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An Investigation into the Clinical Utility of Transfer Functions between the Aortic and Femoral Pressure Waveforms

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Abstract: Management of cardiovascular disease in intensive care would benefit from improved methods for data from clinically available, information rich arterial pressure waveforms. This paper explores the feasibility of using the transfer function between the aortic and femoral pressure waveforms as a diagnostic tool, over an experimental cohort including the progression of sepsis. Transfer functions appeared as physiologically expected, with Bode plot peaks near breathing and heartbeat frequencies. The Bode plot response to clinical interventions and disease progression also matched physiological expectations, with peaks increasing in magnitude in response to fluid infusion and attenuating in response to the progression of sepsis. While there are clear potential diagnostic benefits to the approach, further work is needed to make this information easier to rapidly interpret in a clinical environment, and to evaluate the specificity of the transfer function responses presented here to the progression of sepsis.

Keywords: Bio-signal analysis, processing and interpretation; Cardiovascular system; Decision support

1. INTRODUCTION

Among the foremost health issues in the modern world are cardiovascular disease and dysfunction (CVD), accounting for roughly 31% of global deaths and an $863 billion USD global cost per annum (Roger et al., 2012; Mozaffarian et al., 2016). With aging populations set to drive these figures up further, there is a clear need to reduce the occurrence of inadequate or incorrect diagnosis of cardiac disturbances in the Intensive Care Unit (ICU), which is associated with increased length of stay, cost and mortality (Angus et al., 2001; Pineda et al., 2001).

ICU management of CVD usually occurs in an information rich environment, with significant, patient specific, continuous information available from arterial and venous pressure catheters placed near the heart. However, this volume of available information is not always associated with improved clinical outcomes (Frazier and Skinner, 2008; Chatterjee, 2009), and the information rich pressure waveforms provided by catheters are frequently reduced to simple, lumped averages that can be rapidly parsed, with much information lost in the process. Thus, ICU CVD management would benefit greatly, at minimal cost, from improved real-time analysis and interpretation of these currently measured waveforms.

One means of interpreting waveform information is the transfer function. Transfer functions relate the outputs of a system to their inputs, and are popular in a wide variety of fields (Wei, 1994). Transfer functions are expressed in the frequency domain, rather than the time domain, and are defined for linear time-invariant systems. While real world systems often do not strictly conform to the definition of 'linear time-invariant', within certain boundaries their behaviour generally can be expressed as such. Transfer functions are used to mathematically analyse system behaviour and predict response to a wide range of inputs, for example a building's seismic response (Takewaki, 1997; Chase et al., 1999), as well as to design systems to certain performance criteria (Horowitz and Shaked, 1975).

For a discrete-time system, with an input $x(t)$ and output $y(t)$, the transfer function can be expressed:

$$H(z) = \frac{Y(z)}{X(z)} \tag{1}$$

where $H(z)$ is the transfer function and $Y(z)$ and $X(z)$ are the system output and input, respectively, transformed onto the complex z-plane, which is used to express system behaviour in the frequency domain. Provided the inputs and outputs are periodic, the transformation from time to frequency domain can be achieved using Fourier, or similar, transforms (Bracewell and Bracewell, 1986).

Transfer functions have previously been applied to various biological systems, including the circulatory system. Prior work investigated transfer functions between inter-beat averages of airway pressure, aortic pressure split into diastolic, systolic and pulsatile components, and heart rate (Saul et al., 1991; Berger et al., 1989). These works primarily focus on longer term trends and the circulatory system's auto-regulation mechanisms. Additional results exist using transfer functions to estimate the aortic pressure waveform from a peripheral pressure waveform (Karamanoglu et al., 1993). However,

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there is currently no work exploring the diagnostic potential of intra-beat cardiovascular pressure wave transfer functions.

This paper explores the diagnostic potential of intra-beat transfer functions across an animal trial dataset encompassing the development and progression of sepsis. As sepsis primarily effects the systemic circulation, transfer functions between aortic pressure (P_{ao}) and femoral pressure (P_{fe}), both located within this region of circulation, are investigated here. These waveforms are located near enough each other that both waveforms bear strong resemblance to one another, with minimal influence on either waveform by other active processes in the body, which a transfer function would be unable to account for. Further, both waveforms are measured with relative frequency in intensive care (Gershengorn et al., 2014b; Gershengorn et al., 2014a).

2. METHODS

2.1 Experimental Data

The experimental procedure presented here was approved by the Institutional Animal Care and Use Ethics Committee of the University of Liège, Belgium (Reference Number 14-1726). Their guidelines conform completely with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996), as well as EU DIRECTIVE 2010/63/EU on the protection of animals used for scientific purposes. Five male, pure Piétrain pigs, which weighed between 18.5 and 29.0 kg were sedated, anaesthetised and mechanically ventilated (GE Engstrom CareStation). Aortic and femoral pressures were continuously sampled at a frequency of 250 Hz using pressure catheters (Transonic, NY, USA). The experimental protocol included a model of sepsis, as well as several clinically standard interventions:

- An infusion of endotoxin (lipopolysaccharide from E. Coli, 0.5 mg/kg), performed over 30 mins. This infusion served to induce a model of septic shock, causing inflammatory responses and capillary leakage leading to hypovolemia, global tissue hypoxia, and cardiac failure (Nguyen et al., 2006).
- Several positive end-expiratory pressure (PEEP) driven recruitment manoeuvres, performed both before and after the endotoxin infusion. Recruitment manoeuvres drive a changes in cardiac preload, resulting in an associated decrease in mean blood pressure and cardiac output (Jardin et al., 1981).
- Several 500 mL infusions of saline solution, performed over 30-minute periods both before and after the endotoxin infusion. These fluid infusions served as a simulation of fluid resuscitation therapy, a frequently employed hemodynamic resuscitation method in patients with severe sepsis, which seeks to increase circulatory volume (Boyd et al., 2011; Vincent and Gerlach, 2004; Schierhout and Roberts, 1998; Stewart et al., 2009; Kastrup et al., 2007).

Once sepsis was sufficiently developed and the aortic and femoral pressure waveforms became significantly distorted, remaining information was discarded. As this significant waveform distortion typically occurred at advanced stages of circulatory failure, very near death, it is unlikely this information would be of use for diagnostic ICU monitoring. While not all pigs completed the entire post-endotoxin protocol before circulatory failure occurred, each data set contains at least 5,000 heartbeats worth of data. Overall, this analysis was conducted over 5 subjects across a total of 46,311 heartbeats.

2.2 Data Processing

As experimentally gathered data from a biological system is not strictly linear time-invariant, some post-processing is required to obtain suitable waveforms. First, waveforms were grouped into sets of 8, to provide a sufficient window length to capture lower frequency influences, such as the breathing cycle, given the 250 Hz sampling rate and average 60 bpm cardiac cycle. Second, for each of these sets of 8 heartbeats, the late-diastolic region of the first heartbeat (Region D, Fig. 1) was adjusted via a shear transform (Stevenson et al., 2012) to match the beginning of the corresponding region for the final heartbeat. This transform is illustrated in Fig. 1 by the dashed horizontal line, where only a single heartbeat instead of 8 is shown for ease. The shear transform provides a repeating sequence of heartbeats without any step changes, and thus a 'periodic' waveform suitable for a Fourier, or similar, transform. These operations were performed for both P_{ao} and P_{fe}, though only P_{ao} is shown in Fig. 1.

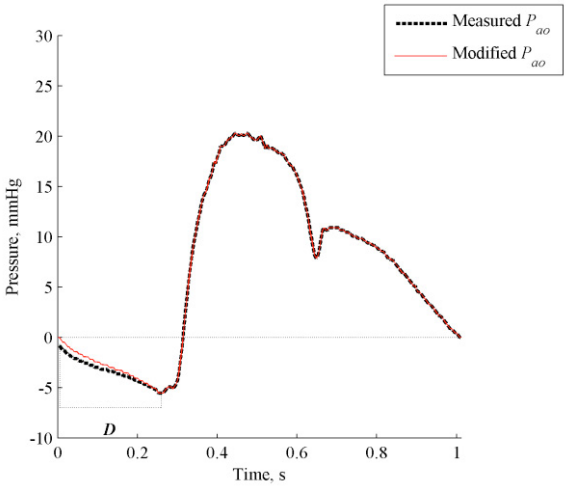

Fig. 1. Modification of P_{ao}. Only one heartbeat is shown for clarity, though this operation actually performed between the 1st and 8th heartbeat of a set.

The set of 8 heartbeats then had its mean set to zero, and was zero padded to a length of 4096 samples. This process provides a frequency resolution of approximately 0.06 Hz, covering an effective range from 0 – 125 Hz, yielding sufficient frequency resolution and range to easily separate breathing cycles set at 0.25 Hz by the ventilator, and heartbeats at ~1 – 2 Hz. Zero padding was used instead of a broader windowing function as

a broad window risks including significant changes in the shape of P_{ao} or P_{fe}, resulting in a signal that changes too dramatically to be approximated by a periodic function or distorts the dynamics in the waveform.

Bode plots were constructed using Thomson multi-taper transforms (Thomson, 2000). These transforms employ a set pairwise orthogonal FIR filters, derived from Slepian sequences, to obtain multiple, statistically independent estimates of the underlying spectrum from a given sample. These statistically independent spectrum estimates can then be averaged to provide an estimate of the overall spectrum. The averaging of multiple independent transfer function estimates tends to provide a smoother, less noisy Bode plot than when Fourier transforms are used. The multi-taper transforms were performed using the MATLAB 'pmtm' function (R2017b, 64-bit, The Mathworks, Natwick, MA, USA).

2.3 Data Presentation

As the cardiovascular system is not linear time-invariant in the long term, this method generates a large number of short term transfer functions, which can evolve over time. Presentation of such a large number of Bode plots was performed in two different fashions. The first manually divides the data into sections between interventions, where the system should behave in an approximately linear time-invariant form. The Bode plots within each region are averaged, providing a small set of representative Bode plots. This approach results in far fewer Bode plots to be displayed, at the cost of averaging large areas of data where changes may be occurring in the shorter term. However, it allows the results to be presented in a 2-D profile, which aids interpreting the data.

The second approach plots full 3-D surface plots, showing the evolution of the transfer functions over the course of the experiment for each pig. This approach provides a full indication of the evolution over time of the transfer function, but is more difficult to visually interpret.

3. RESULTS

Table 1 presents the average heart rate pre- and post-endotoxin infusion for each pig. Of note is a consistent and statistically significant ($p < 0.05$, two-tailed, paired Student t-test), if modest, decrease in heart rate post endotoxin infusion. Note that, as the pigs were sedated, breathing frequency was set by the mechanical ventilator, and thus was roughly identical for all pigs.

Table 1. Average heart rate pre- and post- endotoxin for each pig.

Pig	Pre-Endotoxin	Post-Endotoxin
Pig 1	1.01 Hz	0.96 Hz
Pig 2	1.22 Hz	0.97 Hz
Pig 3	1.50 Hz	1.35 Hz
Pig 4	1.15 Hz	1.02 Hz
Pig 5	1.23 Hz	1.17 Hz

Fig. 2 presents the P_{ao} and P_{fe} waveforms for Pig 1, divided into regions over the clinical trial. This figure provides an example progression of the clinical protocol, and the colours used to designate this progression in later figures. The P_{ao} and P_{fe} waveforms progress from a light to a dark cyan throughout the pre-endotoxin infusion procedures, with recruitment manoeuvres (RMs) denoted by dashed lines, and then magenta to red throughout the post-sepsis procedures, with RMs again denoted by dashed lines.

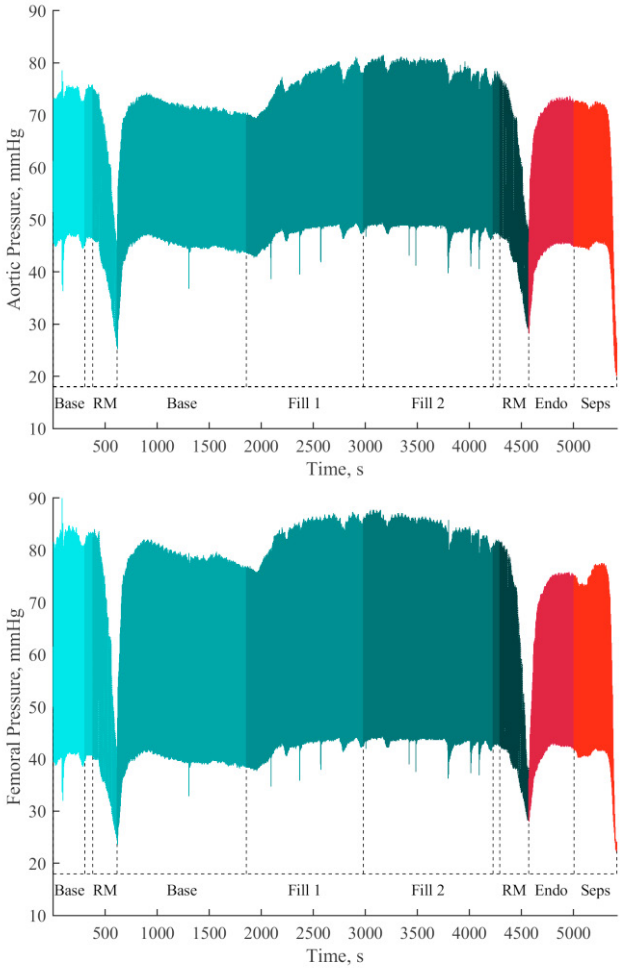

Fig. 2. Progression of P_{ao} and P_{fe} waveforms for Pig 1 throughout the experimental protocol. 'Base' denotes baseline, 'fill' fluid infusion, 'endo' endotoxin infusion and 'seps' sepsis.

Fig. 3 presents the transfer function Bode plots for P_{ao} and P_{fe}, divided into clinical trial regions by hand. The colour system used in Fig. 2 is employed. The vertical dashed lines denote subject specific average breathing and heartbeat frequencies (Table 1) from left to right, respectively. Beyond a frequency of about 3 Hz, the data is overwhelmed by signal noise.

Fig. 4 presents the surface plots of transfer function Bode plots over the experiment. The axes are limited to frequencies below 3 Hz, based on Fig. 3. Here the transfer function progression over time is represented, but the volume of information makes these plots more difficult to interpret.

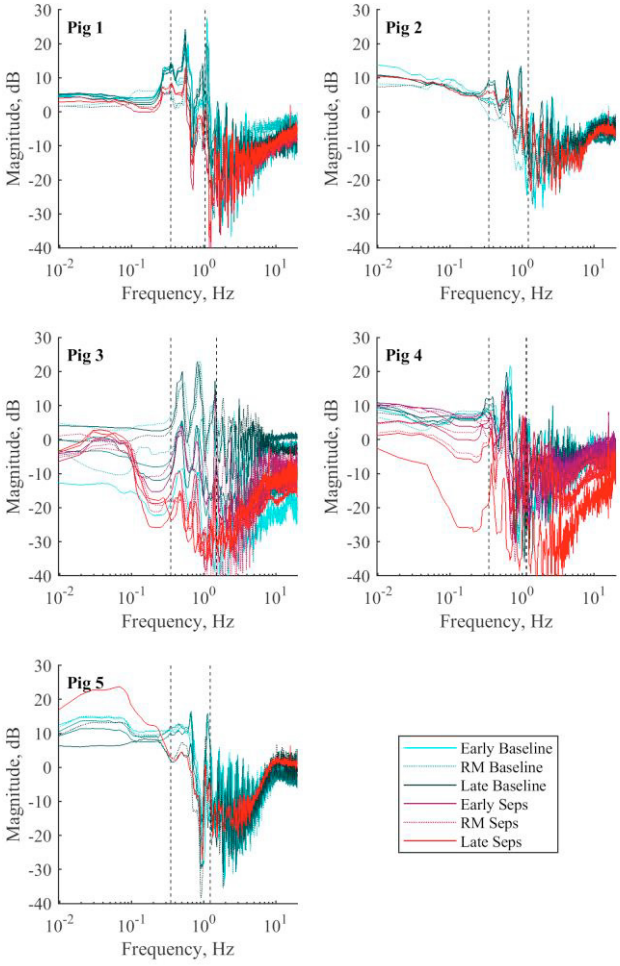

Fig. 3. Transfer function regional profile magnitude plots for Pigs 1 – 5. Vertical dashed lines represent average breathing (left) and heartbeat (right) frequencies.

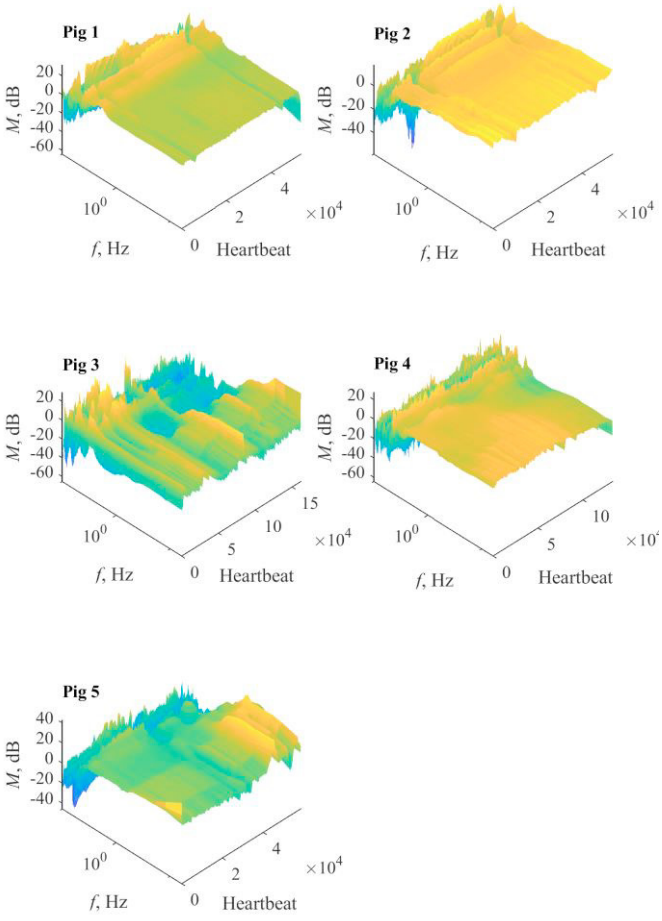

Fig. 4. Transfer function Bode surface plots for Pigs 1 – 5. These plots are essentially the plots in Fig. 3 projected through time along the z-axis, labelled 'Heartbeat'

4. DISCUSSION

Fig. 3 shows the Bode plots for the transfer functions between P_{ao} and P_{fe}. As would be expected, there are relatively consistent peaks at breathing frequency of about 0.25 Hz and heart rate frequency of 1.0 – 1.5 Hz, with the breathing peak generally broader and lower magnitude than the heart rate peak. In general, both peaks appear to increase in magnitude as fluid infusion occurs, and attenuate as sepsis develops.

This behaviour corresponds to what might be physiologically expected, and is likely a response to changes in circulatory volume and arterial tone. Fluid infusions increase circulatory volume without altering arterial tone, thus more pressure-pulse energy is conserved through the arterial system and the magnitude of the Bode plot peaks increases. Conversely, sepsis drives both a loss of arterial tone and a loss of circulatory fluids into the periphery (Dellinger et al., 2008; Dombrovskiy et al., 2005), thus more pressure-pulse energy is lost in the arterial system and the magnitude of the Bode plot peaks decreases.

Another interesting topographical feature of the Bode plots in Fig. 3 are a general change in the shape of the plot at frequencies below breathing frequency. While this change is more pronounced in some pigs than others, and specifically lacking in Pig 2, in general there is a shift from a relatively flat, consistent transfer magnitude at these low frequencies to a roughly sinusoidal shape with higher magnitudes at lower frequencies and a distinct dip at roughly 0.1 – 0.12 Hz. The frequency of this dip roughly corresponds to the frequency of Mayer waves (Julien, 2006), cyclic waves in arterial blood pressure thought to be tied to the baroreceptor and chemoreceptor reflex control systems. As these reflex control systems regulate arterial tone, and sepsis frequently causes a loss in control of arterial tone as well as a loss in arterial tone itself, it is possible the signal attenuation in this region is representative of a failing of these reflex systems. It is possible that the lack of this dip manifesting in Pig 2, and its being less pronounced in Pigs 1 and 5, is due to the rapidity with which these pigs died after endotoxin infusion, which resulted in a relatively truncated period of post-infusion monitoring and less apparent, full progression of sepsis.

At frequencies above ~3 Hz the Bode plot begins to oscillate rapidly. This behaviour suggests that a combination of higher frequency harmonics and noise, generated by discretisation errors in the catheter and mains noise amongst other issues, is dominant, and the signal is no longer easily interpretable. However, as this frequency is at least double the heartrate frequency of approximately 1.0 – 1.5 Hz, it is likely only these higher frequency harmonics, which are of little physiological relevance, rather than important signal information that is being lost.

Fig. 4 shows a full surface plot of the transfer function between P_{ao} and P_{fe}, which reveals several interesting trends that are more difficult to observe in Fig. 3. First, sharp drops in the transfer function across all frequencies occur with reasonable consistency at RM delivery, most obviously in Pigs 1 and 2. This dip is likely due to the aorta, and therefore P_{ao}, being inside the thoracic cavity, and thus, along with the heart, being compressed by the lungs during a RM. Conversely, the femoral artery and P_{fe} sit outside the thoracic cavity, and are not similarly compressed. The general attenuation that occurs as the experimental protocol progresses at frequencies above 0.1 Hz can also be observed in more detail in this figure.

Overall, the transfer function outputs conformed to a variety of expected physiological responses associated with both clinical interventions and disease progression, supporting their potential use as a tool for providing additional diagnostic information in a clinical environment. For example, the potential to detect loss of control of arterial tone through the attenuation of Mayer waves could have diagnostic benefits specific to the detection of sepsis, though a control case involving a disease that does not affect arterial tone would need to be examined. It is of note that the location of P_{ao} and P_{fe}, with both input and output within the arterial side of systemic circulation, provides a wealth interesting information about this region, but is limited to just that. However, as this circulatory area represents the flow of blood from the heart to all organs in the body, it is an extremely important circulatory area with a notable diagnostic relevance.

However, a major question to be raised with regards to this approach is whether these transfer function Bode plots provide additional information that is easier to interpret than what is directly available from observing P_{ao} and P_{fe}. Clinicians are already presented with a large volume of information in the ICU, and additional diagnostic aids should seek to reduce the clinical burden of interpreting these large volumes of information. There is potential for improvements in this area, which could be achieved by focusing on frequencies of interest and providing a single ‘magnitude’ value, or other summary metric, at these frequencies to clinicians over time, a more rapidly interpretable and familiar form of data presentation in the ICU.

A notable limitation of this method is that both P_{ao} and P_{fe} are located upstream from the capillary beds of the systemic circulation, which are the physiological structures most effected by sepsis, as it is disease of the micro-circulation. Intuitively, one would expect the transfer function between P_{fe} and central venous pressure (P_{vc}) would provide better or further information about the state of these capillary beds. However, there are several difficulties involved with using P_{vc}, all of which stem from the low pressures present in the vena cava and venous circulation in general.

First, discretisation error becomes large due to the amplitude of P_{vc}, roughly 8 mmHg to 12 mmHg (Boyd et al., 2011), which is not sufficiently greater than pressure catheter resolution, and can result in a waveform consisting of a series of step changes rather than smooth contours. Second, P_{vc} is significantly affected by the behaviour of the right heart, which is the source of the ‘A’ and ‘C’ peaks in the signal, which have a roughly equal magnitude to the ‘V’ peak from upstream flow (Hall, 2010). Due to these other effective inputs, a large amount of post processing would be necessary to make P_{vc} usable in a transfer function, likely resulting in the loss, or at least distortion, of information.

There are two further limitations in this study. First, the data presented is gathered solely from pigs, not humans. However, pigs and humans are known to have very similar physiology (Weaver et al., 1986). Additionally, an experimental cohort of pigs, as opposed to a clinical human cohort, allows full instrumentation and the ability to directly induce disease states. As such, it provides an excellent and rigorous initial data set for a feasibility study, as presented in this paper.

The second limitation is the fact the data consists of a single protocol and disease state. However, the set of clinical interventions employed are both common and important, and the selected disease state, sepsis, is common, dangerous and varied, as well as significantly impacting the systemic circulation, where the P_{ao} and P_{fe} waveforms are measured. As such, it is both a relevant and challenging condition to diagnose, and an excellent initial condition to evaluate.

Overall, the method shows potential, allowing existing but difficult to interpret information to be evaluated from a new perspective. Further work is required in assessing the uniqueness, and thus diagnostic potential, of certain changes in the transfer function Bode plot to sepsis progression. Another potential area for improvement is, potentially, to provide a further interpretation layer or targeted outputs at specific frequencies, such as Mayer wave, breathing and heartbeat frequencies, in order to make rapid interpretation of results easier in a clinical environment.

5. CONCLUSION

The diagnostic potential of transfer functions between the aortic and femoral pressure waveforms was investigated over an experimental data cohort involving the progression of sepsis, along with a number of clinically standard interventions. The transfer function bode plots were found to conform to physiologically expected behaviour, with peaks at breathing and heartbeat frequency, as well as increased magnitude in response to fluid infusion and attenuation in response to sepsis. Longer term signal attenuation at the frequency of Mayer waves as control of arterial tone was lost was also observed. While there are clearly potential diagnostic benefits to the method, further work is required to make the method outputs easier to rapidly interpret in a clinical setting,

and to investigate the specificity of the response observed in this paper to the progression of sepsis.

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