Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Thale Maria Bjørnbeth

Qualitative changes in microvascular resistance in early sepsis

Graduate thesis in Medicine

Supervisor: Audun Eskeland Rimehaug, Idar Kirkeby-Garstad

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Abstract

Introduction: Early detection and management is crucial for sepsis survival. Sepsis is detected with the SOFA scoring system, including severe hypotension. However, hypotension is a late and unspecific symptom of sepsis. Our aim is to explore if there are qualitative changes in peripheral resistance among septic patients compared to healthy control subjects, which can possibly be used in earlier detection of sepsis.

Method: We have gathered simultaneous and continuous recordings of arterial blood pressure and arterial peripheral blood flow, from 10 septic patients and 18 control subjects, and done a spectral analysis. By transferring data from the time domain to the frequency domain, we got an overview of the frequencies embedded in the signal. The frequency plots were studied visually, from 0 to 0,5 Hz. By studying the relationship between pressure and flow curves, qualitative changes in resistance were assessed.

Results: We observed a discrepancy between arterial flow and arterial blood pressure in the control group at low frequencies, which was less evident in patients with septic shock. Among a total of 18 controls, 16 had deviating plots with extra peaks in either flow or pressure. Among a total of ten sepsis patients, three had deviating plots, and seven patients had equal number of peaks in flow and pressure, the patterns in the two parameters matching. The deviating peaks in both groups were mainly at low frequencies; between 0 – 0.2 Hz.

Conclusion: Our results suggest that spontaneous oscillations in peripheral resistance is decreased in septic shock. Based on previous literature, we can assume that this is a result of disturbance of the autonomic interplay which regulates the arteriolar vasomotors. This can possibly be used as a diagnostic tool in the future, for earlier detection of sepsis. This is a pilot study, and the data set is too small to make a conclusion.

Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined by the SOFA-score, which detects altered function of the circulation, liver, coagulation, CNS, kidneys and the respiration system. The word life-threatening is defined as 10% risk of death, which is present with a score of one in any of the SOFA criteria [1].

In current clinical practice, we detect sepsis when a patient with suspected infection meets at least two of the clinical criteria on the quick SOFA-score, and set the diagnosis when there is an increase in SOFA-score by two points or more. Septic shock is defined when the patient has hypotension requiring vasopressors to maintain a mean arterial pressure above 65 mmHg, despite of adequate fluid resuscitation, and elevated serum lactate concentration of more than 2 mmol/L [2].

Quick SOFA is a score consisting of three clinical parameters, that can easily be measured without any time-consuming tests, and is used in early detection of sepsis. A hospital patient with infection is at high risk of death or a long stay in the ICU if they meet at least two of the criteria: alteration in mental status, systolic blood pressure of less than 100 mm Hg, or a respiratory rate of more than 22 breaths per minute [2].

Earlier, sepsis was defined by the satisfaction of any two of the Systemic Inflammatory Response Syndrome-criteria (SIRS) [3], combined with a suspected source of infection. However, this applies to a great portion of infectious patients, and there was a need for a way of separating early septic stages from the normal course of infection. In 2016, the guidelines were revised [4], and sepsis is now defined as what we earlier termed severe sepsis. While the former criteria recognised signs of inflammation, the new criteria focus on signs of organ failure. The downside with the new guidelines is obvious - the patient already has, by definition, at least one end organ failure and 10% risk of dying when sepsis is diagnosed. Mortality increases drastically with increasing organ failure. For a SOFA-score of 13, mortality is expected to be 50%, and for scores above 15, 90% mortality should be expected [5]. How far the organ failure can proceed depends on time from debut to management. Countless studies emphasize the importance of early management in sepsis. A retrospective study from California by Liu VX et al., including 35 000 randomly selected septic patients in

21 emergency departments between 2010 and 2013, concluded that "hourly delays in antibiotic administration were associated with increased odds of hospital mortality, even among patients who received antibiotics within 6 hours. The odds increased within each sepsis severity strata, and the increased odds of mortality were greatest in septic shock" [6]. A study by van Ruler O et al. from The Netherlands, which reviewed mortality data from severe sepsis in large randomized trials, showed that death from severe sepsis declined from 44% to 35% between 1990 and 2000, the two most effective strategies being early appropriate antibiotics and early goal-directed therapy [7]. A study from Germany by Christ M. et al. showed a substantial decrease in in-hospital mortality among septic patients who were given prehospital treatment following sepsis guidelines [1].
Early management is therefore crucial, and to accomplish this, we need a way for early detection of sepsis.

In most septic patients, there is a decrease in peripheral resistance due to a massive arteriolar dilatation, resulting in low blood pressure. However, low blood pressure is a late and also unspecific symptom of sepsis, especially among the young and otherwise healthy patients, who have great ability to compensate by increasing cardiac output. Serious hypotension in this situation is often difficult to treat, and without effect of treatment, inadequate organ perfusion can lead to multi-organ dysfunction and death.

Peripheral resistance can be estimated by an analogue of Ohm´s law: $resistance = \frac{\text{systemic pressure gradient}}{\text{Flow}} = \frac{\text{MAP} - \text{CVP}}{\text{CO}}$. This model is however a gross simplification, as the interaction between blood pressure and flow is more complicated. The model assumes that we have rigid pipes (which blood vessels are not), non-pulsatile flow and Newtonian fluid (whereas blood is non-Newtonian). By doing simultaneous and continuous measurements of arterial pressure and –flow, we can gather not only quantitative, but also qualitative information on changes in resistance.

There are peripheral autoregulation mechanisms which ensures smooth flow to the tissue by regulating the resistance locally. The mechanism consists of precapillary sphincter muscles, called vasomotors, which regulate flow from the arteriole to the capillary bed. These are important for the distribution of blood flow between organs. When resistance changes, the relationship between pressure and flow is affected.

To unravel the exact relationship between blood flow and –pressure, and through this look at different components of flow resistance, continuous flow- and pressure measurements are necessary. This enables spectral analysis of these two signals. Spectral analysis is based on the principle that any repetitive signal can be decomposed to a set of sine waves with different frequencies. By transferring data from the time domain to the frequency domain, we get an overview of the frequencies embedded in the signal, and their amplitude. This means that we can tell which frequencies constitute a greater part of the signal power.

There are several studies which have detected spontaneous oscillations both in arterial pressure and cardiac output, and also seen significant deviation from the control subjects among patients with septic shock, especially regarding low frequency oscillations (≈ 0,1 Hz), overall variability and ultra-low frequencies (≈ 0.05-3 mHz) [8-10]. However, none of the previous studies have done simultaneous recordings of both pressure and flow, which is necessary to identify contributions from peripheral resistance.

In this study, we want to look closer on the peripheral resistance during sepsis. By studying the relationship between pressure and flow curves, we have tried to detect qualitative changes in resistance. By comparing septic patients with the control group, we can see if the qualitative changes are divergent, as a sign of arteriolar dysfunction in sepsis. These qualitative changes can possibly occur before the quantitative changes, and can thus be used in earlier diagnostics of sepsis. Naturally, flow and pressure correlate to a great extent, both dominantly following the pulse frequency. What we will study carefully is however the frequencies in flow that deviate from pressure, where changes in flow cannot be attributed to changes in pressure. Based on earlier studies, we expect to see this in low frequencies.

Method

Study populations

Patients. We have gathered data from 10 sepsis patients, recruited from the Intensive Care Unit at St. Olavs University Hospital. These recordings were done by anaesthetist Daniel Bergum, within the first couple of hours after admission to the ICU. Inclusion criteria were patients at the age of 18 years or more, in the ICU with a suspected infection and an increase in SOFA score of two or more, based on the most severe measurements done within the first 24 hours after hospitalization.

Control subjects. We have gathered data from 21 control subjects, recruited using an ad at the internal website for employees at the Norwegian University of Science and Technology (NTNU). These recordings were done by fifth year medical student Thale Maria Bjørnbeth. We asked verbally for current or past diseases and the use of medication. They were also asked not to drink caffeinated beverages until 4 hours before measurements, which led to most of the measurements being done in the morning. Exclusion criteria were age less than 18 years, and use of blood pressure medication that affects the peripheral vessel tonus, i.e. ACE-, ATII- and calcium inhibitors.

The study was approved by the Regional Ethics Committee (REK) in advance, with reference number 2019/782.

Data recording

Continuous arterial flow-recording. The device is an ultrasonic doppler using unfocused transmit beams. The probe is developed at NTNU by the professor Hans Torp. It was placed on the back of the hand, between the first and second metacarpal bones. Flow recordings are taken from a side branch of the radial artery. This was done in the same manner in patients and control subjects.

Continuous arterial blood pressure-recording. Blood pressure in sepsis patients were recorded from the Philips IntelliVue X2 patient monitor version M8010A (Philips, Amsterdam, Netherlands), which gathered the signal from a fluid filled radial artery cannula. Data from control subjects were gathered non-invasively with a photopletysmographic cuff,

which is placed on the third finger, middle phalang. The device is a Human Nano NIBP (ADInstruments Ltd, Oxford, United Kingdom), where the technology for the device has been developed by Finapres (Finapres Medical Systems, Enschede, Netherlands). Previous versions of this hardware have been validated in both healthy volunteers and in patients with sepsis [11-13]. The NIBP was placed on the opposite hand from the flow-recordings, as we experienced it to cause noise in the flow-signal when put on the same hand.

Synchronization. The flow- and pressure recordings were done simultaneously over four minutes. To compensate for delays in the signal acquisition chain, the signals were synchronized based on the normalized cross-correlation between corresponding signal pairs. The estimated delay was the lag for which the normalized cross-correlation had the maximum value. Furthermore, the signals were re-sampled to a common sampling rate in order to simplify further analysis. An in-house developed Matlab-based framework was used for synchronization purposes. We also cut the first 20 seconds of data, i.e. the 10 000 first samples of both flow and pressure, to eliminate the part of the recording the NIBP used to detect a pressure signal.

Spectral analysis

The data were transformed from time to frequency domain using a Fast Fourier Transform (FFT), in MatLab (R2018b, MathWorks, Natick, MA, USA). We subtracted the value "x-mean" from x in the function, to remove sidelobes. We also put on a Hanning Window to remove noise, however at the cost of a great deal of information. Consequently, the curves were visualized both with and without a Hanning Window.

Data analysis

Frequencies of interest. As mentioned, we were mostly interested in frequencies below 1 Hz, based on findings in previous literature.

Visual analysis. We analysed the spectral plots visually. First, we compared the spectral plots for arterial pressure and –flow, in each of the patients and control subjects separately, to see where the frequency spectra differed in pressure and flow. Second, we compared the degree of discrepancy between patients and healthy subjects. When comparing the two groups we looked at the whole population and their tendencies, not a one-to-one matching.

Results

We saw a discrepancy between arterial flow and arterial blood pressure in the control group, which was less evident in patients with septic shock. Among control subjects, flow tends to have additional frequency peaks, in addition to the ones which correlate with pressure. This is especially seen at low frequencies; below 0,05 Hz. Among patients, when counting peaks, the number is about the same in flow and pressure.
We looked at frequencies below 1 Hz, but as our findings were in frequencies below 0,5 Hz, this is the range in the plots, to make the findings easier to visualize.

Among the 21 control subjects, two used blood pressure medication which affects the peripheral vessels, and one had caffeinated beverages less than 4 hours within measurements. All three were excluded from the study, but they followed the same trend with discrepancies between arterial flow and arterial blood pressure. We therefore have results from 18 control subjects in this study.
The study was designed for 30 sepsis patients, but we only got appropriate measurements of 10, the other recordings being too short.

Patient 2

Flow and pressure have the exact same peaks. This trend is seen in seven of the patients. The lack of peaks makes this example especially clear, same as for patient 3 and 9.

Patient 3

Flow and pressure have the exact same peaks.

Patient 5

Flow and pressure have very close to the exact same peaks, making out the same pattern.

Patient 6

Flow and pressure have very close to the exact same peaks, making out the same pattern.

Patient 9

Flow and pressure have the exact same peaks. The lack of peaks makes this example especially clear.

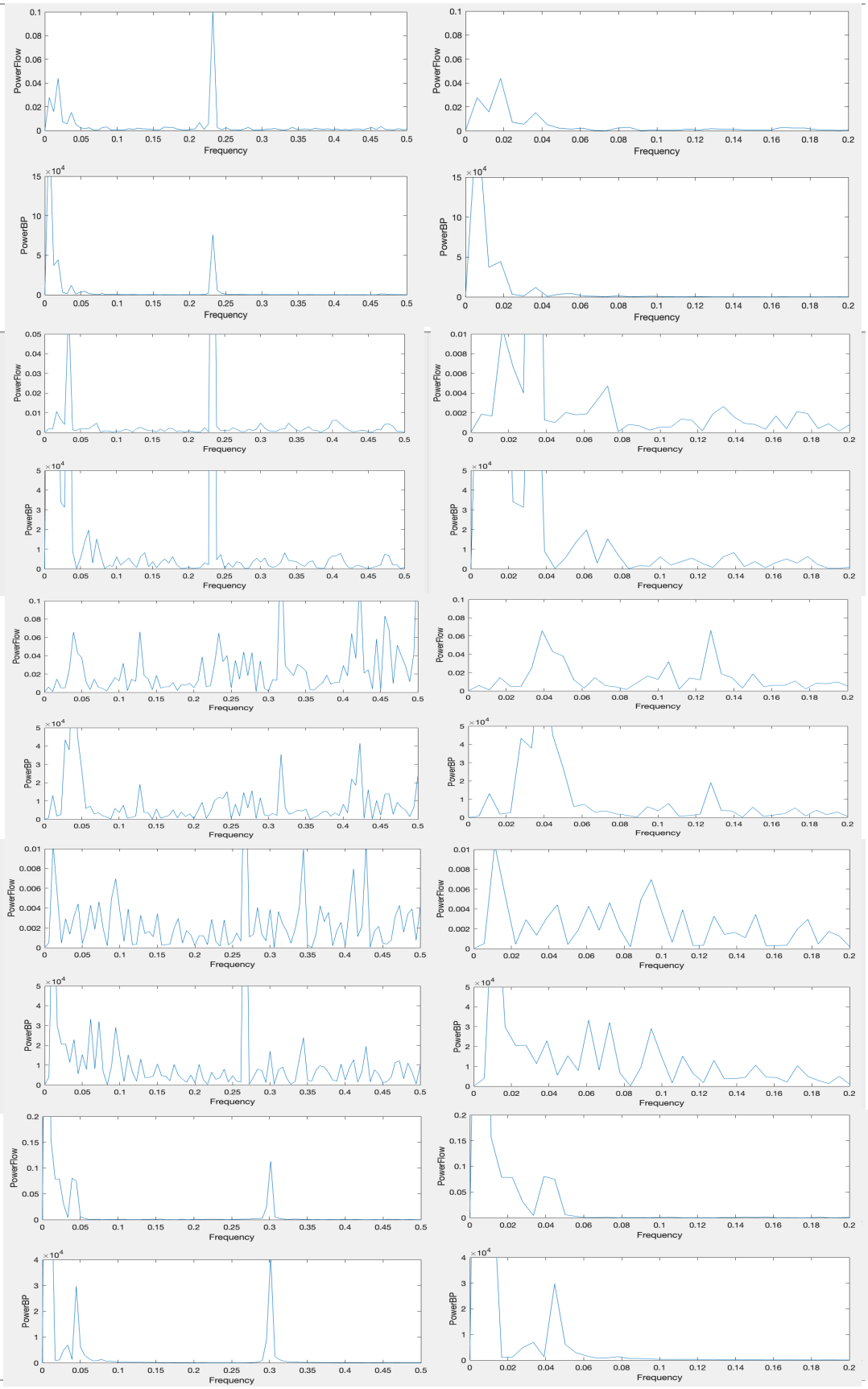

Figure 1: *Examples of spectral analysis of arterial flow and -pressure among septic shock patients. The x-axis is the frequency, and the y-axis the signal power, which is proportional with the amplitude of each frequency. The two columns have different zoom on the x-axis, to clearly display the peaks. The peaks picture the different oscillations, which are counted regardless of the absolute values. Therefore, the scale on the y-axis is not important.*

Control subject 9

Flow has two peaks below 0,02 Hz where pressure has only one.
One additional peak in flow without a match in pressure were seen in nine control subjects.

Control subject 10

Flow has peaks at 0,03 and 0,06 Hz which is not seen in pressure. Two additional peaks in flow without matches in pressure were seen in three control subjects.

Control subject 11

Pressure has one peak below 0,01 Hz, while flow has two broader complexes with at least two definitive peaks from 0-0,05 Hz. Peaks in pressure without a match in flow were seen in seven control subjects. Four of these are overlapping with the group that have peaks in flow without a match in pressure, like this case.

Control subject 15

Flow has a peak from 0,01-0,02 Hz which is not seen in pressure.

Control subject 20

Pressure has a peak at 0,02 Hz, while flow has two peaks - one below and one above 0,02 Hz.

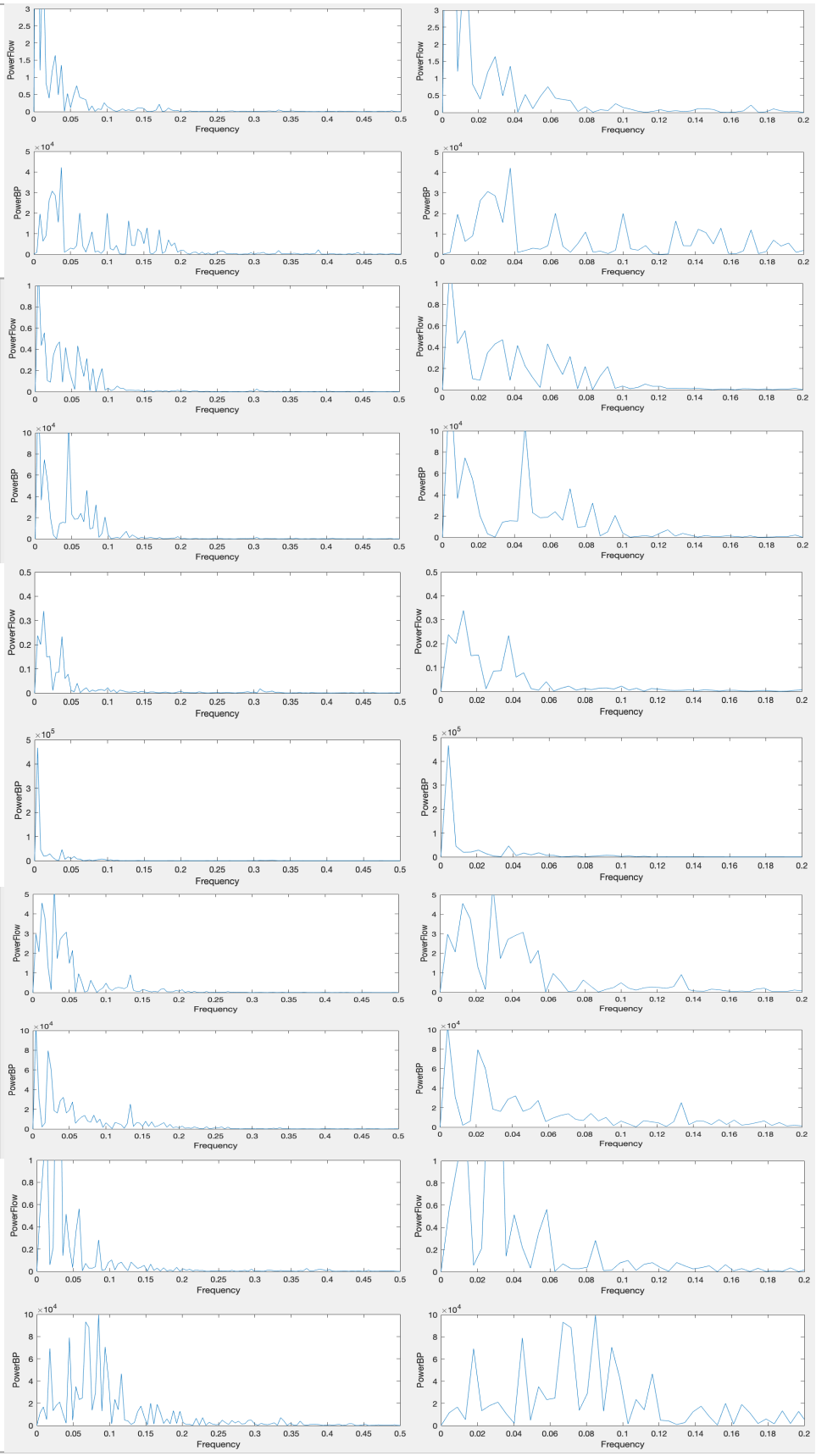

Figure 2: *Examples of spectral analysis of arterial flow and -pressure among healthy control subjects. The x-axis is the frequency, and the y-axis the signal power, which is proportional with the amplitude of each frequency. The two columns have different zoom on the x-axis, to clearly display the peaks. The peaks picture the different oscillations, which are counted regardless of the absolute values. Therefore, the scale on the y-axis is not important.*

Patient	Sex	Age	ICU day of measurement	Noradrenaline	MAP	Total days in the ICU, hospital survival
				[ug/kg/min]	*[mmHg]*	
1	Male	74	2	0,53	71	10, alive
2	Male	74	1	0,33	67	5, alive
3	Female	73	1	0,17	83	7, alive
4	Male	52	2	0,07	76	28, alive
5	Male	72	1	0,11	85	8, alive
6	Male	84	1	0,33	64	8, dead
7	Male	83	1	0,28	64	8, alive
8	Female	67	1	0,16	79	5, dead
9	Male	61	1	0,34	62	82, alive
10	Male	73	1	0,6	65	13, alive

Table 1: *Clinical and demographical data on all the sepsis patients included in the study.*

Control subject	Sex	Age
1	Female	24
2	Female	36
3	Female	45
4	*Excluded*	
5	Female	32
6	Female	57
7	Male	44
8	*Excluded*	
9	Female	52
10	Male	62
11	Male	59
12	Female	51
13	Female	65
14	Female	48
15	Female	68
16	Female	57
17	*Excluded*	
18	Female	26
19	Male	34
20	Male	24
21	Female	57

Table 2: *Demographic data on all the control subjects included in the study.*

Summary of all the cases included in the study

Among a total of 18 controls, nine had one -, and three had two or more peaks in flow without a matching peak in pressure. All these additional peaks in flow were at frequencies 0,06 Hz or below, except in one, which had several additional peaks up to 0,2 Hz. Four controls had one extra, and three had two extra peaks in pressure without a matching peak in flow. Three of these were overlapping with first 12 mentioned cases. Two controls had equal amount of frequency peaks in flow and pressure, where the patterns were matching especially in one. Among a total of ten sepsis patients, two had one extra peak in flow compared to pressure, and one had one extra peak in pressure compared to flow. All these deviating peaks were at frequencies below 0,02 Hz. Seven patients had equal number of peaks in flow and pressure, the patterns in the two parameters matching.

Discussion

In the present study, we found a tendency that the discrepancy between flow and pressure is more evident among healthy control subjects than in patients with septic shock. Where there are peaks in flow and not in pressure, or vice versa, there is an oscillation in resistance, affecting the relationship between the two parameters. This is how simultaneous measurements of arterial flow and pressure enables the examination of qualitative changes in resistance. These oscillations in resistance may suggest that peripheral autoregulation mechanisms are active. Our findings suggest therefore that these mechanisms are more active in healthy control subjects than in septic patients, which is consistent with the theory that there is less activity in the vasomotors in septic patients.

Some of the spontaneous oscillations among the healthy population, in addition to respiratory oscillations, are probably due to vasomotors (flow) and a complex interplay between autonomous nuclei in the brainstem and the peripheral baroreceptor system (pressure) [10]. The vasomotors are part of multiple feedback-loops. The input is balanced between sympathetic and parasympathetic stimuli. Each loop takes a different amount of time, leading to oscillations with different frequencies [14]. Some of these oscillations are described as Mayer waves. They have a frequency of 0,1 Hz, and are tightly coupled with oscillations of efferent sympathetic nervous activity, and also often enhanced with sympathetic

activation[15]. Indeed, more than half of our control subjects had a peak at, or very close to, 0,1Hz. However, this frequency peak did not stand out in this dataset compared to other peaks close to the same frequency. This might be because our control subjects were not, at least not intentionally, sympathetically activated. Our data is nevertheless too uncertain to make a conclusion regarding Mayer waves.

In healthy subjects, there is an increase in overall variability with increased sympathetic drive, seen both in arterial pressure and heart rate [10]. In patients with sepsis on the other hand, and especially septic shock, this is not seen [12], although we assume septic patients to have increased sympathetic drive. As the activity is even lower than normal for septic patients, where sympathetic stimuli are expected to be present, the findings become even more conspicuous. In this study, four of the ten septic patients showed clearly less variability in both arterial flow and pressure, meaning fewer frequency peaks, than the other patients. Examples of this are patient 2, 3 and 9, with only three evident peaks below the frequency of 0,5 Hz. In addition, only four out of ten patients had a peak close to 0,1 Hz, which is associated with Mayer-waves as described above. No clinical data that we could find explained these findings, but they support the trend of less variability in septic shock, as found in other studies. Considering that the spontaneous oscillations in healthy subjects are caused by an autonomous interplay between sympathetic and parasympathetic stimuli on the vasomotors, it is reasonable to believe that this interplay is affected in sepsis. Studies suggest that a dysfunction in the autonomic nervous system, with inadequate sympathetic drive to the heart and peripheral vessels, may contribute to the development and progression of shock in patients with sepsis [10, 12].
The other patients, on the other hand, had a lot more frequency peaks between 0,2 and 0,9 Hz than the control group, both in flow and pressure. The control group had almost no peaks in this range of frequencies. We do not know the reason for these oscillations and whether they are a result of central or peripheral regulation, but when there is compliance between flow- and pressure peaks in a small artery branch, it is reasonable to believe that they are due to oscillations in the blood pressure.

An important question for further study is whether these qualitative changes occur earlier than the massive quantitative decline in pressure, which we already recognize in the clinic. This question requires studies with measurements of patients on arrival at the hospital, before the diagnosis is obvious with current methods. If the autonomous nervous system and its

regulation of vasomotors are affected at an early stage of disease, it is possible that similar measurements as done in this study may contribute to earlier detection of sepsis, if applied in the emergency room. Our results suggest that a larger study should be performed, where an impedance analysis is also included, to separate the resistance into underlying physiological processes. This would enable the knowledge on where the different oscillations in resistance originate, such as peripheral arterioles, aortic compliance and wave reflections.

Limitations

We did flow measurements from a medium sized artery, while the term "microcirculation" refers to the arterioles and capillary beds. However, peripheral measurements will be more unstable, depending on factors such as the temperature and position of the hands. The blood flow velocity in the true microcirculation is too low for our method to detect it. Also, changes in the microcirculation will likely propagate proximally to larger arteries. If we had done recordings from an even larger artery, we could have known the exact location the measurements were taken from, and gained a more powerful signal. This *might* be equally sensitive to flow oscillations as the more peripheral locations, but we cannot know that.

We did not measure the cross-sectional area of the artery in question, and thus it is velocity, and not flow, that is measured. Flow measurements would have been possible if the measurements were taken from a larger artery. Yet, we have reason to believe that velocity-recordings can replace flow-recordings for this application. With increased pressure the vessel cross sectional area will also increase, but if the elastic properties of the artery stay the same, this will be uniform. With spectral analysis, absolute values of flow are however not necessary. Also, flow velocity is used as a surrogate for flow when calculating indexes for end organ blood flow pulsatility and resistivity, e.g. placenta, brain and kidneys [16-18].

As the measurements are done with an unfocused Doppler, we cannot know at what angle the ultrasonic waves hit the vessel in question, which would be crucial if we wanted data on the power of flow. This means that the observed absolute values of power are of limited interest in this study.

We gathered data on continuous blood pressure from patients invasively, whereas a non-invasive method was used on control subjects. This could lead to oscillations caused by the

apparatus, that we would only see in either the control group or the patients. The non-invasive technology, developed by Finapres, has however been thoroughly validated against intra-arterial measurements regarding absolute values and low frequency oscillations [12, 13], both in healthy volunteers and in septic shock patients [11] .

The respiration will have impact on both arterial pressure and –flow, and this impact may be greater in mechanically ventilated patients. We have not listed the respiration frequencies during recordings, which is another weakness. However, the respiratory frequency is much higher than the frequencies we look at, as it will normally be around 0,3 Hz.

The patients and the control group could have been better matched, to avoid possible confounders such as age, sex, medication, cardiovascular disease and other lifestyle diseases. We were not allowed by REK to recruit control subjects by contacting them directly, as the intention initially was to be able to match with the sepsis patients based on age and sex. To implement the matching, we would have to recruit a very large group of controls. Due to the sharply reduced number of patients and limitations from REK, we considered it to be too comprehensive to achieve matching, and of limited value. The study was therefore redefined as a pilot study. The control subjects are recruited through a platform for employees as per instructions from the regional ethics committee, which means that they are only up to a certain age, whereas most of the patients are older. When it comes to sexes there is an excess of men among the patients, whereas the control group is dominated by women. The control group is also in general a healthy population. Two had hypertension, but the use of vasoactive medication meant they had to be excluded from the study.

Other possible confounders could be that the patients were in septic shock, which means they were given vasopressors. All the measurements except from two were taken on the first day in the ICU, only few hours after admission. The level of noradrenaline is shown in table 2. We cannot rule out that this is affecting the measurements. Other factors that apply only to the patients and not the control group are for instance the use of anaesthetics, excessive volume administrations and the physiological stress from fighting an acute condition like sepsis.

As we look for the oscillations in flow that deviate from pressure and vice versa, the factors which affects both parameters become less important. This applies to “other possible

confounders", as well as the respiration. From the approximation $resistance = \frac{pressure}{flow}$, we see that if flow and pressure are affected differently, there must be a change in resistance. Hence, disturbing factors in this study may be changes in resistance which is *not* due to the arterioles and their regulatory mechanisms. For instance, with volume treatment, the high tension in the vascular system may cause the vessels to become less compliant, which can affect the resistance. This will affect the absolute values of resistance, and when in a massive degree, maybe also the oscillations. Changes in blood composition and therefore –viscosity will also change resistance, but this is not likely to make oscillatory disturbances. Changes in reflections from arterial bifurcations, on the other hand, will cause oscillations in resistance, and can therefore affect the flow and pressure differently. To completely determine where in the vasculature changes in resistance arises, and separate contributions from arterioles, reflections and compliance, an impedance analysis is necessary. That was considered outside of the scope of this pilot study, but should probably be performed in a larger follow up study.

Conclusion

Our results show a trend with less discrepancy between arterial flow and arterial pressure in septic patients compared to healthy control subjects, which suggest that spontaneous oscillations in peripheral resistance is decreased in sepsis. Based on previous literature, we can assume that this is a result of disturbance of the autonomic interplay which regulates the arteriolar vasomotors. This can possibly be used as a diagnostic tool in the future, for earlier detection of sepsis. This is a pilot study, and the data set is too small to make a conclusion. Further studies are required to investigate this topic more thoroughly.

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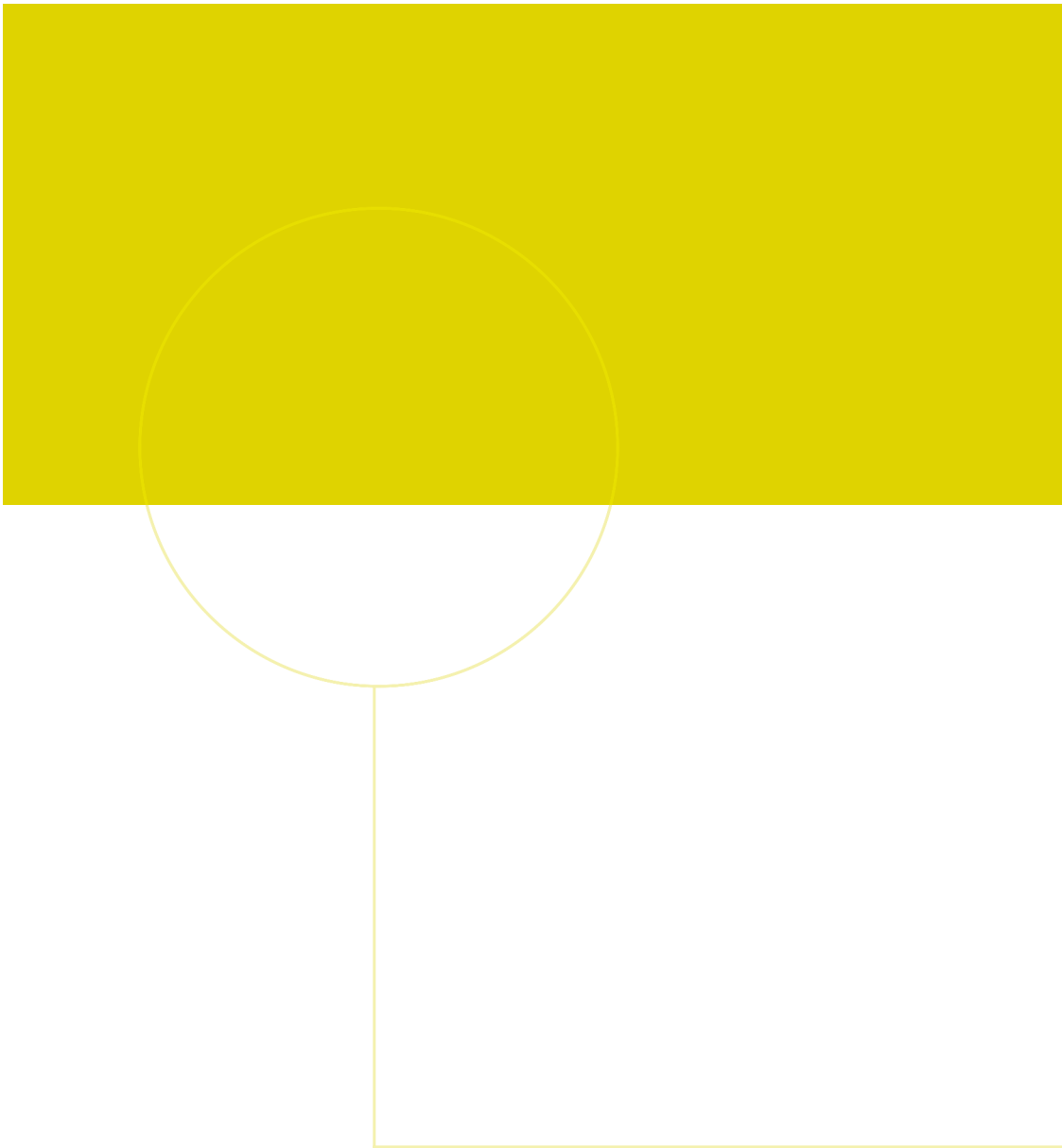

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