via a smartphone (4). A continuous flow MCS generates a typical sound that is easily registered by routine auscultation. A temporary or permanent change in sound would then indicate a change in pump function. The cause of this phenomenon is not clear. One suggestion is that a sudden change in sound may reflect an imminent pump thrombosis located within the pump and/or in the in- and/or outflow cannula.

Slaughter et al. in 2007 published results from a study on nine patients receiving the pulsatile assist device HM XVE where acoustic signals from the assist device were collected and analyzed using a hydrophone data acquisition system, including a sensor, an AD converter, and a data storage system, which was correlated to the electrocardiogram. They found that acoustic signal monitoring successfully identified HM XVE device end of life (5).

Makino et al. have published data from animal studies on an automatic diagnosis system designed for detecting early stages of malfunction of an artificial heart. The automatic diagnosis system was based on an electronic stethoscope system. Using this system, it was possible to identify initial signs of malfunction of the artificial heart (6). Bowles et al. presented two cases at the International Society for Heart and Lung Transplantation (ISHLT) meeting 2011, where acoustic changes showing typical frequency spectrum peaks were observed in association with pump thrombosis in the HeartWare centrifugal blood pump (7). At the ISHLT annual meeting in 2013, a group from Sydney showed in an experimental model as well as in patients that by analyzing the peaks in the frequency spectrum, pump thrombosis could be detected (8).

To our knowledge, there is no article published, apart from abstracts, on acoustic data from continuous flow devices (4,9).

The aim of this study was to design an experimental in vitro model to register and analyze acoustic signals from the HMII continuous flow MCS, and to detect changes in sound correlating to artificial and blood clot/thrombosis, using modern telecom techniques.

MATERIALS AND METHODS

Experimental setting

The HMII pump was placed in a plastic bag filled with water to allow sound recordings via a smartphone. To mimic the clinical situation of sound recording, the smartphone's microphone was attached to the plastic bag at approximately 3 cm from the pump housing.

Measurements to detect acoustic changes with increases in speed recorded with HMII pumping at speeds of 6000–10 000 rpm were performed with the pump in a closed circuit and performed earlier. For that reason, these recordings were not used as baseline. The experimental setting was performed in eight steps at 8000 rpm, with the HMII in an open circuit to facilitate rinsing of the pump system between clots. Different artificial thrombosis (Clot) situations were arranged: pump out- and inflow tube narrowed by a ball valve (one ball valve at a time was introduced to the circuit); a gelatin clot of two different viscosities (5 and 10 g gelatin of animal origin, Oetker [Bielefeld, Germany], in 0.2 L water each and prepared 12 h in advance); and finally, a human blood clot passing through the pump. The pump was flushed with water for 10 min between clots, and the experiments were repeated three times for each situation. For each clot, the sounds were recorded and the HMII monitor power consumption (watts) and flow (L/min) were registered.

1 *Baseline 1*: recorded with the ball valve connected to the inflow tubing and before narrowing of the tube.
2 *Pump inflow tube narrowed 50%*: the inflow tube was narrowed by 50% of the inner diameter. The ball valve was then removed.
3 *Baseline 2*: recorded with the ball valve connected to the outflow tubing and before narrowing of the tube.
4 *Pump outflow tube narrowed 50%*: the outflow tube was narrowed by 50% of the inner diameter. The ball valve was then removed.
5 *Baseline 3*: open tubes with no ball valves connected.

6 *Clot 1 through the pump*: 20 mL of a gelatin formulation with low viscosity was injected into the inflow tube.

7 *Clot 2 through the pump*: 20 mL gelatin formulation with higher viscosity was injected into the inflow tube.

8 *Human blood clot through the pump*: a blood clot collected after removal of thoracic drainage from a patient that had undergone cardiac surgery the day before was finally injected (20 mL) into the inflow tubing.

Acoustic recordings

Sounds from the HMII in the different experimental settings named previously were recorded using an iPhone (Apple, Inc., Cupertino, CA, USA) with the commercially available stethoscope application iStethPro (Dr. Peter J Bentley, London, UK) and transferred via telecommunication to a frequency analysis software program (Audacity 1.3.13-beta, Unicode, Ash, Chinen and Crook, Pittsburgh, PA, USA) and analyzed. Three 8-s sound samples from each experiment were collected and analyzed.

Frequency spectrum and acoustic analysis

Sound is composed of multiple sound waves of different frequencies (Hertz: fluctuations or unit/time) and amplitudes (sound strength). It is possible to analyze the noise level at each frequency and also present the data as a frequency spectrum graph with amplitude on the y-axis in decibel (dB) and frequency on the x-axis in Hertz (Hz). The frequency measurements are set by the software program between 0 and 23 000 Hz, and at 255 different standardized frequency levels with 400 Hz intervals. In this analysis, the description of amplitude is as noise level (−dB).

The acoustic fingerprint from an HMII has the broadest frequency spectrum between 1000 and 10 000 Hz. In this interval, a peak is seen at ~1000 Hz, and an additional smaller peak at ~7000 Hz may be present. At higher frequencies, peaks around ~15 000 and ~22 000 Hz are commonly present. For that reason, the frequency spectrum in the present study was divided into different frequency regions (R1–3) and peaks (P1–4) in order to facilitate calculations and clarify changes in frequencies of the spectrum during each experimental situation (R1: 1000–6500 Hz; R2: 8500–14 000 Hz; R3: 15 000–21 000 Hz; P1: 0–1000 Hz; P2: 6500–8500 Hz; P3: 14 000–15 000 Hz; P4: 21 000–23 000 Hz) (Fig. 1).

All data are presented as mean and standard deviation. Changes were calculated using the two-tailed Student's *t*-test and a *P* level of <0.05 was considered significant.

RESULTS

It was possible to collect and analyze acoustic data from HMII in the experimental setting using available telecom techniques, and the baseline acoustic fingerprint of this specific HMII was registered.

Change in pump speed

Changes with increases in pump speed are shown in Table 1. The overall increases in amplitude due to increase in speed are similar to those seen in a previous study (9). With each increase in pump speed, significant changes were detected in regions R1–R3 and in P1, P3, and P4, but not P2. P2 is not sensitive to increases in pump speed (Table 1).

Changes seen with the different clot situations

As the introduction of a ball valve to a tube may change the flow conditions, a baseline measurement was performed between the different clot experiment settings. There were minor nonsignificant changes in baseline measurements between the open tube and that when the open ball-valve was attached to the out- or inflow tubing.

When the ball valves, connected one at a time, were sequentially narrowed by ~50% of the inner diameter, the frequency spectrum changed significantly ($P < 0.005$) in P1–2 and R1 when the outflow tubing was narrowed. This change was not seen to the same extent when the ball valve was connected to the inflow tube followed by narrowing the lumen by ~50%. When artificial clots and human blood clots passed through the pump system, similar but more distinct acoustic changes were detected in P1 and P2 and R1 and R3, most occurring in the lower frequencies in R1 and P2 (Fig. 1). At higher frequencies, significant changes in dB in R3 and P4 were detected when clots passed through the pump system (Table 1).

Pump monitor

At the three baseline measurements, the power was 4.0-3.9-4.2 W and the flow was 3.8-3.8-3.9 L/min. After narrowing the in- and outflow tubing, the power decreased and the flow was reduced compared with the original output (pump inflow tube narrowed 50%: 3.2 W and 1.9 L/min, and pump outflow tube narrowed 50%: 3.2 W and 2.1 L/min). When the artificial clots passed through the pump, there was a decrease in power (Clot.1: 2.7 W and Clot.2: 2.4 W), but when the blood clots passed through the pump, there was a 48% increase in power to 7.4 W. No flow data were presented on the monitor when the three different clots passed through the pump.
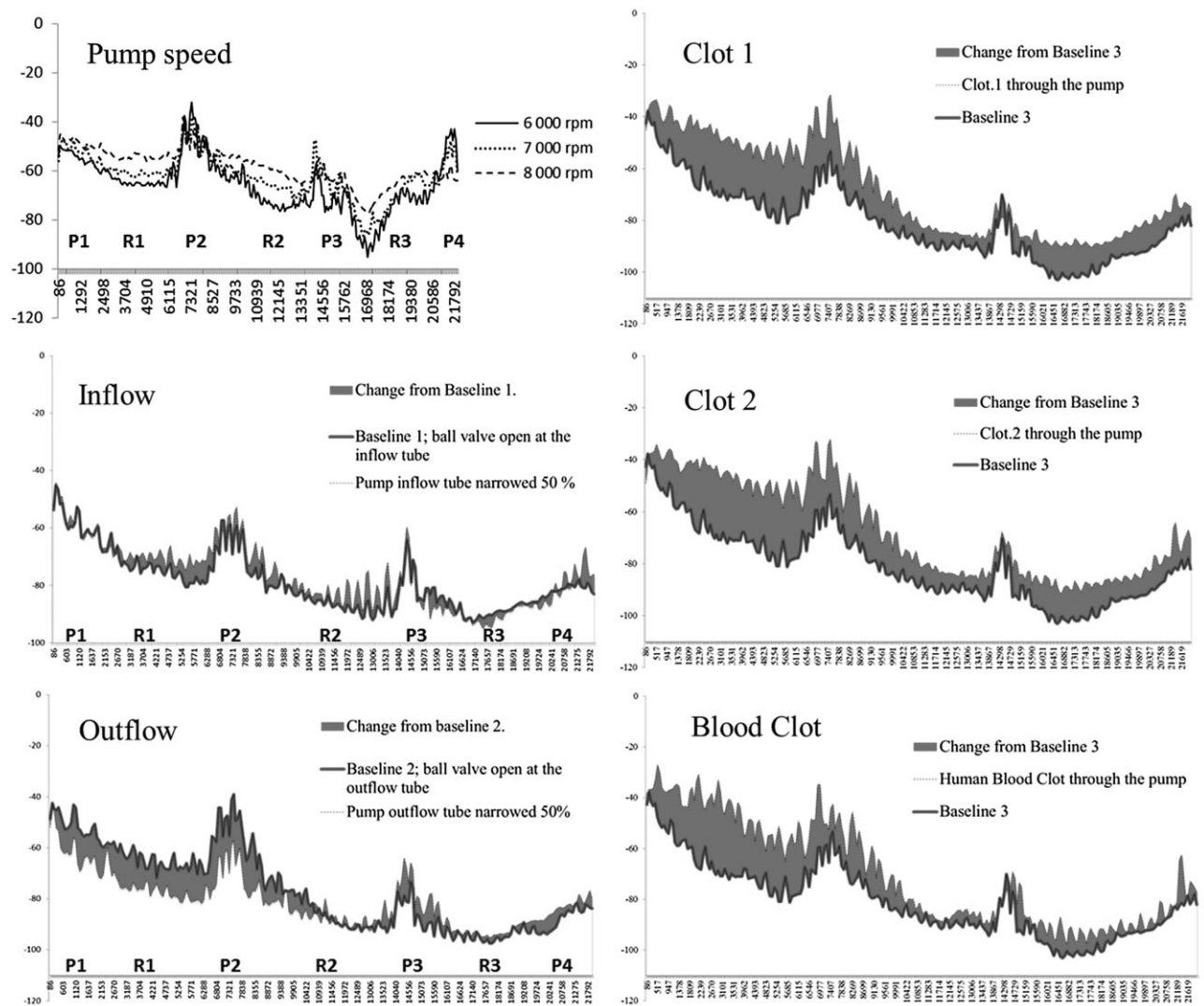
FIG 1. Change in the frequency spectrum at increased pump speed curves (upper left panel) shows example of change in acoustic fingerprint when pump speed increased from 6000 to 7000 to 8000 rpm.
Acoustic changes in gray, when narrowing the inflow and outflow tubes with 50%, respectively (left panel), and at different clots: two different viscosities of clots and a human blood clot (right panel) passed through the pump. R = regions (R1: 1000–65 000; R2: 8500–14 000; R3: 15 000–21 000) Hz. P = peaks (P1: 0–1000; P2: 6500–8500; P3: 14 000–15 000 P4; 21 000–23 000) Hz. Frequency (*x*-axis) in 0–23 000 Hz, and amplitude (*y*-axis) in –dB.

DISCUSSION

LVAD has become an important treatment option for patients with advanced heart failure, and technology is continually improving (2,10–12). However, adverse complications do occur and may have devastating consequences (3). Pump thrombosis may develop at various locations in the pump system, resulting in thromboembolic events, changes in pre- and afterload, or pump failure. In this experimental model, we used artificial and human blood clots in an attempt to mimic the sound properties of a pump clot/thrombosis. With the present experimental model, using commercially available telecom techniques, we found it possible to register sounds from the HMII and to define a baseline acoustic fingerprint and its variation with increases in pump speed. One frequency interval, P2 was found to be insensitive to changes in speed.

Each HMII has its own acoustic fingerprint in the experimental setting as well as in the clinical situation. Any change from the baseline acoustic pattern (fingerprint), at a given pump speed, appears to be of importance. It is difficult to compare the actual dB figures at different speeds as the dB scale is logarithmic and will only be comparable in the same region or peak, and should be valued as a change from the

TABLE 1. *Change of noise in dB in peaks (P) and regions (R) at a total of 255 different frequencies (Hz), at increased pump speed and at the different experimental settings*

Change at increased speed (rpm)	Peaks and regions (no. of frequencies)													
	Change in noise level dB: mean (SD) and mean %													
	P1 (11)		R1 (64)		P2 (23)		R2 (64)		P3 (12)		R3 (69)		P4 (12)	
6 000 to 7 000	2 (2)**	4%	3 (2)**	5%	4 (3)ns	0%	5 (3)**	8%	7 (3)**	18%	5 (4)**	6%	4 (3)ns	7%
7 000 to 8 000	2 (2)**	5%	5 (2)**	10%	4 (2)ns	1%	5 (2)**	8%	5 (3)ns	6%	5 (3)**	7%	7 (5)**	14%
8 000 to 9 000	3 (2)**	7%	3 (2)**	3%	5 (5)ns	2%	5 (2)**	8%	6 (2)**	12%	4 (2)**	5%	9 (4)**	15%
9 000 to 10 000	3 (2)**	8%	2 (1)ns	2%	3 (3)ns	4%	3 (2)**	4%	3 (2)**	5%	4 (2)**	5%	3 (2)ns	6%
Change from baseline														
Pump inflow tube narrowed 50%	2 (1)ns	3%	4 (3)**	5%	5 (2)**	7%	4 (3)**	4%	2 (1)ns	3%	2 (8)**	3%	6 (4)**	7%
Pump outflow tube narrowed 50%	8 (4)**	16%	11 (4)**	19%	16 (4)**	31%	4 (3)ns	5%	8 (3)**	10%	3 (3)**	4%	3 (2)**	4%
Clot 1	9 (5)**	19%	20 (5)**	29%	19 (5)**	29%	8 (5)**	10%	7 (3)ns	8%	10 (3)**	10%	7 (3)**	9%
Clot 2	10 (5)**	20%	22 (6)**	32%	20 (6)**	31%	10 (5)**	12%	8 (4)**	9%	10 (3)**	10%	10 (4)**	12%
Blood clot	12 (7)**	24%	22 (7)**	31%	16 (7)**	24%	6 (5)**	7%	7 (6)**	9%	5 (4)**	5%	6 (7)**	8%

R = regions (R1: 1000–6 500. R2: 8500–14 000. R3: 15 000–21 000) Hz. P = peaks (P1: 0–1000. P2: 6500–8500. P3: 14 000–15 000 P4. 21 000–23 000) Hz. **$P < 0.005$, *$P < 0.05$. ns, no significant change; rpm, revolutions per minute.

A significant change in frequencis from the baseline acoustic fingerprint was detected at all experimental settings. Significant acoustic changes and the largest numeric change were seen in low frequencies when artificial clots and blood clots passed through the pump system.

baseline. The peaks at ~1000, ~7000, ~15 000, and ~22 000 Hz, which are commonly present in the acoustic fingerprint of the HMII, may depend on the characteristics of sound waves in liquid, and the size and configuration of the pump, or the record devices, and have no known clinical significance.

Water was used in this experimental model in order to maintain a stable level of viscosity during the different parts of the experiment, and to avoid interaction between heparinized blood and the clots. The acoustic properties of sounds transmitted through the chest wall, together with the noise from blood flow in the heart and major vessels in the clinical situation, and those transmitted through water in a plastic bag as in the experimental model, are not comparable. This study did not show if a change in the acoustic fingerprint signifies turbulence, a vortex phenomenon, large eddies from narrowing of the in- and/or outflow, or a normal change in the pump's natural frequency range. Further animal studies on the interaction between the heart, hemodynamics, and blood clotting in acoustic analyses are needed if we are to confirm that experimental measurements can be extrapolated to a clinical system for the detection of pump thrombosis.

The same recording devices and analyzing techniques used in the ongoing SoundMate study were chosen for this study as it is patient friendly, easily usable, and a currently available technique. Further technical models will reveal if this is the optimal technique for this purpose. The lower parts of the frequency spectrum, that showed the greatest changes when clots passed through the pump, are also the frequencies chosen to be prominent in the sound-detecting devices (optimized for voice and music). Whether another system, including software, recording device, microphones, or accelerometers, either without or with other low- and high-pass filters, will reveal other regions and peaks of interest is yet to be determined.

This study shows similar significant changes in the specific acoustic fingerprint regardless of whether it was an artificial or a human blood clot that passed through the pump system, but different changes when the out- or inflow tubes were narrowed by 50%. This suggests that the spectral changes observed contain information about where the clot/thrombosis is located in the pump system, and might be dependent on the direct influence of the clot material on the impeller in the pump house, compared with the change in flow, resistance, and pressure when narrowing the tubes.

In the clinical setting, a sudden increase in power consumption at a fixed pump speed has aroused suspicion of pump thrombosis (3). The sensitivity of this phenomenon is not known due to diagnostic

difficulties with current available diagnostic methods for detecting pump thrombosis, including echocardiography, CT scanning, blood samples, or echocardiographic ramp test (13). In this study, we used an acute clot model, but in the clinical situation the most common scenario is probably that the clot/thrombosis builds up over a longer period of time and includes fibrin as well as fresh clot material in its structure. Due to the difference in clots as well as the hemodynamics between this experimental situation and clinical situation, our power analyses are not directly applicable clinically. It is well known from clinical experience that the first symptoms suffered by a patient with pump thrombosis are sometimes neurological events, including stroke, despite no change in power consumption of the pump. This study shows that even when the pump is filled with material that causes a change in sound and decreases the flow, it does not necessarily induce a rise in power level, so the acoustic analysis cannot be validated against power at this stage. In future clinical studies, the correlation between acoustic analysis and power consumption will hopefully be revealed.

CONCLUSION

This study shows similar significant changes in the acoustic fingerprint of a HeartMate II regardless of whether an artificial or a human blood clot passed through the pump system. Our results indicate that acoustic monitoring of pump performance may become a future tool in left ventricular assist device surveillance.

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Testosterone and Hemoglobin in Hemodialysis Male and Female Patients

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Abstract: It has been speculated that testosterone stimulates erythropoiesis. We hypothesized that hemoglobin levels in hemodialysis (HD) patients are associated with serum testosterone concentrations. Testosterone, hemoglobin, and other biochemical parameters were measured in a representative sample of 98 chronic HD patients (50 male, 48 female; age 30–90 years, mean 65 ± 13.9 years). We investigated relations among serum testosterone concentration, hemoglobin, ferritin, albumin, body mass index, lean body mass, total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein (hsCRP), calcium (Ca), P, intact parathyroid hormone, N-terminal pro-brain natriuretic peptide, Karnofsky performance status, and blood pressure (BP) before and after HD. A statistically significant positive correlation between testosterone and hemoglobin was found in all patients ($r = 0.25$, $P < 0.01$), men ($r = 0.34$, $P < 0.02$), but not in women ($r = 0.27$, $P = 0.07$). Multiple regression analysis for all patients has shown statistically significant association between hemoglobin and testosterone ($P < 0.001$), hsCRP ($P < 0.005$), lean body mass ($P < 0.05$), post-HD systolic ($P < 0.04$), and