Title:
Changes in ventriculo-arterial coupling and myocardial work during treatment of sepsis and septic shock: a prospective interventional study.

Proposer: prof.dr. Matej Podbregar, specialist in Internal and Intensive Care Medicine
Department of the study: Internal Intensive Care Medicine (OIIM), General Hospital (SB) Celje
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Type of study: Prospective interventional.
Funding of the study: This is an academic study which is not funded and has no payer.
Doctor or researcher responsible for the safe conduct of the research: prof.dr. Matej Podbregar.
Estimated duration of the study: 12 months
Ethical committee approval ID: 70/2025/6-1, 24.01.2025
NCT number: not yet assigned.

Celje, 25.01.2025

Study rationale:

Patients with septic shock are treated according to the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. Despite prompt and targeted treatment, the mortality of patients with sepsis and septic shock remains very high.

Current recommendations state that one of the goals is to establish an adequate perfusion pressure or Mean Arterial Pressure (MAP). The current recommended target MAP value is 65-70mmHg. A study (Asfar P. et al. NEJM 2014) looking at two different target MAP values (65-70mmHg vs. 80-85mmHg) found no difference in survival. Patients in the higher target pressure group had more atrial fibrillation paroxysms. The group of patients with chronic arterial hypertension had statistically fewer treatment alternatives due to renal failure. We hypothesize that a modern cardiovascular assessment approach could be used to individually set target blood pressures in patients with sepsis and septic shock.

Ventriculo-arterial coupling (VAC) is the connection between the left ventricle and the arterial system. VAC is a key concept in cardiovascular physiology and describes how well the heart and the arterial system work together to ensure efficient blood flow and optimal cardiac function.

Two main variables are needed to assess VAC: ventricular elastance (Ees) and arterial elastance (Ea). Ees describes the ability of the left ventricle (LV) to generate pressure and eject blood during systole. Ees is related to myocardial contractility and the LV pressure-volume ratio. Ea describes the stiffness of the arterial system and expresses the resistance of the arteries to blood ejection; it is influenced by factors such as arterial tone and compliance.

VAC is defined as the ratio of Ees to Ea or as the ratio of LV end-systolic pressure to LV ejection volume. VAC is crucial because it tells us how efficiently the heart and arteries work together during the cardiac cycle. Optimal coupling occurs when the ventricle and the arterial system are coordinated in their mechanical properties, allowing efficient energy transfer and minimizing the load on the heart. A normal VAC value is between 0.7-1.3. If the ventricle or arterial system is too stiff, the connection may be suboptimal (VAC >1.3). This can eventually lead to increased strain on the heart, inefficient blood flow and eventual heart failure.

Myocardial work (MW) is a non-invasive tool in echocardiography that incorporates the average left ventricular strain into the Global Longitudinal Strain (GLS) analysis. MW is correlated with myocardial oxygen consumption and work efficiency can be assessed. MW analysis combines analysis of apical views from transthoracic echocardiography (synchronized with ECG tracing, which is necessary to derive the timing of mitral and aortic valve opening and closure), with blood pressure measurement to produce a graph showing myocardial tissue energy expenditure. The MW analysis allows us to calculate the Global Work Index (GWI), Global Constructive Work (GCW), Global Wasted Work (GWW) and Global Work Efficiency (GWE).

The aim of our study is to combine MW assessment with VAC to assess the appropriateness of fluid and vasopressor treatment in sepsis. However, the question of whether a patient should receive a fluid infusion and when is far from being certainly defined. It is also not clear whether VAC and MW analysis can be used to assess the optimal concentration of vasoconstrictor and inotropic drugs to use in the treatment of patients with sepsis and septic shock. There is still a paucity of knowledge in the literature in this area, and investigators believe that the combination they wish to investigate could be a promising and reliable non-invasive method that would allow clinicians to identify patients suitable for fluid infusion or treatment with vasoactive drugs.

Patients and methods:

The study will start after obtaining the approval of the Medical Ethics Committee of SB Celje.
Patients aged 18 years and older admitted to the Department of Internal Intensive Care Medicine (OIIM), SB Celje, due to sepsis or septic shock will be included in the study. Patients will be enrolled in the study after obtaining informed consent from the patient or relatives if the patient is unable to give consent.
Will not be enrolled in the study:
- Patients who do not consent to inclusion
- under 18 years of age
- pregnant women
- patients with more than moderate aortic stenosis (AVA <1.4 cm2, AVAi <0.85, DVI <0.5)
- patients with more than mild mitral regurgitation (IVC width<=3mm, MR EROA<20, MR RegV <30mL)
- patients with arrhythmic cardiac rhythm disturbances (e.g. atrial fibrillation, frequent ventricular and supraventricular nodal activity, atrial flutter)
- patients for whom renal replacement therapy will be performed
- patients who will not be artificially ventilated with continuous modes of ventilation.

Definition of sepsis/septic shock:
Sepsis and septic shock will be defined according to current recommendations (Surviving Sepsis campaine guidliness 2021). The diagnosis of sepsis will be confirmed in case of sequential organ failure (SOFA) ≥ 2. Septic shock will be defined by the need for a vasopressor to maintain the patient's mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate level ≥ 2 mmol/l, despite adequate fluid replacement.

Patient information:
General data (age, sex, weight and height, underlying cause of admission, previous diseases) and specific data (microbiological findings, C-reactive protein, procalcitonin, interleukin 6, serum lactate, arterial and venous blood gas analysis of the patients) will be obtained from the hospital information system (Birpis, Slovenia) and the electronic temperature sheet (Centricity, GE HealthCare, USA). Will be obtained data on the amount of fluid added and the peak concentration of vasoconstrictors during the first 24 hours of treatment, length of artificial ventilation, renal replacement therapy, cardiac rhythm disturbances, ICU treatment outcome and 28-day survival. The data will be anonymized in the databases collected.

Clinical examination of the patient:
On clinical examination, investigators will specifically look for sacral and pretibial edema.

Ultrasound of the lungs:
Ultrasound will be used to examine the upper, apical parts of the lungs, in the midclavicular line. If the patient has more than 3 B-lines in 2 consecutive intercostal spaces, will be classified as hypervolemic.

Transthoracic ultrasound of the heart:
All enrolled patients will undergo trans thoracic echocardiography (TTE) (Vivid E95 or Vivid S70, GE HealthCare, USA) immediately on admission to the OIIM as part of the routine work-up on admission to the ward. Investigators will measure inferior vena cava dimensions in inspiration/expiration, cardiac volumes, systolic and diastolic function and filling (E/E') of the left ventricle (LV), estimate minute cardiac volume from flow to flow (VTI) (10 second recording)

in the left ventricular outflow tract (LVOT). Investigators will assess right ventricular dimension and function (TAPSE, PAPs). The LV will be imaged in three planes (apical 2 cavity projection (A2C), apical 4 cavity projection (A4C) and apical 3 cavity projection (A3C, APLAX) with an image capture of at least 40Hz and 4 heartbeats. During TTE, the ECG signal and respiratory waveform will be monitored on ultrasound. Patients with a VTI LVOT >10% difference between inspiration and expiration will be assessed as fluid responsive.

In control TTEs, investigators will measure the minute cardiac volume from VTI to LVOT (10-second recording) and make LV recordings in three planes (A2C, A4C, A3C-APLAX) with an image capture of at least 40Hz and 4 heartbeats while monitoring the ECG signal for later analysis. A control TTE will be performed on admission before specific treatment (fluid, vasopressor) and when the target blood pressure is reached. At that time, investigators will also record the invasively measured blood pressure.
The ultrasound recordings will be stored for analysis using EchoPac (GE Healthcare, USA).

Analysis of TTE images:
Using the EchoPac computer program (GE Healthcare, USA), investigators will perform an additional analysis of cardiac function, measuring LV end-systolic and diastolic volumes in two planes, LV ejection fraction and LV VTI LVOT during inspiration/expiration. LV recordings in three planes will be used to calculate LV GLS and LV MW. GWI, GCW, GWW and GWE will be calculated.

Ventriculo-arterial coupling (VAC):
To calculate VAC investigators will use the iElastance app (VACi, by Pietro Bertini, MD, Department of Cardiothoracic Anaesthesia and Intensive Care Medicine, University Hospital of Pisa) available in the Apple store or Google play store. To calculate VACi, investigators will use invasively measured systolic (mmHg) and diastolic blood pressure (mmHg), and data obtained from TTE recordings (LV pulse volume (ml), LV ejection fraction, Total Ejection Time (msec), Pre Ejection Time (msec)). The formula has been evaluated in previous studies (Chen CH et Al J Am Coll Cardiol 2001). VACi will be calculated on admission before specific treatment (fluid, vasopressor) and on reaching the target blood pressure.

Estimation of VAC from GLS and MW data:
From the TTE analysis data obtained in EchoPac (GE Healthcare, USA) (GLS LV, MW, blood pressure and LV systolic/diastolic volume), investigators will calculate the VAC (VACpy) with the help of a program written in the Python programming language.

Haemodynamic monitoring of patients:
Patients admitted to the OIIM for sepsis/septic shock are monitored using the transpulmonary thermodilution method (EV1000, Edwards, USA). The pulse volume variation (PVV) will be read from the monitor. Patients with SVV >10% and ELWI <12ml/kg will be considered fluid responsive. When vasoactive therapy is given, investigators will check the adequacy of flow in the blood gas analysis of the central venous blood.

Vasopressor treatment:
Following the recommendations for the treatment of sepsis/septic shock, investigators will start treatment with noradrenaline in a continuous infusion to achieve the target MAP. All patients, once receiving norepinephrine, will additionally receive hydrocortisone 50mg iv/6h. Norepinephrine will be escalated when target pressure is not reached up to the dose (0.4

μg/kg/min). If target pressure is not reached at a norepinephrine dose of 0.4 μg/kg/min, vasopressin (Empressin, Amomed, Austria) will be added to the therapy at a dose of 0.03 i.e./h. Norepinephrine will be escalated to a dose of 0.4 μg/kg/min. If target pressure is not reached with the addition of vasopressin after 2 hours of therapy, the dose of noradrenaline will be increased accordingly.

Patient treatment and protocol for MW and VAC measurements:

Patients will be treated according to the current recommendations for the management of sepsis and septic shock (Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021).

On admission to the ward, all patients will undergo a clinical examination, lung ultrasound and TTE and VACi will be calculated.

The exact treatment protocol and measurements are presented graphically (fig. 1).

Based on clinical examination, absence of B-lines on lung ultrasound, SVV >10% (EVO 1000 or VTI LVOT) and inferior vena cava respiratory variability >10%, patients will be divided into treatment arm A (fluid responsive patients). The remaining patients will be classified into therapeutic arm B (fluid non-responsive patients-without initial fluid therapy).

In therapeutic arm A, the patient will receive fluid (8ml/kg/30min of balanced saline) after initial evaluation. In case of SVV<10% and MAP<65mmHg after fluid infusion, or at the discretion of the treating physician, the patient will be jumped to therapeutic arm B, where he/she will receive a vasopressor according to the protocol.

In case the patient from therapy arm A has SVV>10% and MAP<65mmHg after receiving the first fluid therapy, he/she will receive additional fluid (8ml/kg/30min of balanced saline). In case he/she has SVV<10% and MAP<65mmHg after the second fluid replacement, or at the discretion of the attending physician, the patient will continue treatment in therapy arm B, where he/she will receive a vasopressor. If the patient still has SVV>10% and MAP<65mmHg in treatment arm A after 2 doses of fluids, the patient will receive additional fluids (14ml/kg/60min of balanced saline). If MAP<65mmHg persists after 3 doses of fluids, the patient will receive vasopressor according to protocol B.

In the primary classification of the patient in the therapeutic arm B, patients will be treated with vasopressor in a stepwise fashion until the first target MAP blood pressure of 65-70mmHg for a duration of at least 30min with unchanged norepinephrine dose. Investigators will then increase the dose of vasopressor according to the protocol until a target MAP blood pressure of 80-85 mmHg is achieved over a duration of at least 30 min with unchanged vasopressor dose.

A control TTE and a bedside VACi assessment will be performed after completion of the fluid infusion in therapeutic arm A, or 30 minutes after reaching a stable target blood pressure.

If VAC > 1.3 at a target MAP of 80-85mmHg, investigators will lower the patient to a target blood pressure of 65-70mmHg and potentially initiate inotropic therapy in the setting of insufficient cardiac output (<2.0L/min/m2 and/or central venous hemoglobin saturation (ScvO2) <65%).

After reaching the final target pressure for 30minutes, protocol treatment and measurement will be terminated. Treatment will be continued at the discretion of the treating physician.

A control TTE and a bedside VACi assessment will be performed 24-32hrs after the patient's admission to the OIIM.

Estimation of the number of patients included:

There are no studies evaluating MW with TEE in critically ill patients. Investigators estimate that will be included 30 patients (each group of 15 patients) to be able to demonstrate changes in MW and VAC with therapy.

Statistics:
Investigators will use classical statistical methods. Data will be tested for normality of distribution (D'Agostino-Pearson test). Presentation of results as mean±standard deviation (SD) or median (95% confidence interval, 95%CI) or proportion for uncontinuous variables. For group comparisons, investigators will use Student's t-test for paired data or, in the case of non-normal distributions, the Wilcoxon test for paired data, and the chi-square test for non-continuous covariates. Bland-Altman analysis will be performed to compare VACi and VACpy. A 10% difference between VACi and VACpy measures will be considered clinically insignificant. With a P value <0.05, the difference between the groups will be statistically significant.

Expected results:
Investigators expect to be able to categorize fluid-responsive and non-responsive patients based on VAC and MW. Investigators also expect to be able to individually determine the optimal target MAP based on MW and VAC, which will not be associated with a reduction in cardiac output and a reduction in myocardial useful work. Investigators also expect that VACi and VACpy values will not differ in a clinically meaningful way.

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Assessment of the ethical aspects of the research, the potential benefits, risks and burdens for those involved:
The proposed research is not ethically controversial. The patients included will be treated according to current recommendations. Apart from routine collection of biological samples or blood from the patient, no other procedures will be performed for the purpose of the study. For more accurate monitoring, investigators anticipate that they will be able to treat patients with an individualized target blood pressure, which could reduce the incidence of arrhythmias (e.g. atrial fibrillation) and the need for renal treatment and increase the chance of survival. There will be no additional risk of participation in the study.

Information on monetary and any other compensation to study subjects:
Patients will not receive any monetary or other compensation for participation in the study.

Illustration of the costs of the study:
There are no costs associated with the study.

Information on monetary and any other compensation to researchers:
No monetary or other compensation will be paid to the investigators.

Description of the safety concerns and benefits of the people involved in the study:
Patients will be treated according to current recommendations for the treatment of sepsis/septic shock. Patients will be hemodynamically monitored with methods routinely used in the management of OIIM (semi-invasive monitoring, EVO 1000, Edwards, USA). They

will be treated with respiratory support and possibly renal replacement therapy. For more accurate monitoring, investigators anticipate that they will be able to treat patients with an individualized target blood pressure, which could reduce the incidence of arrhythmias (e.g. atrial fibrillation) and the need for renal therapy and increase the chance of survival. The protection of patients' personal data will be ensured. Data collected electronically will be anonymized and will not include any identifiable patient data.

Explanatory notes on the study for participants and declarations of informed and free consent:
Attached.

Specific explanations for persons invited to participate in the study:
Not required.

Informed Consent for Data Collection and Research

Research Title:
Changes in the ventricular-arterial coupling and myocardial function during the treatment of sepsis and septic shock: a prospective interventional study.

Principal Investigator:
Prof. Dr. Matej Podbregar, Specialist in Internal and Intensive Medicine
Research Department: Department of Internal Intensive Medicine, SB Celje, Tel. 03 321 3418

Dear Patient,
At the Department of Internal Intensive Medicine (OIIM) of SB Celje, we are conducting a research study to improve our understanding of sepsis and enhance our knowledge and treatment methods for sepsis/septic shock, which could potentially improve patient survival. Your participation in this study is entirely voluntary, and you have the right to withdraw at any time without any consequences for your care. Your non-participation in the study will not affect the treatment of your condition.
Sepsis/septic shock treatment at OIIM follows international guidelines (Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock), which currently do not allow for an individual assessment of optimal cardiovascular function using the new ultrasound methods available for evaluating heart and vascular function. These methods will form the basis of our study.
In the study, we will collect data such as your medical history (disease progression and previous illnesses), laboratory results, and other relevant health data during treatment. Your personal data will be anonymized (without the use of your personal information or date of birth) and will be used exclusively for research purposes. Your participation in this study will not harm you in any way. Advanced ultrasound assessment of heart function and the calculation of the relationship between heart and vascular function will be performed during your treatment in the first few hours until the target blood pressure is reached, as per international treatment guidelines. If we detect a worsening relationship between heart function and the vascular system, we will adjust the target blood pressure, which could help improve the performance of your cardiovascular system during treatment.
Your privacy and confidentiality will be fully protected. All collected data will be strictly confidential and securely stored. Only authorized members of the research team will have access to your data. The results of the study will be used for scientific purposes only, and no personal data will be publicly disclosed.

Patient (Printed name and signature):_____ Date: _____

Patient's Representative (Printed name and signature): _____ Date: _____

Researcher (Printed name and signature):_____ Date: _____