Cardiovascular markers for the early detection of hemorrhagic shock

by

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Title in Norwegian: "Kardiovaskulære markører for tidlig påvisning av truende sjøkk."
Abstract
Hypovolemic shock is characterized by an acute failure of the cardiovascular system to perfuse the body tissues adequately. If the patient is not resuscitated appropriately, it can lead to organ failure and death. It is well known that the body’s compensatory responses often maintain an almost normal blood pressure while hemorrhaging. When the blood pressure finally decreases, management is much more difficult. Due to high variability, the vital signs heart rate and blood pressure is therefore not very sensitive markers of evolving hemorrhage.
In this project we wanted to simulate the development of a hemorrhagic shock by using a lower body negative pressure chamber. Simultaneously we recorded several cardiovascular variables at a high sampling rate (100 Hz). The idea was to investigate whether any of these variables could be used to predict a cardiovascular collapse on an early stage.
10 healthy non-smoking subjects (5 female) were investigated. They were instrumented with different cardiovascular and respiratory instruments recording variables like heart rate, stroke volume, cardiac output, blood pressure, skin blood flow, respiratory movements, concentration of expiratory CO$_2$ and O$_2$ and skin temperature. In addition many variables could be calculated, like cardiac output and total peripheral resistance. This was a large project involving 6 researchers. More than 6.4 million unique data points were collected. In this paper only preliminary results are presented.
MAP and HR were confirmed to be unreliable as an early marker. SV fell almost linearly and can be used, but is difficult to measure. Further investigation of data is necessary before conclusions can be drawn.
**Introduction**

In my project I have worked together with a cardiovascular research group at the Department of Physiology, Institute of Basic Medical Sciences, University of Oslo. The main research technique is the ultrasound Doppler method for measurement of blood flow, but in this particular research project several other research tools have been used.

My role has been to participate together with other students and senior researchers in the planning and execution of the study. To illustrate the size of the project, more than 6.4 million unique data points are collected. The project involves 2 other researchers, 2 students, and 2 supervisors. We are currently in the process of analyzing the dataset, and the first paper is estimated to be in manuscript by December 2010.

The project has been given some attention in the media, and news coverage has been given in the radio program “Verdt å vite” in NRK P2 (available as podcast in iTunes). A presentation is also given in the university newspaper Apollon (apollon.uio.no) and on the internet (http://www.forskning.no/artikler/2009/oktober/232019). I chose to write in English because this is the language of the papers that we will try to publish our results.

I present my project in a classic disposition with background, material and methods, results, discussion and conclusion. I have added acknowledgements and a reference list. The results I present are only preliminary and do not cover the entire specter of data collected. Some results are analyzed and used by other students for their project. The preliminary results are a result of my independent analyzes, and the final results and conclusions of the research group work may therefore differ. I have attached the research protocol and the permissions given by the Regional Ethics Committee (REK).

There is a limitation as to how extensive a 12 weeks project can be. I chose to be part of a larger project, and therefore the main body of my work so far has been planning and execution. A lot of work remains to be done, but this will hopefully result in my first publications. This paper is a summary of my work so far, and this is reflected on the focus of this paper.

**Abbreviations:**
- MAP – mean arterial pressure
- SP – systolic pressure
- DP – diastolic pressure
- CO – cardiac output
- SV – stroke volume
- HR – heart rate
- TPR – total peripheral resistance
- LBNP – lower body negative pressure
- ECG – electrocardiogram
- SkBF – skin blood flow
- FVR – forearm vascular resistance
- LDF-fing – laser Doppler flowmetry finger
- LDF-nas – laser Doppler flowmetry non-acral skin
Background
Clinical shock is characterized by acute failure of the cardiovascular system to perfuse the tissues of the body adequately. If it is not treated appropriate, it can lead to organ failure and death. Hypovolemic shock is most common, and is caused by a fall in blood or plasma volume, which may be due to external or internal fluid loss. It’s well known that the body’s compensatory responses maintain an almost normal blood pressure while bleeding. When the blood pressure starts to fall, it can be too late to start treatment. In acute medicine it is desirable to prove a threatening shock early, so a proper treatment can be provided as soon as possible.

A rapid 20-30% blood loss may or may not reduce the mean arterial pressure, depending on the compensatory responses, but it causes clinical shock. With prompt treatment a 20-30% blood loss in not usually life-threatening. A 30-40% blood loss reduces arterial pressure to 50-70 mmHg, and causes severe sometimes irreversible shock, with anuria and impaired coronary and cerebral perfusion.

The immediate effect of acute hypovolemia is to reduce the central blood volume and the ventricular end-diastolic volume. This reduces the contractile energy through the Starling mechanism, so the stroke volume and pulse pressure decline. A set of reflex responses helps to support the arterial pressure in shock, and maintain the cerebral and myocardial perfusion. The activity of cardiopulmonary stretch receptors and arterial baroreceptors declines or ceases. Arterial chemoreceptor activity is raised by a metabolic acidosis and by reduced chemoreceptor perfusion. The arterial chemoreflex input drives the rapid ventilation of shock. The body defenses during a compensated, non-hypotensive hypovolemia occurs over three time scales:
Rapid reflexes that act within seconds:
A reflex increase in sympathetic vasomotor activity constricts the resistance vessels in the coetaneous, skeletal muscle, splanchnic and renal vascular beds. The resulting increased total peripheral resistance provides immediate support to the arterial pressure. Reflex venoconstriction in the splanchnic and coetaneous circulations partially restores the thoracic blood volume and cardiac filling pressure. The reduction of cardiac output is partly counteracted by increased cardiac sympathetic activity, which causes tachycardia and enhances myocardial contractility. The sympathetic-mediated responses are reinforced by increased levels of circulating vasoconstrictor hormones (angiotensin II, adrenaline, noradrenaline and vasopressin). Because of the compensation provided by the increased peripheral resistance, reduced venous capacitance and increased cardiac performance, mean arterial pressure may be well maintained in a moderate hemorrhage. This means that arterial blood pressure is not a reliable index of blood loss.
Intermediate responses that act over 5-60 min:
The fall in venous pressure and the sympathetic mediated reduction in capillary blood pressure allow the plasma colloid osmotic pressure to dominate. This results in a transient absorption of interstitial fluid. This internal transfusion of up to 0,5 l of fluid can be absorbed into the human vascular compartment within an hour, partially restoring the
depleted plasma volume, but reducing the hematocrit and plasma protein concentration. The internal transfusion helps to raise the low cardiac filling pressure. The haemodilution reduces the blood viscosity and improves tissue perfusion, but also reduces the O2-carrying capacity of blood.

In compensated shock the above responses preserve the perfusion of the heart and brain. Other organs have a reduced perfusion, due to a subnormal amount of body water, electrolytes, plasma protein and red cells. These deficiencies are corrected gradually over days (1).

The vital signs heart frequency and blood pressure can vary considerably when shock is evolving, so they are not sensitive enough to show the outcome of a hemorrhage. The last years, it’s been a growing interest to identify a cursor for an early point out of threatening shocks. A hypothesis is that analysis of the ECG-curve during a threatening shock, could be a cursor (2). Recently has pulse pressure and RR-interval variability been launched as a promising cursor (3). Probably is a measurement of the cardiac stroke volume better in relation to reduction in central blood volume during a hemorrhage (4), but it needs further clarification. In studies of experimental bleeding in humans, a model with negative pressure over the lower limbs (5). This is called a LBNP (lower body negative pressure). – 60 mmHg probably simulates a hemorrhage of 1 – 1,5 liter.

A common list of general features for a definition of shock is as follows:

- Hypotension (sp<100mmHg)
- Tachycardia (>100/min)
- Cold, clammy skin
- Rapid, shallow respiration
- Drowsiness, confusion, irritability
- Oliguria (urine output <30ml/hour)
- Elevated or reduced central pressure
- Multi-organ failure

Clinically it’s also common to use tables to make an early identification of those patients who will require critical care. One example is MEWS (Modified Early Warning Score):

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>&lt;9</td>
<td>9-14</td>
<td>15-20</td>
<td>21-29</td>
<td>&gt;29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>&lt;40</td>
<td>41-50</td>
<td>51-100</td>
<td>101-110</td>
<td>111-129</td>
<td>&gt;129</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>&lt;70</td>
<td>71-80</td>
<td>81-100</td>
<td>101-199</td>
<td>&gt;199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (C)</td>
<td>&lt;35</td>
<td>35-38,4</td>
<td>&gt;38,4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVPU score</td>
<td>Alert</td>
<td>Reacting to voice</td>
<td>Reacting to pain</td>
<td>Unresponsive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: A score of 3 or more means a patient is likely to need urgent assessment, and a score of 5 or more indicates that the patient is likely to require critical care usually in intensive care unit.
Clinically it is also common to use tables to make an early identification of those patients who will require critical care. One example is MEWS (Modified Early Warning Score).

MEWS is a systematic approach to detect early signs of cardiovascular collapse. One improvement of this approach would be to have a cardiovascular instrument continuously measure one or several variables, and then use an algorithm to warn the doctor or the medic that the patient is developing a shock. Pre-hospital medicine is characterized by lack of resources, and hostile environments. Therefore can such a device be of outmost help.

The basic idea of our project is therefore to use a reproducible model for human hemorrhaging to measure a wide range of cardiovascular variables and analyze them with respect to other early signs of shock. We will also try to confirm clinically known physiological variables, and use the experience to generate new hypothesis for further research.

Our hypothesis is that there are measurable changes in the circulation on an earlier time during shock development than the traditional measurements pulse and blood pressure can reveal. Our test protocol will not bring our trial persons to a threatening shock, but rather focus on the development prior. Other purposes of the project are to compare three different methods for non-invasive measurement of stroke volume. The three methods are ultrasound Doppler measured completely proximal in the aorta, estimation of stroke volume from the blood pressure curve and finally impedance measurement. I will not discuss this part of the project any further, and the data are not ready for analyzes yet.
Material and methods

General
All experiments were conducted in a laboratory designed for cardiovascular experiments. The room temperature and humidity was stable and similar in all experimental runs. All equipment used to measure cardiovascular variables (listed below) was connected to a computer through an analog/digital converter. The different variables were recorded and also displayed real time. The highest sample frequency was 100 Hz. Many data was also recorded heartbeat by heartbeat, gated by the ECG-R wave. All data was stored on the computer for recapture later. Since the LBNP chamber is rather noisy, a vacuum cleaner was turned on and placed in a corner during the entire experiment. This was done to avoid sudden changes in the noise load experienced by the subjects, which could lead to unwanted vasoconstriction (6).

Safety
The negative pressure applied to the subjects could potentially lead to syncope. As a precaution a medical doctor with resuscitation capabilities was present at all times. Two independent researchers observed the subjects during the experiment, and were able to turn of the negative pressure and decompress the chamber within less than a second. An observation protocol was made to observe the subjects vital signs, and absolute limits to blood pressure was set at 70 mmHg systolic. Dizziness, nausea, cold sweat, warm flushes, reduced vision, sudden bradycardia (> 15 beats/min) or sudden drop in blood pressure (> 15 mmHg) would prompt a decompression of the chamber to avoid fainting.

Subjects
The subjects (n = 10) were recruited among healthy non-smoking medical students. They were asked not to exercise or drink caffeinated beverages on the day of the experiments (12 hrs limit), and no alcohol for the last 24 hours. Since a large meal will increase baseline CO (), we also asked the participants not to eat for the last 2 hours before the experiment.

Lower body negative pressure
The research group has designed a lower body negative pressure (LBNP) chamber and control system that makes it possible to apply LBNP in the range of 0 to – 60 mmHg (7). The pressure can be applied either very rapidly (< 300 ms), or more gradually, depending on the protocol. The chamber consists of 3 main parts: a tube where the lover part of the body is placed, a negative pressure generator and a control system that interfaces with the user and monitors the negative pressure. A rubber and neoprene skirt closes the chamber around the subject’s waist.
The LBNP chamber (fig.1.) consists of a bench with a footboard. This is mobile and the subjects are placed on the bench and then rolled into the negative pressure chamber. The footboard of the bench is adjustable (1). A small wheel (2) that fits the rail at the bottom of the tube places the LBNP chamber into the right position. A reservoir tank (3) is connected to the transparent PMMA tube (4). A large-diameter hose connects the reservoir tank and the tube (5). Sub-atmospheric pressure is generated in the tank and the tube by a vacuum cleaner that is insulated and enclosed in the box beside the tank (6). With the control box (7) you operate the chamber. An alternative is to use digital signals generated from pre-programmed profiles stored in a computer. The PMMA tube lies in a soft rubber "cradle" (8).

Instrumentation

Ultrasound Doppler
SD-100 and CFM-750 (GE Vingmed, Horten, Norway), a bidirectional ultrasound Doppler velocimeter was used to measure stroke volume. It was operated in the pulsed mode with a 2 MHz Doppler probe hand-held at the suprasternal notch. The aim was to get an angle of 20 degrees between the sound beam and the direction of the bloodstream in the ascending aorta. The sample volume was adjusted so that the measurements were made 1-2 cm above the aortic valve. We assumed that the aortic valvular orifice was circular, and used this diameter when calculating the SV. SV was then calculated by
multiplying the value obtained by numerical integration of the recorded instantaneous maximum velocity during each R-R interval by the area of the orifice. This calculation is based on the assumption that the velocity profile is rectangular in that area (8).

To measure the brachial blood flow velocity (SkBF), we used SD-50 (GE Vingmed, Horten, Norway) bidirectional ultrasound Doppler velocimeter with a pulsed 10 MHz Doppler probe. The circular transducer had a fixed angle of 45° between the sound beam and the underlying surface, and was fastened by adhesive tape to the skin in the cubital fosse over the brachial artery. The mean velocity signal was transferred to the recording computer and the velocity integral was calculated.

ECG
The subjects were monitored by a three-lead ECG (lead II). All the ultrasound Doppler velocimeters (SD-50, SD-100 or CFM-750, Vingmed Sound A/S, Horten Norway) had a built-in ECG monitor. The R-wave in the ECG signal was detected for every heartbeat. The time interval between each detected R-wave was measured and used to calculate HR.

Laser Doppler
A laser Doppler flowmeter (MBF3D, Moor Instruments, Devon UK) was used to measure blood flow (in arbitrary units) on the finger pulp, and on non-acral skin on the lower arm. The laser Doppler probes were fastened to the skin with double-sided tape. The noise limiting filter was set at 21 kHz (highest possible), and emitted wavelength was 820 nm.

Continuous finger arterial blood pressure
We used a Finometer® PRO (FMS, Finapres Medical Systems, Amsterdam, The Netherlands) is a stand-alone solution for accurate non-invasive beat-to-beat blood pressure monitoring. This instrument requires a finger cuff on one finger, and this finger was at heart level during the whole experiment. The Finapres uses a clamp to keep the blood volume in the finger constant, and then calculates the finger arterial blood pressure by converting the pressure of the clamp (9). The Finometer® PRO is widely used in clinical settings and advanced scientific research. The absolute accuracy of the Finometer® PRO can be calibrated with an upper arm cuff measurement using the Return To Flow (RTF) technology.

Other instruments that was used, but not discussed in this paper

- respiratory chest volume changes
- expiratory O₂
- expiratory CO₂
- skin temperature
- cardiothoracic impedance (TaskForce)
- SaO₂
Figure 2. Setup for one experimental run. At least 4 persons had to be present to perform the experiment.

Cardiovascular variables

SV and HR were calculated from both the ultrasound and the finapres instruments. CO was calculated beat by beat from corresponding HR and SV values. TPR was calculated by dividing MAP by CO beat by beat, and FVR by dividing MAP by SkBF. We had no measure of central venous pressure and calculated resistance by assuming central venous pressure and femoral venous pressure to be zero (10).

Cardiovascular variables that was sampled, but not discussed in this paper

- respiration: rate, depth, frequency, SaO₂, expiratory O₂ and CO₂
- ultrasound Doppler: aortic blood velocity, stroke length, aortaflow-wave
- peripheral volume
- ECG: R-wave height
- skin temperature
- SV, HR, CO, TPR ++ from TaskForce.
Analysis
Data handling
The recording computer received the signals, and different calculations were made by the software (version REGIST3, Morten Eriksen, Oslo, Norway), like integration and heart rate. The data was then moved to a new computer where they were the sorted and filtered (automatic calibration signals from different instruments were removed) in a MathLab® designed program. The final data was used for statistics and illustrations. The illustrations are drawn in SigmaPlot® 8.0.

Statistical methods
The statistical tools used are estimation by nonparametric Wilcoxon median. In table 2 the 95% confidence interval for the Wilcoxon median is presented.

Possible analysis that is not discussed in this paper
Spectral analysis of the variations from MAP, ECG and SaO2 signal sampled at 100 HZ is not done in my paper.

Protocol
The subjects were informed in every detail about the experiment and signed a written consent on a separate day prior to the day of the experiment. On the day of the experiment, the subjects were lightly dressed, and rested comfortably in the supine position on a bench. The bench was adjusted to fit the chamber, and the subjects wore warm polar socks to avoid feeling cold from the draft created when the chamber was emptied of air. A vacuum cleaner was placed running in a corner, creating a background sound resembling the noise of LBNP chamber. The room temperature was adjusted to a level where the subjects felt normothermic, having approximately 2-3 opening and closing of AVAS pr minute confirmed by ultrasound Doppler measurements (11).

The protocol timeline was as follows (see figure 3):

- 5 minutes baseline readings, pressure 0 mmHg
- pressure decreased to – 30 mmHg at 5 minutes
- 3 minutes of – 30 mmHg
- pressure gradually decreased from – 30 mmHg to – 60 mmHg over a 10 minute period, from 8 – 18 minutes.
- pressure stable at – 60 mmHg for 3 minutes, from 18 to 21 minutes.
- pressure raised to 0 mmHg (atmospheric pressure) at 21 minutes
- 5 minutes post experiment recording
- the experiment lasted a total of 21 minutes
If the subject showed signs or symptoms of syncope during the period of linear pressure drop (8 – 18 min), the pressure was raised to 0 mmHg, and the experiment continued with 5 minutes of post experiment recording.

Figure 3. Protocol timeline with relations to negative pressure and flags. Statistics (table 2) were calculated from 4 periods: period 1: 120s – 240s before Flag 2, period 2: 0s – 60s before Flag 4, period 3: 0s – 60s after Flag 4, period 4: 120s – 240s after Flag 4
Results

General

See fig 3. and 4. for illustrations. The main finding is that mean arterial blood pressure is rather stable during a simulated hemorrhage, and when MAP finally decreases or show a tendency to decrease, this inevitably leads to syncope. This is in accordance with our hypothesis and clinical experience that a drop in MAP is occurring late in the development of hemorrhagic shock. 7 out of 10 subjects fainted before the end of the period with increasing negative pressure. All subjects with near-syncope had one or more of the symptoms: dizziness, nausea, cold sweat, warm flushes or reduced vision. Characteristically there was a sudden bradycardia that preceded a drop in blood pressure. No subjects actually fainted due to the prompt decompression of the chamber.

Figure 4. illustrates how SV decreases, almost in linear fashion. HR increases, but there is a great variability between subjects, and the absolute increase in HR is rather small. CO decreases, but the decrease in CO is to some degree buffered by the increased HR. TPR increases and the measurements of forearm SkBF and FVR show that the skin does participate in a general vasoconstriction.

Subjects

The subjects were recruited by putting up posters on the campus. The criteria to participate were filled by all individuals. These were to be a healthy individual between 18-30 years, non-smoker and not use medication except contraceptive pills.

<table>
<thead>
<tr>
<th>Person</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>Exercise (h/week)</th>
<th>Max LBNP</th>
<th>LBNP aborted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot</td>
<td>M</td>
<td>181</td>
<td>80</td>
<td>24,4</td>
<td>3</td>
<td>-55</td>
<td>Y</td>
</tr>
<tr>
<td>A</td>
<td>F</td>
<td>170</td>
<td>63</td>
<td>21,8</td>
<td>6</td>
<td>-40</td>
<td>Y</td>
</tr>
<tr>
<td>B</td>
<td>F</td>
<td>168</td>
<td>53</td>
<td>18,8</td>
<td>5,5</td>
<td>-60</td>
<td>N</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>175</td>
<td>73</td>
<td>23,8</td>
<td>8</td>
<td>-45</td>
<td>Y</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>167</td>
<td>55</td>
<td>19,7</td>
<td>2</td>
<td>-60</td>
<td>N</td>
</tr>
<tr>
<td>E</td>
<td>F</td>
<td>165</td>
<td>67</td>
<td>24,6</td>
<td>5</td>
<td>-56</td>
<td>Y</td>
</tr>
<tr>
<td>F</td>
<td>M</td>
<td>182</td>
<td>85</td>
<td>25,7</td>
<td>14</td>
<td>-60</td>
<td>N</td>
</tr>
<tr>
<td>G</td>
<td>M</td>
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<td>H</td>
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<td>I</td>
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<tr>
<td>J</td>
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<tr>
<td>Average</td>
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<td>173,6</td>
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<td>22,3</td>
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<tr>
<td>Median</td>
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<td>172,5</td>
<td>68,5</td>
<td>23,1</td>
<td>5,75</td>
<td>-53,5</td>
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</tr>
</tbody>
</table>

Table 2. Subject anthropometrics.
Figure 4. Illustration of cardiovascular data from one subject: LBNP, MAP (black middle), SP (gray upper), DP (gray lower), CO, SV and HR.
Figure 5. Illustration of cardiovascular data from one subject: LBNP, SkBF, LDF-nas, LDF-fing, TPR, and FVR.
### Table 3. Comparison of the variables HR, SV, CO, MAP, SP, and DP at the different stages in the protocol

<table>
<thead>
<tr>
<th>Time Period</th>
<th>HR</th>
<th>SV</th>
<th>CO</th>
<th>MAP</th>
<th>SP</th>
<th>DP</th>
</tr>
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<tbody>
<tr>
<td><strong>120-240 seconds before Flag 2 (1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W(28)</td>
<td>62.7</td>
<td>78.2</td>
<td>4.9</td>
<td>83.0</td>
<td>128.9</td>
<td>64.6</td>
</tr>
<tr>
<td>W(9)</td>
<td>54.6</td>
<td>68.2</td>
<td>4.0</td>
<td>73.5</td>
<td>113.0</td>
<td>57.6</td>
</tr>
<tr>
<td>W(47)</td>
<td>69.9</td>
<td>94.5</td>
<td>5.9</td>
<td>89.7</td>
<td>140.3</td>
<td>70.0</td>
</tr>
<tr>
<td><strong>0-60 seconds before Flag 4 (2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W(28)</td>
<td>88.2</td>
<td>39.9</td>
<td>3.6</td>
<td>72.7</td>
<td>102.4</td>
<td>59.3</td>
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<tr>
<td>W(9)</td>
<td>77.1</td>
<td>31.8</td>
<td>2.9</td>
<td>59.5</td>
<td>88.6</td>
<td>47.3</td>
</tr>
<tr>
<td>W(47)</td>
<td>99.1</td>
<td>53.3</td>
<td>4.3</td>
<td>85.2</td>
<td>119.1</td>
<td>71.2</td>
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<tr>
<td><strong>0-60 seconds after Flag 4 (3)</strong></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>W(28)</td>
<td>68.1</td>
<td>76.8</td>
<td>5.1</td>
<td>78.9</td>
<td>118.6</td>
<td>60.8</td>
</tr>
<tr>
<td>W(9)</td>
<td>61.4</td>
<td>61.4</td>
<td>3.9</td>
<td>68.9</td>
<td>101.8</td>
<td>54.1</td>
</tr>
<tr>
<td>W(47)</td>
<td>72.9</td>
<td>91.0</td>
<td>6.2</td>
<td>89.8</td>
<td>131.4</td>
<td>69.6</td>
</tr>
<tr>
<td><strong>120-240 seconds after Flag 4 (4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W(28)</td>
<td>55.6</td>
<td>81.8</td>
<td>4.3</td>
<td>82.3</td>
<td>123.9</td>
<td>65.2</td>
</tr>
<tr>
<td>W(9)</td>
<td>49.8</td>
<td>68.2</td>
<td>3.6</td>
<td>75.4</td>
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<td>58.5</td>
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<td>W(47)</td>
<td>62.1</td>
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<td>5.1</td>
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<td>134.6</td>
<td>70.1</td>
</tr>
<tr>
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Blood pressure
Systolic pressure: in our trials, 4 of 10 persons had a SP <100bpm in the last minute before the LBNP was switched off. In the minute before the LBNP was switched off, the average SP was 102,4 mmHg. That is a decrease of 26,5 mmHg, compared to the period before the LBNP was applied.

Diastolic pressure: in the minute before the LBNP was switched off, the average DP was 59,3 mmHg, which is a decrease of 5,2 mmHg compared to the period before the LBNP was switched on.

Mean arterial pressure: in the minute before the LBNP was applied, the average MAP was 72,7 mmHg. That is a decrease of 10,3 mmHg, compared to the pre-pressure period.

Heart rate
In our trials, 3 of 10 persons had a HR >100 bpm in the last minute before the LBNP was switched off. In the minute before the LBNP was switched off, the average HR was 88,2 bpm. That is an increase of 25,5 bpm compared to the pre-LBNP period, and this is a significant increase.

Stroke Volume
In the minute before the lbnp was switched off, the average SV was 39,9 ml, which on average is a decrease of 38,4 ml compared to the pre-LBNP period.

Cardiac output
In the minute before the LBNP was switched off, the average CO was 3,6 l/min. That is a decrease of 1,3 l/min, compared to the period before the LBNP was switched on.

Total peripheral resistance
TPR increases during the LBNP period, but with increasing variability.

Skin blood flow
SkBF in measured distally, where the AVAs are abundant, there was a large variability in blood. This variation lasted throughout the experiment, and did not show any decrease. The SkBF on non-acral skin did have a linear small decrease during the increasing LBNP period. A marked increase in SkBF is seen when the pressure is released at 20 minutes. The FVR also increases in the same period, but not as distinctly as TPR.
Discussion

I will discuss the cardiovascular variables one by one, and to a certain degree carefully speculate on the preliminary results.

Blood pressure

It is striking to see how little the pressure changes despite the reduction in central blood volume available for the heart (fig.4). There is obviously a compensatory mechanism that has come into play to avoid syncope and reduced cerebral function as discussed in the introduction.

Systolic pressure: the SP was reduced by 21% on average. All persons in the trial had a reduction in the SP. The variation was from a reduction of 44 mmHg to a reduction of 13 mmHg. Clinically the palpation of peripheral pulses is used to predict internal incompressible hemorrhage, and often used to initiate resuscitation or confirm successful fluid resuscitation. The failure of palpating the radial pulse is considered a sign of systolic pressure below 90 mmHg. Our findings indirectly indicate that this is logical and sensible. The peripheral pulses are dependent on the SP, and SP have the largest decrease within the 3 defined arterial pressures.

Diastolic pressure: the DP was reduced by 8% on average. 6 of 10 persons had a reduction in the DP. The 3 persons who were able to complete the protocol, all had an increase in the DP. The variation in the DP was from a reduction of 18 mmHg to an increase of 12 mmHg. This is interesting because it indicates that the prediction of a “survivor”, a person that is less susceptible to the effects of a hemorrhage, has an increased ability to sustain the DP. DP is very dependent on the resistance to flow, and further research in this field should include different measures to look at how the body, and the sympathetic nervous system, addresses the different mechanisms to increase TPR.

Mean Arterial Pressure: the MAP was reduced by 12% on average. 8 of 10 persons had a reduction in the MAP. The 2 persons, who had an increase in MAP, both completed the trial. The last persons, who completed the protocol, had a 4 mmHg reduction of MAP. This finding is not very surprising, the characteristic of these subjects will be studied in detail in our further analyzes, is there something special in of these subjects responses to LBNP challenge.

Heart rate

30% of the persons in our trial had a HR above 100 bpm during their last minute of LBNP challenge. This indicates that focusing solely on the absolute HR can be an unreliable predictor to show whether a person is about to enter a state of hypovolemic shock. The change in HR is significant, but this may be because the pre-LBNP period recordings were taken from a subject with relatively little stress. In a pre-hospital trauma setting the patient could have a substantial tachycardia from stress, pain, arousal etc,
which is independent of a developing hemorrhage. Therefore a significant increase in HR could not be expected from all from patients, even when they are bleeding internally. In our experiment the HR was increased with 41% on average, but the variation between individuals was from 10 bpm to 47 bpm increase. This illustrates that it is difficult to set an absolute limit to decide when the chances of an increase in HR is representing a hemorrhage. A close look at the HR in figure 6 also reveals a large intravariability. When HR is used for monitoring a patient, HR has to be recorded for quite some time allow for increases to be detected.

Limitations to this study is that the LBNP-method is not representative enough when simulating a hemorrhage, even if the subjects faints (there are other unknown mechanisms in play). One can argue that a HR increase in the range of 50-90 bpm is low compared to clinical experience, and that in this range the parasympathetic effect of the vagus nerve is still in play. This will also give a higher HR variation compared to a HR driven totally by sympathetic input.

### Stroke volume

The SV was nearly halved (49%). This indicates that SV could be a good predictor of a hypovolemic shock in development. In our trials the variation between the individuals

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Figure 6. Heart rate in one individual. Note the large intravariability in HR.
was between 15ml and 51ml reduction. The decrease in SV developed in a linear fashion in all subjects, with little intravariability. This makes it a more suitable candidate for a cardiovascular marker than HR. A closer look at the development of the stroke volume in figure 7 show how the steep decrease in pressure at 5 minutes is followed by proportional drop in SV. The drop is delayed for some seconds compared to the drop in pressure. There is no difference in SV pre-and post LBNP, which indicates that SV is less sensitive to stress. A medtech devise can maybe use SV in an algorithm to detect a developing hemorrhage. The challenge here would be to measure SV pre-hospitally, and even in hospital. The methods we used in our project are not very portable.

![Stroke volume graph](image)

**Figure 7. Stroke volume in one individual.**

**Cardiac output and total peripheral resistance**

The CO was reduced by 26% on average. All persons in the trial had a reduction in CO, and it varied between 0.5 l/min and 3.0 l/min. CO = SV x HR, and the reduction in SV is not compensated by an equivalent increase in HR. From the equation MAP = (SVxHR) x TPR, one can see that the raise in TPR is necessary to maintain MAP throughout the
experiment. One question that has to be raised is why HR did not increase more before syncope in those patients who fainted before the end of the increasing LBNP period.

Skin blood flow

The main effectors in temperature regulation in the thermoneutral zone are skin blood flow. When AVAs are synchronously constricted and dilated, this is taken as a measure of thermo neutrality. Many of the subjects did display this activity throughout the experiment, and this was rather surprising. In figure 5. SkBF is displayed as a measurement of brachial blood velocity. It is the AVAs that are responsible for the variations. As one can see, there is little vasoconstriction during the LBNP period. The blood flow recorded in non-acral skin show a small but (probably) significant reduction representing a vasoconstriction. This is part of the total activity to increase TPR. The skin in this area is without AVAs, and is controlled by active adrenergic vasoconstrictor system.
Conclusion

It is not recommendable to try to draw any conclusions based on preliminary data, but maybe the analyzes so far confirm that in a progressive LBNP model to simulate hemorrhage:

- MAP does not decrease until pre-syncope
- SV decreases in a almost linear fashion
- HR does increase, but there is large inter- and intravariability
- SkBF contributes to increased TPR, but variations in SkBF due to temperature regulation persists

Acknowledgements

This project was undertaken at the Department of Physiology, Faculty of Medicine, University of Oslo, with Professor Johan Ræder as main advisor. Indispensable contribution was given by my co-advisor PhD-student Erling Bekkestad Rein. Dr. Maja Elstad and stud.med Natalie Holme were crucial co-workers. Dr. Karin Toska and Professor Lars Walløe, has been a good support in the understanding of different aspects during the project. I am also grateful to the persons who participated as volunteers, and made the project possible.

Reference List


