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**Predictors of fluid responsiveness
in patients with
intra-aortic balloon pump
early after cardiac surgery**

Extended summary

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The presented dissertation contains a total of 126 pages and is illustrated with 37 figures and 6 tables.

The bibliography contains 248 titles, all of which are in Latin.

The dissertation study was carried out in the Anesthesiology and Intensive Care Department of UMBAL St. Ekaterina - Sofia for the period August 1, 2018 - August 30, 2019

The thesis has been discussed, accepted and scheduled for defense before a scientific jury by the Departmental Council at the University Department of Anesthesiology and Intensive Care at the Medical Faculty of MU-Sofia.

The defense will take place on 24.10.2024 at 2:15 p.m. in the auditorium of UMBAL St. Ekaterina - Sofia before a scientific jury composed of:

Internal Members:

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Thesis materials are available in the University Department of Anesthesiology and Intensive Care.

- With gratitude to the teachers -

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Abbreviations used

ACB - aortocoronary bypass

ASA - American Society of Anesthesiologists classification

AUC – area under the curve

AUC ROC – area under the ROC curve

BMI - body mass index

BSA – body surface area

CI – confidence interval

CHF - congestive heart failure

CI - cardiac index

CKD - chronic kidney disease

CO - cardiac output

COPD - chronic obstructive pulmonary disease

CPB – cardiopulmonary bypass

CVD - cerebrovascular disease

CVP - central venous pressure

EEOT – end-expiratory occlusion test

EF - ejection fraction

ES - EuroScore

FiO₂ - fraction of inspired oxygen

Hb - hemoglobin

HR - heart rate

IABP- intra-aortic balloon pump

IHD - ischaemic heart disease

MAP - mean arterial pressure

MPP - mean perfusion pressure
NYHA - New York Heart Association
OR – odds ratio
PAD – peripheral artery disease
PAM – pulmonary artery pressure mean
PaO₂ - partial pressure of oxygen in arterial blood
PAWP - pulmonary artery wedge pressure
PEEP – positive end expiratory pressure
PLR - passive leg raise
PPV - pulse pressure variation
PTCA – percutaneous transluminal coronary angioplasty
PVR - pulmonary vascular resistance
PVRI - pulmonary vascular resistance index
RAP - right atrial pressure
ROC – receiver operating characteristics
SAP - systolic arterial pressure
ScvO₂ - central venous saturation
SD – standard deviation
SE – standard error
SPV - systolic pressure variation
SV - stroke volume
SVV - stroke volume variation
SVR - systemic vascular resistance
SVRI - systemic vascular resistance index
VP - valve prosthetics

Introduction

When resuscitating a patient in circulatory shock indications for administration of fluid therapy are often present. However, scientific evidence shows that about half of critically ill patients have a low response to fluids, defined as minimal change in cardiac output after infusion [3]. This group of patients does not benefit from fluid loading and is subject only to side effects, therefore they need to be identified and treated differently.

Methods for prediction of fluid responsiveness are a hot topic in the field of perioperative medicine. Static markers of cardiac preload, dynamic indicators and functional tests are used as predictors.

A significant amount of data has accumulated that dynamic hemodynamic parameters have a higher predictive value than static ones. A high predictive value of dynamic hemodynamic parameters requires multiple conditions that occur only in a limited cohort of patients.

There are also functional tests for prediction of fluid responsiveness that overcome some of the shortcomings of dynamic indices. They are divided into fluid challenge tests and dynamic hemodynamic tests. A relatively new method is the mini-fluid challenge, consisting of a small amount of fluid infused. A small change in cardiac output is sought [8]. A dynamic hemodynamic test that avoids any fluid loading is the end-expiratory occlusion test (EEOT) [9]. It reduces intrathoracic pressure and induces a bolus of blood volume to the heart. An increase in CO above a certain value is sought.

Cardiac surgery patients have been subject of numerous fluid responsiveness studies [11, 12, 13], but research involving intra-aortic balloon pump (IABP) patients is not available. Intra-aortic balloon counterpulsation is a method for hemodynamic stabilization by inflating a balloon in the proximal descending aorta synchronously with the cardiac cycle. In the field of cardiac surgery IABP is frequently implanted when separation from cardiopulmonary bypass is difficult.

Evaluation of fluid responsiveness predictors in patients with IABP is a white field to date. This group of patients is excluded from all cardiac surgery studies. We believe there is strong foundation warranting the conduct of a fluid responsiveness study in cardiac surgical patients with an implanted IABP.

Literature review conclusions

Literature review revealed a large number of scientific works related to fluid responsiveness generally and in specific populations including cardiac surgery patients. In summary, substantial evidence shows good predictive value for fluid responsiveness of dynamic hemodynamic parameters and functional tests, and poor predictive value of static hemodynamic parameters.

The lack of any data for fluid responsiveness in patients with IABP should be emphasized. There is a lack of scientific data on fluid management in these patients.

After conducting the literature review following conclusions were drawn:

1. There is lack of data on the probability of being fluid responsive in cardiac surgery patients with IABP.
2. There is no data on the predictive value of static hemodynamic parameters for fluid responsiveness in cardiac surgery patients with IABP.
3. There is no data on the predictive value of dynamic hemodynamic parameters for fluid responsiveness in cardiac surgery patients with IABP.
4. There is no data on the predictive value of functional tests for fluid responsiveness in cardiac surgery patients with IABP.
5. There is lack of data on which is the best method for predicting fluid responsiveness in patients with IABP.
6. There is lack of an algorithm for predicting fluid responsiveness in patients with IABP at the bedside.

It is these reasons that prompted our interest and desire to conduct a study that would shed light on the issues of predicting fluid responsiveness in this specific patient population on mechanical circulatory support.

Hypothesis, aim and objectives, materials and methods

Hypothesis

The working hypothesis of the present study is: "Hemodynamic indices and functional tests are good predictors of fluid responsiveness in patients with implanted IABP early after cardiac surgery".

Aim and objectives

The aim of the present work is to evaluate the predictive value of hemodynamic indices and functional tests for the response to fluid therapy in the early postoperative period in cardiac surgery patients with an implanted IABP.

Objectives:

1. To determine the probability of a positive response to fluid therapy in cardiac surgery patients with IABP.
2. To evaluate the predictive value of static hemodynamic parameters (CVP, changes in CVP, PAWP) for fluid responsiveness in cardiac surgery patients with IABP.
3. To evaluate the predictive value of dynamic parameters (SVV) for fluid responsiveness in cardiac surgery patients with IABP.
4. To evaluate the predictive value of functional tests (mini-fluid challenge, EEOT) for fluid responsiveness in cardiac surgery patients with IABP.
5. To determine the best method for predicting fluid responsiveness in patients with IABP.
6. To develop an algorithm for prediction of fluid responsiveness in patients with IABP applicable in daily practice.

Subject and object of the study

The subject of the present study is the response to fluid therapy in patients with intraoperatively implanted IABP tested early after cardiac surgery.

The object of the study are the ways of predicting fluid responsiveness in this population of intensive care patients, and specifically the static parameters CVP, changes in CVP after fluid challenge, PAWP, the dynamic hemodynamic index SVV and the functional tests mini-fluid challenge and EEOT.

Materials and methods

The study was conducted in the Anesthesiology and Intensive Care Department of UMBAL "St. Ekaterina", Sofia. The survey period spans between August 1, 2018 and August 30, 2019.

Patients in the early period after elective or emergency cardiac surgery who underwent IABP implantation intraoperatively were considered for inclusion in this prospective interventional study. The study received approval from the "St. Ekaterina" University Hospital Ethics Committee and informed consent was signed by all included patients.

The following inclusion criteria were applied when assessing applicants:

- implanted IABP
- closed chest
- controlled mechanical ventilation
- lack of spontaneous breathing movements
- regular heart rhythm
- presence of circulatory shock, defined as:
 - Hypotension defined as systolic arterial pressure <90 mmHg or mean perfusion pressure <60 mmHg or
 - Serum lactate above 3 mmol/L or
 - ScvO₂ below 50% (at PaO₂ above 80 mmHg) or
 - Cardiac index below 2.2 L/min/m²

Patients with implanted veno-arterial ECMO were excluded from selection due to partial bypass of the left ventricle. Patients with ultrasound data of high-grade tricuspid insufficiency were also excluded due to inaccurate determination of CO by thermodilution.

Inclusion criteria were developed in concordance with recommendations for optimal predictive value of SVV. A state of shock was used as an indication to initiate fluid loading.

All patients underwent cardiac or large vessel surgery with conventional access. After transfer to the operating room, induction of general anesthesia was initiated. Operative access was provided through a median sternotomy. After standard preparation, cardiopulmonary bypass (CPB) was initiated with a minimum perfusion flow equal to a cardiac index of 2.0 L/min/m². For coronary revascularization, vein grafts from the lower extremities and a left internal mammary artery graft for LAD (left anterior descending artery) were used. Valvuloplasty was performed by ring implantation, cusp resection, or neochordal

implantation. Valve replacement was performed by implantation of a biological or mechanical prosthesis. After cardiac reperfusion of appropriate duration, CPB was gradually terminated.

In the studied patients, there was an inability to discontinue CPB due to hypotension refractory to fluids and catecholamines. According to the hospital's protocol for IABP implantation, it was necessary to notice signs of low-flow syndrome (arterial hypotension defined as systolic arterial pressure <90 mmHg or mean perfusion pressure <60 mmHg, ScvO₂ below 50% with PaO₂ above 80 mmHg or a cardiac index below 2.2 L/min/m²) after adequate fluid resuscitation and a catecholamine index (CI) above 10.

CI = dose of dopamine + dobutamine + adrenaline*100 + noradrenaline*100 (µg/kg/min)

The Maquet Datascope Model CS300 IABP was implanted with femoral access and initiated in 1:1 pressure-triggered mode. The hemodynamics of the patients were stabilized.

In all patients a Swan-Ganz catheter (Edwards Lifesciences 7.5 F 110 cm) was placed intraoperatively in the pulmonary artery - a five-lumen catheter for pulmonary thermodilution CO measurement.

Upon operation completion patients were transferred to the intensive care unit in a state of deep sedation, on mechanical ventilation. Standard monitoring of vital signs was applied. Transthoracic echocardiography was performed by a cardiologist in all patients within two hours of ICU admission.

Intermittent measurement of CO by pulmonary thermodilution was performed repeatedly according to the study protocol.

All patients were sedated, without spontaneous respiratory activity, and ventilated with a tidal volume of 8 mL/kg and a PEEP of 5 cm H₂O (VC A/C mode) and a respiratory rate lower than 20/min. All patients had regular heart rhythm. All patients were in a stable hemodynamic state without sudden changes in values before starting the measurements.

TM MHM1E monitor (Edwards Lifesciences, Irvine, CA, USA) and a FloTrac TM sensor were connected to the arterial cannula to measure SVV. Biometric data were entered according to the requirements of the software - gender, age, weight, height.

Immediately after connecting the patient to the monitoring devices the study algorithm was executed.

Algorithm of measurements and interventions:

1. Perform first set of hemodynamic parameters (baseline):
HR₁, SAP₁, MAP₁, CVP₁, PAWP₁, PAM₁, CO₁
2. Put IABP on standby for 1 minute
3. Obtain SVV value
4. Put IABP back to 1:1 mode

5. Wait 2 minutes
6. Obtain CO- Vigileo₁
7. Perform EEOT - 15 seconds of end-expiratory occlusion
8. Obtain CO- Vigileo₂ after the 15 second interval is over
9. Infusion of 2 ml/kg Gelafusin over 5 minutes (mini fluid challenge)
10. Perform second set of hemodynamic parameters (post-mini fluid challenge):
HR₂, SAP₂, MAP₂, CVP₂, PAWP₂, PAM₂, CO₂
11. Infusion of 4 ml/kg Gelafusin over 10 minutes
12. Perform third set of hemodynamic parameters (final) :
HR₃, SAP₃, MAP₃, CVP₃, PAWP₃, PAM₃, CO₃

Step 1 of the algorithm of measurements and interventions aims to collect initial values of hemodynamic parameters, which will subsequently be used for comparison with the corresponding values of parameters after the interventions, as well as for the calculation of derived parameters of interest. Such are, for example, systemic and pulmonary vascular resistance, mean perfusion pressure. CVP and PAWP values will be tested as predictors of fluid responsiveness. CO value is of particular importance because it will serve to determine the response to fluid loading and differentiate responders and non-responders.

Step 2 of the algorithm - placing the IABP on standby for 1 min - is necessary to allow the reading of the SVV by the Vigileo monitor, which would be impossible with simultaneous operation of the IABP due to the fluctuations in the arterial pulse contour caused by the counterpulsator.

Step 3 is the reading of the SVV value from the Vigileo monitor, which will be used to calculate the predictive value of SVV for the response to fluid loading.

Step 4 is to return the IABP to 1:1 operation mode as before the standby was placed. The 1:1 mode is the typical working modality of IABP in the early postoperative period, in which each cardiac contraction is followed by one cycle of balloon inflation and deflation.

Step 5 – waiting 2 minutes – is necessary to wait for the circulation to stabilize if significant changes in vascular tone have occurred during the period of IABP withdrawal. This is a necessary preparation for the subsequent EEOT.

Step 6 consists of measurement of a baseline value of CO measured by the Vigileo monitor using the arterial pulse contour analysis method.

Steps 1, 2, 3, 4, 5 and 6 generally represent measurement of initial values of hemodynamic parameters.

Step 7 is performing EEOT. This is essentially an intervention on the cardiac preload - occlusion at the end of exhalation for 15 seconds by activating the "Expiratory hold" function of the ventilator.

Step 8 - Immediately after termination of the occlusion, a second CO value is measured using the Vigileo monitor to subsequently determine the predictive value of EEOT by CO change analysis.

Step 9 is a mini fluid challenge with 2ml/kg Gelafusin over 5 minutes.

The measurements in step 10 are intended to determine the difference between CO from the baseline set of measurements and CO after mini fluid challenge, which will be analyzed as a predictor of fluid responsiveness.

Step 11, infusion of 4 ml/kg Gelafusin, is a fluid challenge necessary to determine the fluid response of the study group patients.

In step 12, hemodynamic parameters are measured after the end of the fluid challenge. These values will be compared to baseline to differentiate responders and non-responders and to calculate derived metrics.

In summary, the algorithm of measurements and interventions was designed to allow obtainment of all the values determined in the objectives of the study (CVP, PAWP, difference in the initial and final value of CVP after a fluid bolus, SVV), as well as mini fluid challenge and EEOT. The sequence of steps in the algorithm is dictated by the aim to respect conditions for a good predictive value of each predictor.

Position of the tip of the Swan-Ganz catheter in West zone 3 was confirmed by the method of Teboul et al. [221]. This is necessary for the measured PAWP to be valid.

It was determined that CO monitoring should be performed by pulmonary thermodilution, a gold standard in the field and a routinely performed method in our clinic for high-risk patients. Measurements were performed according to the manufacturer's recommendations with the patient in a horizontal position, high-speed infusions of intravenous solutions were paused. Each measurement was performed after injection of 10 ml of saline at room temperature. The final CO recorded value was obtained by exclusion of the largest and smallest measured values and calculating an average of the remaining three. It was decided not to include patients with subsequently diagnosed high-grade tricuspid regurgitation because of the poor reliability of the measured CO.

For the EEOT it was judged that measurement of CO by pulmonary thermodilution is not practical. According to the methodology described above, the measurements take about 5 minutes, which is an extremely long time, considering that a value must be measured immediately after the end of the fifteen second duration of the test. As a result, it was decided to use the Vigileo monitor, which was connected to the patients for the purpose of SVV measurement. Vigileo is an uncalibrated system for measuring CO by analysis of the arterial pulse contour. According to the algorithm of the used software model 1.07, an updated CO value is displayed every twenty seconds.

Placing the IABP on standby mode for one minute was dictated by scientific data indicating inaccurate determination of dynamic hemodynamic parameters in patients with intra-aortic counterpulsation due to arterial curve artifacts caused by cyclic inflation and

deflation of the balloon. These artefacts interfere with the measurement of SVV. According to the algorithm of the Vigileo system SVV is calculated after analyzing the arterial pulse contour and, more precisely, the area under the curve by the formula:

$$SVV(\%) = \frac{SV_{\max} - SV_{\min}}{(SV_{\max} + SV_{\min})/2} \times 100$$

The standby duration was determined to be one minute, since the calculation of SVV is based on 20 second intervals of the arterial pulse contour. Prolonged balloon deflation carries the risk of hemodynamic collapse in some patients with critically counterpulsation-dependent hemodynamics.

For safety reasons, when switching to standby mode, the values of MAP were monitored. A drop in MAP below 65 mmHg, or by more than 20% of the initial value, if the value was initially below 65, would warrant IABP counterpulsation prompt restart. During the intervention no such values of MAP were noticed.

The controlled infusion of Gelafusin was carried out by means of an infusion pump at an assigned rate according to the calculated amount of solution. In order to ensure patient safety, a protocol was carried out to control and limit the infused volume based on hemodynamic parameters. Discontinuation of the fluid infusion was warranted if there was a rise in CVP above 20 mmHg or a fall in SBP below 65 mmHg or by at least 20% of baseline if it was below 65. None of the study participants suffered such changes in their hemodynamics.

After implementation of the experimental protocol, demographic, anamnestic, and clinical data relevant to the study were taken from the records of all participants.

After obtaining the experimental directly measured hemodynamic values, certain calculations were undertaken to obtain derived indices of interest. Indexes 1, 2 and 3 denote values from baseline, post-mini fluid challenge and final set of hemodynamic parameters, respectively.

Cardiac index values were calculated as follows:

$$CI_1 = CO_1 * BSA$$

$$CI_2 = CO_2 * BSA$$

$$CI_3 = CO_3 * BSA$$

Differences between baseline and post-intervention values of hemodynamic parameters were calculated.

$$\Delta CVP_1 = CVP_2 - CVP_1$$

$$\Delta CVP_2 = CVP_3 - CVP_1$$

$$\Delta PAWP_1 = PAWP_2 - PAWP_1$$

$$\Delta\text{PAWP}_2 = \text{PAWP}_3 - \text{PAWP}_1$$

$$\Delta\text{CO}_1 = \text{CO}_2 - \text{CO}_1$$

$$\Delta\text{CO}_2 = \text{CO}_3 - \text{CO}_1$$

$$\Delta\text{CO-Vigileo}_1 = \text{CO-Vigileo}_2 - \text{CO-Vigileo}_1$$

Systemic and pulmonary vascular resistance (SVR, PVR), as well as resistances indexed by body surface area (SVRI, PVRI) were calculated for better understanding of hemodynamic profiles.

A significant increase in CO after completion of a fluid challenge with a cumulative volume of 6 ml/kg was defined as an increase in CO of at least 10%. Based on this, after completion of the experimental algorithm and subsequent analysis of the results, patients were defined as responders - those with an increase in CO of at least 10%, and the rest - as non-responders.

To achieve the objectives of the study, the following calculation methodology was used:

To achieve objective 1. - determining the probability of a positive response to fluid loading - after completing the experimental part of the study, an assessment of the percentage increase in CO before and after a fluid challenge (ΔCO_2) was made. Patients with an increase in CO of at least 10% were defined as responders and their proportion of the total group was calculated.

To achieve objective 2. - determination of the predictive value of CVP, PAWP and changes in CVP after fluid challenge - CVP_1 , PAWP_1 and ΔCVP_2 were tested for a statistically significant difference between the groups of responders and non-responders. ROC curves were constructed based on the values of CVP_1 and ΔCO_2 , PAWP_1 and ΔCO_2 , ΔCVP_2 , and ΔCO_2 .

In order to achieve objective 3. - assessment of the predictive value of SVV - the values of SVV in the groups of responders and non-responders were tested for a statistically significant difference. A ROC curve was constructed based on the values of SVV_1 and ΔCO_2 .

To achieve objective 4. - assessment of predictive value of functional tests - for predictive value of mini fluid challenge, the values of ΔCO_1 were tested for a statistically significant difference in the responder and non-responder groups. A ROC curve was constructed based on the values of ΔCO_1 and ΔCO_2 . To assess the predictive value of EEOT, $\Delta\text{CO-Vigileo}$ values were tested for statistically significant difference in the responder and non-responder groups. A ROC curve was constructed based on the values of $\Delta\text{MCO-Vigileo}$ and ΔMCO_2 .

To achieve objective 5. - determination of the best method for predicting fluid responsiveness - indices of the ROC curves of the studied predictors were compared: p - value, AUC, sensitivity and specificity of the determined best threshold values.

To achieve objective 6. – designing an algorithm for patients with IABP- results of the clinical study were used for the synthesis of a logical and rational model to guide clinicians step by step through a sequence of binary answers.

Statistical methods

Obtained data was analyzed using Microsoft Excel Data Analysis Toolpack and IBM SPSS 25.

A method described by Negida et al was used to determine the size of the study group. [222]. Sample size is based on the predictive value of parameters from previous studies, value of alpha (statistical significance) = 0.05 and beta (1-power of the study) = 0.2. The ratio of responders to non-responders was set as 1 based on studies cited in the literature review. Two sets of study group sizes were used - one group size for static hemodynamic parameters and one group size for dynamic variables and functional tests. In the first group, AUC ROC for static indicators 0.55 was used based on the low predictive value determined from studies included in the literature review and null hypothesis AUC ROC 0.8 for a test with good predictive value. The estimated group size was 30 people. For the second group, AUC ROC 0.80 was used as a reference value for a test with good predictive value and a null hypothesis AUC ROC 0.5 - a test with the lowest predictive value was used. The estimated group size was 26 people. The larger value was considered and it was determined to collect at least 30 consecutive patients with an intraoperatively implanted IABP.

Normality of data was determined with the Jarque-Bera test.

Hemodynamic parameters before and after intervention were compared by Student's t-test. Difference in mean values of various parameters in responders and non-responders was also tested by Student's t-test.

Construction of receiver operating characteristic (ROC) curves was used to assess the predictive value of used hemodynamic parameters and clinical tests. The diagram was constructed according to a standard methodology, where "1" indicated a positive response to fluid, and "0" indicated a negative response. Area under the curve (AUC ROC), sensitivity and specificity for the parameters of interest were derived from the data thus calculated.

Predictive value of studied parameters to the response to fluid loading was estimated by means of the area under the corresponding ROC curve. Values below 0.75 were judged as low, those between 0.75 and 0.85 as moderately high and values above 0.85 as high. In addition to area under the curve, the value of "p" (asymptotic significance) was taken into account to reject the null hypothesis that the AUC ROC value does not differ from 0.5 (a

predictive value equivalent to a coin toss). A “p” value of less than 0.05 is required to reject the null hypothesis.

A best threshold value for predictors of fluid responsiveness was defined as the value with the greatest sum of sensitivity and specificity minus 1 (Youden's index).

Correlation analysis between selected variables was performed by calculating a correlation coefficient (r).

Graphics:

Bar and pie charts with standard normalization to 100% were used to visualize values and distribution of selected patient characteristics.

To visualize values and distribution of selected hemodynamic indicators, "boxplot" graphs were built with presented 25th, 50th and 75th percentile of distribution, maximum and minimum value of the value of interest, as well as "outliers" - values above 1.5 boxplot lengths.

Results

Characteristics of the study group

For the period of the study from August 1, ²⁰¹⁸ to August 31, ²⁰¹⁹, 761 operative interventions with CPB were performed at UMBAL St. Ekaterina. Thirty-four of these patients had an implanted IABP. Four of the patients also had implanted ECMO, and therefore were excluded from the study group. The remaining 30 patients met the inclusion criteria.

All included patients met criteria for low CO syndrome. In 18 people (60%) $CI < 2.2$ L/min/m² was observed. A serum lactate level above 3 mmol/L was observed in 19 subjects (63%). ScvO₂ below 50% was observed in 10 patients (30%). Two people had a SBP below 90 mmHg and six had an MPP below 60 mmHg. All patients had at least one catecholamine in continuous infusion.

Of the 30 patients included, 18 (60%) were men and 12 - women (40%). The lowest age in the group was 43 years, the highest was 83, mean 67.9 (SD+/- 8.1) years. Mean height (and standard deviation) for the group - 166.4 cm (SD +/-9.7), mean weight - 80.3 kg (SD +/- 14.3), mean BMI 29 (SD +/-4.9).

All studied patients had diagnosis of CHF preoperatively. NYHA class II CHF was present in four patients, class III in 23, and class IV in three (Fig. 9).

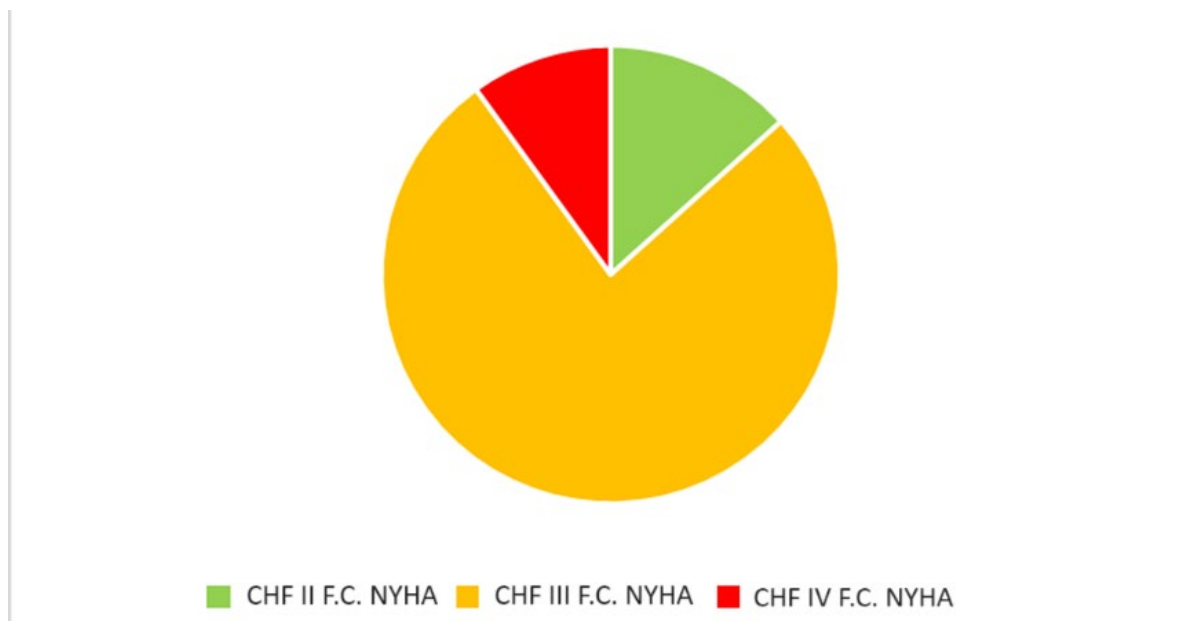


Fig. 9 Distribution by severity of heart failure

The studied group of patients had the following distribution by ejection fraction: >60% - three (10%), between 30% and 60% - 18 (60%), below 30% - 9 people (30%).

Twenty-one subjects (70%) had preoperative echocardiographically documented regional abnormalities in left ventricular kinetics. One person had severe left ventricular hypertrophy (wall thickness greater than 17 mm). Average LV wall thickness for the group was 11.8 mm. Average size of the left atrium - 50.2 mm.

Regarding accompanying diseases, 3rd degree CKD was diagnosed in 13 people, one person with 4th degree CKD (total 47%), in 15 people type 2 diabetes mellitus was present (50%), in five people - CVD (16.7%), in two - COPD (6.7%).

Of the 30 examined patients, 26 were elective cases and 4 emergency cases.

In terms of preoperatively calculated risk, the mean logarithmic Euroscore II of the group was 22.8% (SD +/- 19.3), which means that the expected risk of death for the studied group was 22.8%. Patients with low risk (Euroscore < 4%) were 4, those with moderately high risk (>4%, <20%) were 13, and those with high risk (>20%) were 13 (Fig. 11).

Distribution by operative intervention is as follows (Fig. 13):

Aortocoronary bypass: 11

Valve prosthetics/plasty: 5

Combined operation: 13

Pulmonary artery thrombectomy for PTE: 1

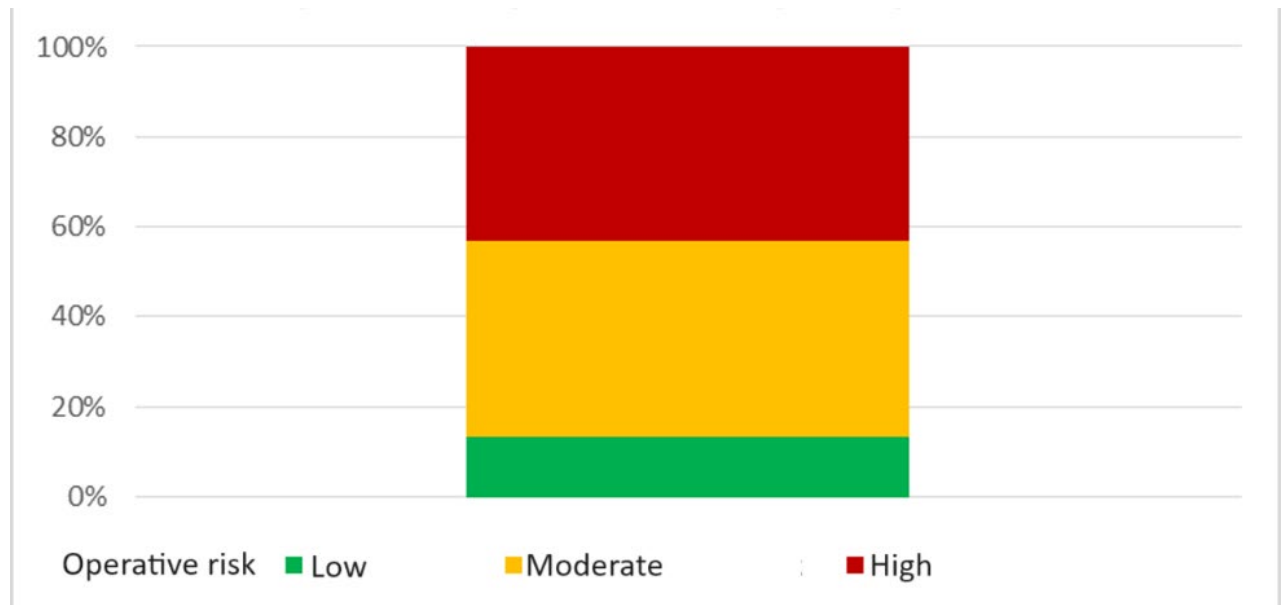


Fig. 11 Logarithmic Euroscore II

Stratification according to ASA: class III – 5 people, class IV – 24 people, class V – 1 (Fig. 12)

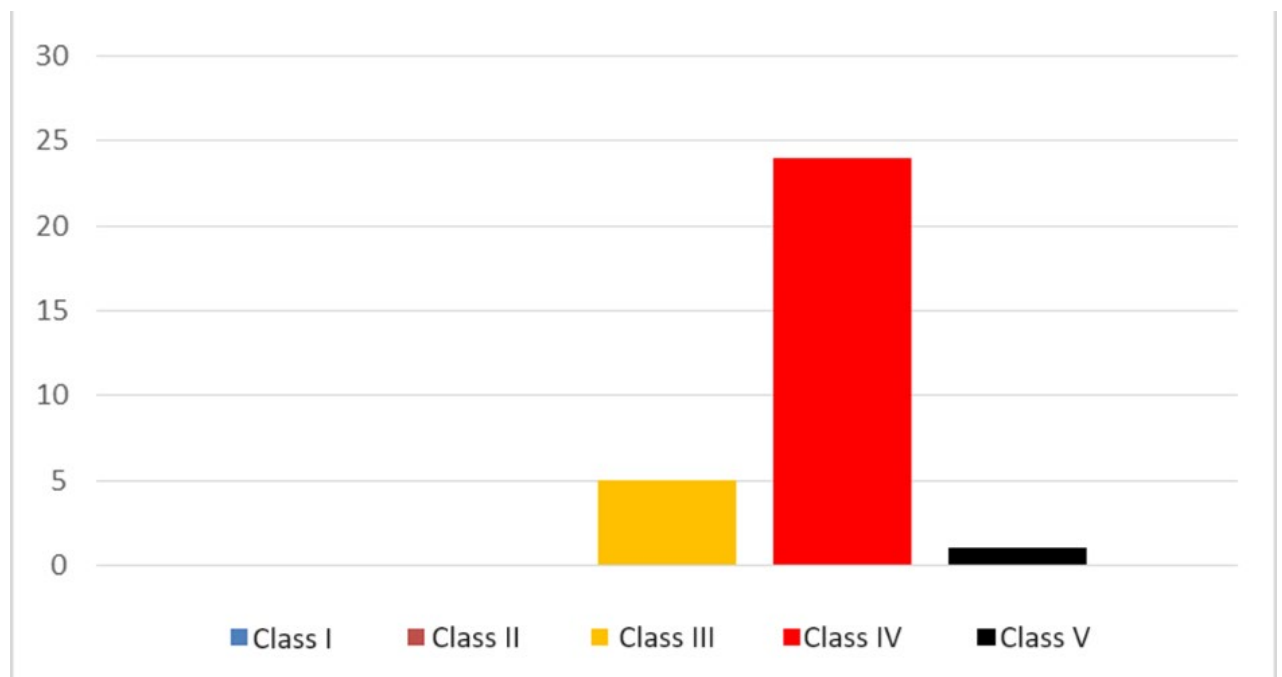


Fig. 12 ASA class

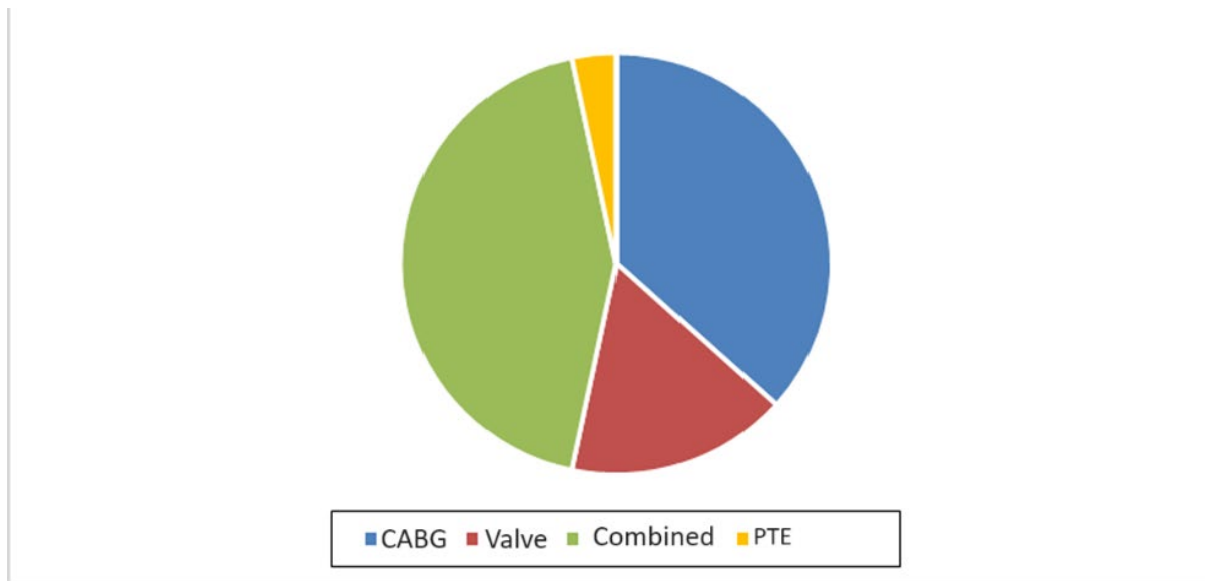


Fig. 13 Distribution of patients according to operation type

Average duration of the operation in the group was 308 minutes (SD +/- 47), average duration of cardiopulmonary bypass (CPB) - 116 minutes (SD +/- 36), average crossclamp time 58 (SD +/- 25). Two patients had a CPB duration of more than 180 minutes and in 11 people crossclamp time was more than 60 minutes. Mean cumulative intraoperative fluid balance was +1080 mL (SD +/- 779).

All but one patient had a continuous dopamine infusion with a mean dose of 8.9 µg/kg/min (SD +/- 2.7). Of the 29 patients, 13 also had norepinephrine in continuous infusion at a mean dose of 0.11 µg/kg/min (SD +/- 0.08). Five patients had continuous infusion adrenaline at a mean dose of 0.11 mcg/kg/min (SD +/- 0.12). Five patients had dobutamine at a mean dose of 5.1 mcg/kg/min (SD +/- 1.5). Levosimendan infusion was prescribed in three patients at a dose of one vial for 24 hours.

Catecholamine index of the group was 16.29 (mean), 13.3 (median), 9.8 (mode), SD +/- 16.3.

Mean serum lactate value of the patients was 4.2 mmol/L (SD +/- 2.7). A lactate level above 3 mmol/L was observed in 19 subjects (63%) (Fig. 14).

Central venous blood oxygen saturation level (ScvO₂) was 57.3% (SD +/- 11.9). ScvO₂ below 50% was observed in ten patients.

Partial pressure of oxygen in arterial blood was above 80 mmHg in all patients studied, mean value 141 mmHg (SD +/- 38). PaO₂/FiO₂ ratio was between 200 and 300 in 10 patients and between 100 and 200 in 20 patients, with none of the subjects having a ratio below 100.

All patients had regular heart rhythm. Six of them were in sinus rhythm, 24 were paced with a temporary pacemaker in DDD/D00 or AAI/A00 mode.

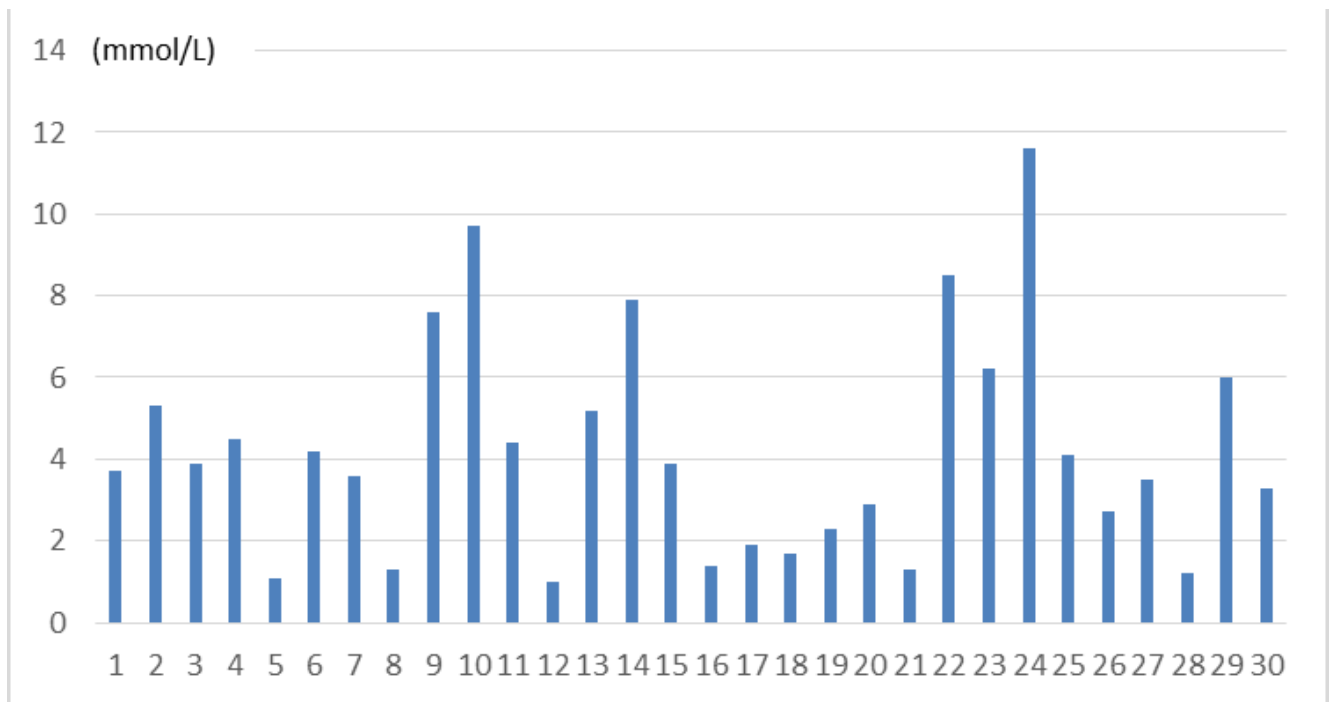


Fig. 14 Serum lactate level

During hospital stay, 15 people died and 15 people were discharged, resulting in a mortality rate of 50% (Fig. 15).

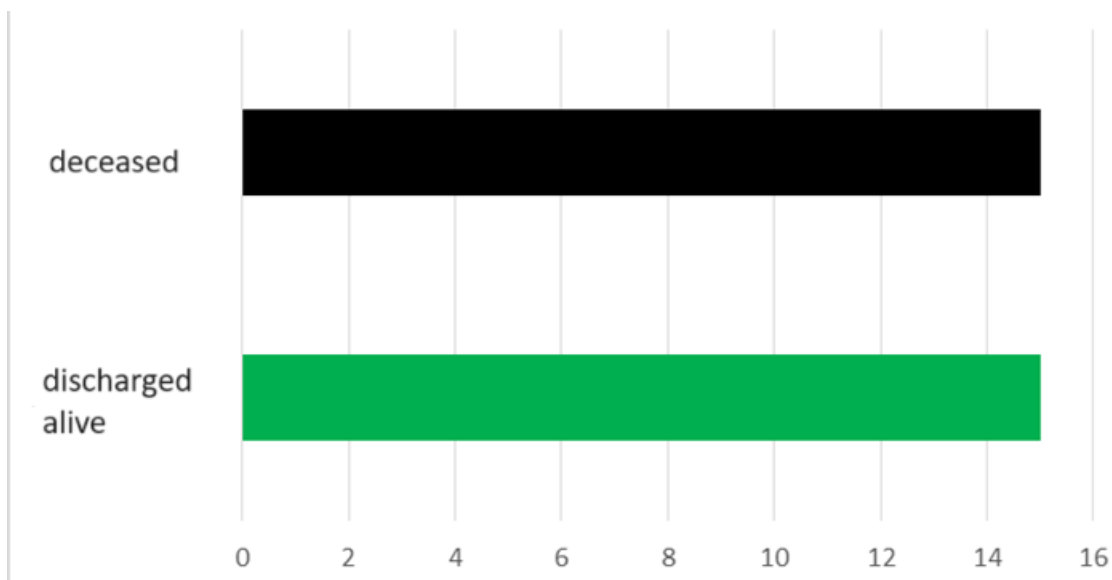


Fig. 15 Survival within hospitalization

Statistical analysis results

Frequency of positive response to fluid

To determine responders and non-responders CO₁ and CO₃ values were tested for normality using the Jarque-Bera test, according to which the distribution of both sets of data is normal ($p=0.80$ and 0.99 respectively under the null hypothesis "the distribution of the data is not normal"). The two data sets were tested for mean differences by Student's t-test. The result showed that the two data sets differ statistically significantly ($P(T \leq t)$ two-tail $2.22123E-06$ under the null hypothesis "the two data sets differ").

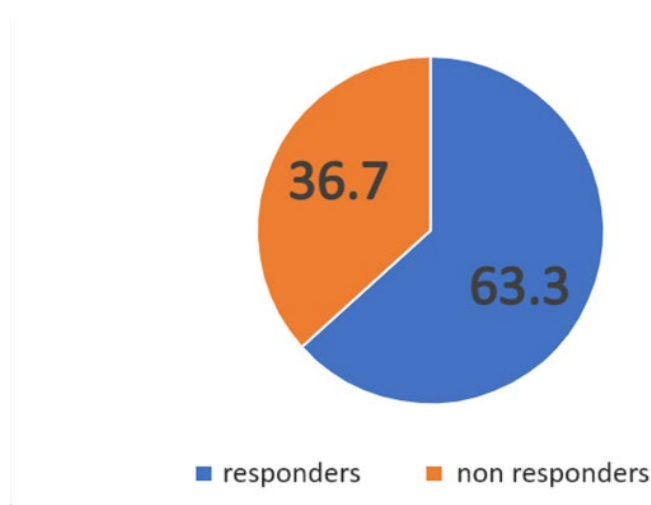


Fig. 16 Frequency of positive response to fluid

In the studied group 19 people (63%) were defined as responders after a fluid challenge with a total of 6 ml/kg of Gelafusin (ΔCO_2 at least 10%). 11 people (37%) showed lower increase in CO and were identified as non-responders (Ratio resp./non resp. 1.73) (Fig. 16).

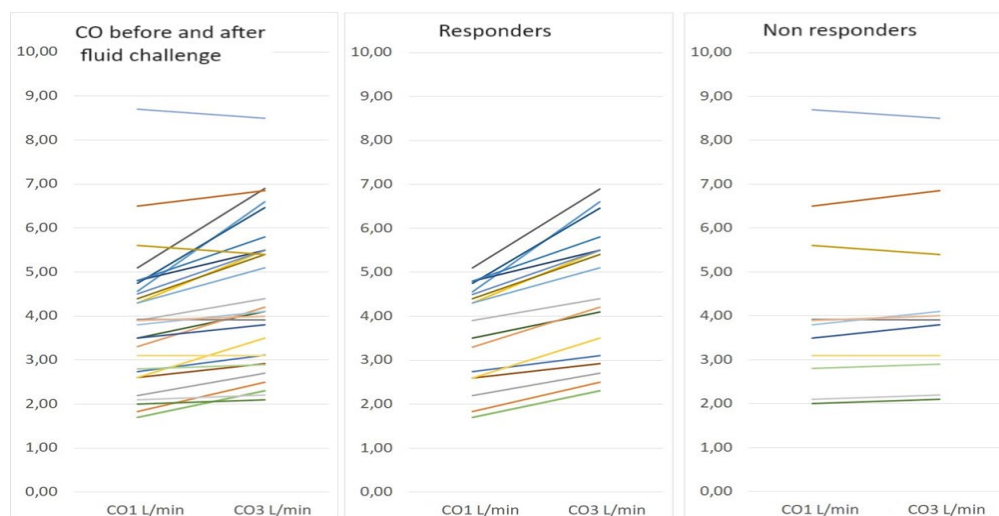


Fig. 17 CO values at the beginning and in the end of a fluid challenge with Gelafusin 6 ml/kg

Predictive value of CVP_1

Values of CVP_1 in responders and non-responders were compared by unpaired t-test for unequal variance, the result of which showed that there was no statistically significant difference between the mean values for the two groups. Means for both groups were 6.9 (SD +/- 3.3) and 9.5 (SD +/- 4.5) for responders and non-responders, respectively.

Predictive value of CVP_1 was assessed by means of ROC curve analysis. ROC curve was constructed by input of the binary response to a fluid challenge and baseline CVP value for the patients of the study group. ROC curve thus obtained is presented in Fig. 19.

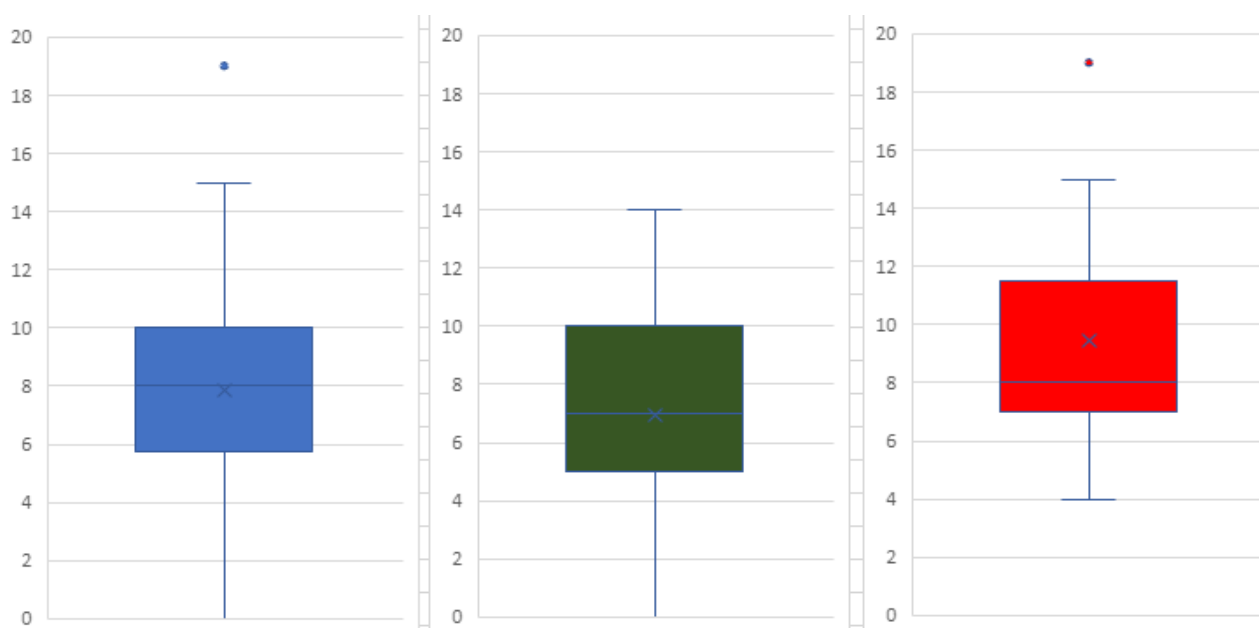


Fig. 18 Values of CVP_1 in total for the group, in responders and non-responders

The obtained value of AUC ROC 0.65 indicates a low predictive value of CVP for the response to fluid. Moreover, the value of $p=0.19$ does not allow rejecting the null hypothesis that AUC ROC = 0.5. A threshold value of CVP for differentiating responders and non-responders could not be determined.

Predictive value of $PAWP_1$

$PAWP_1$ was tested as a predictor of fluid responsiveness similarly to CVP_1 . Values of $PAWP_1$ in responders and non-responders were compared by unpaired t-test for unequal

variance, the result of which showed that there was no statistically significant difference between the mean values for the two groups. Means for both groups were 13.3 (SD +/- 5.1) and 12.5 (SD +/- 3.3) for responders and non-responders, respectively.

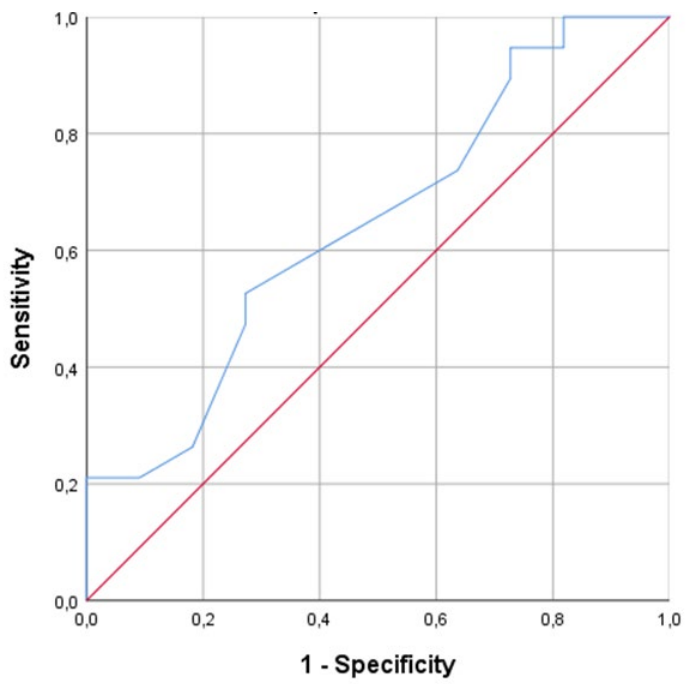


Fig. 19 ROC curve for CVP₁ and fluid challenge response

The obtained AUC ROC value of 0.45 indicates a low predictive value of PAWP for the response to fluid, and the value of $p=0.67$ does not allow rejecting the null hypothesis that AUC ROC = 0.5. A threshold value of PAWP for differentiating responders and non-responders could not be determined.

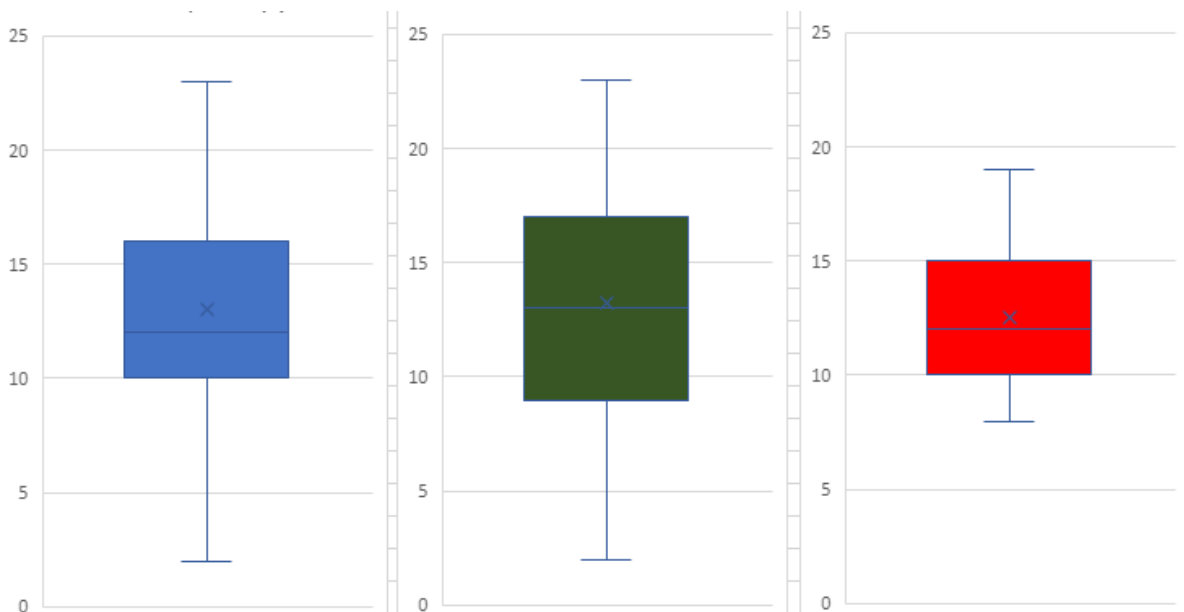


Fig. 20 Values of PAWP₁ for the group, responders and non-responders

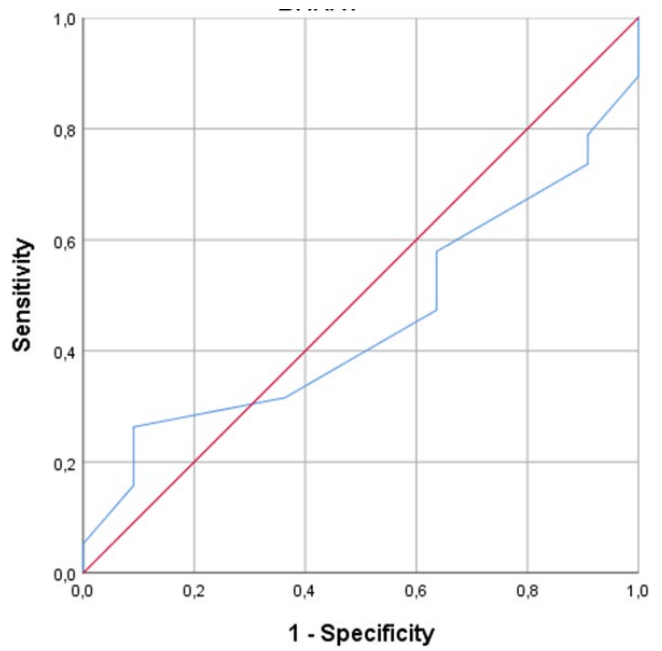


Fig. 21 ROC curve for PAWP₁ and fluid challenge response

Predictive value of ΔCVP_2

Values of ΔCVP_2 in responders and non-responders were compared by unpaired t-test for unequal variance, the result of which showed that there was no statistically significant difference between the mean values for the two groups. Means for both groups were 1.7 (SD +/- 3.8) and 1.7 (SD +/- 1.9) for responders and non-responders, respectively.

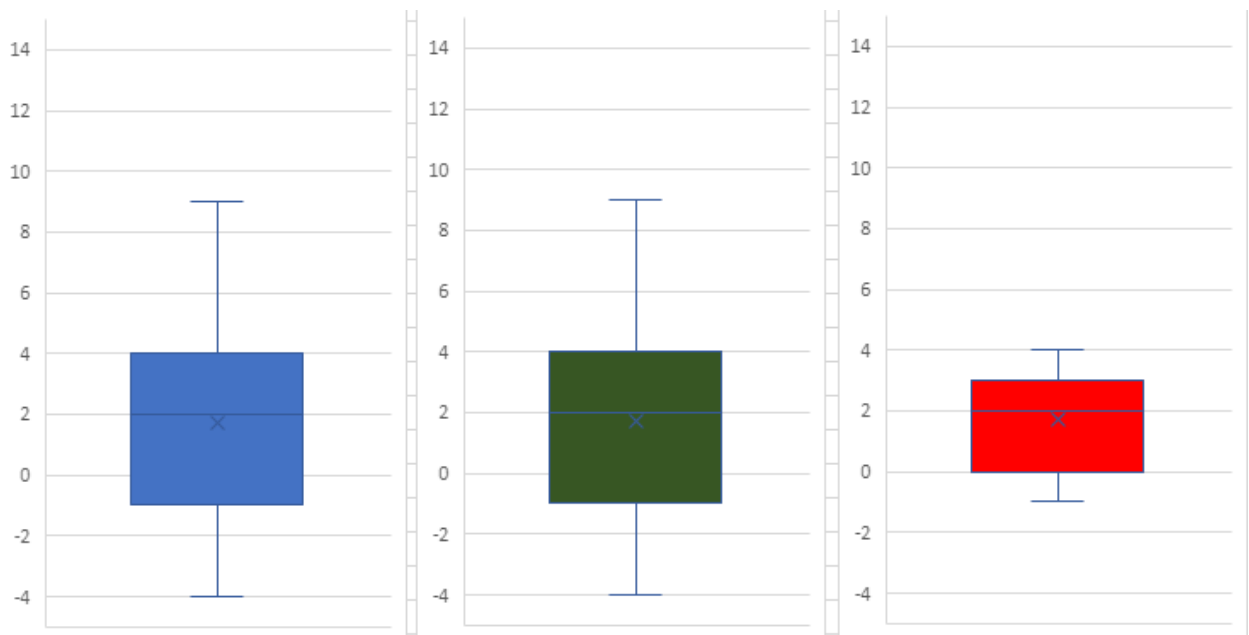


Fig. 22 Values of ΔCVP_2 in total for the group, in responders and non-responders

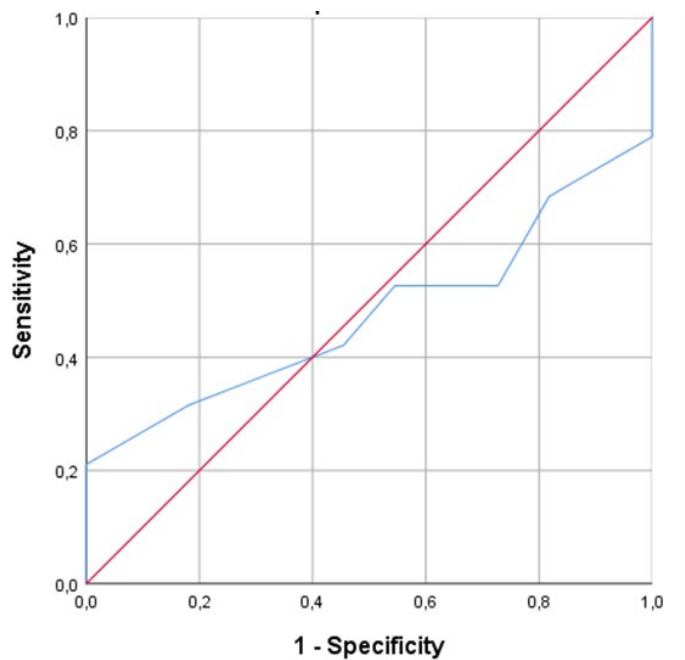


Fig. 23 ROC curve for ΔCVP_2 and fluid challenge response

Predictive value of ΔCVP_2 was evaluated by means of ROC curve analysis constructed by binary response to a fluid challenge and the baseline value of ΔCVP_2 in the studied patients. ROC curve thus obtained is presented in Fig. 23

The obtained value of AUC ROC 0.48 shows a low predictive value of the indicator ΔCVP_2 for the response to fluid, and value of $p=0.83$ does not allow rejecting the null hypothesis that AUC ROC = 0.5. A threshold value of ΔCVP_2 for differentiating responders and non-responders could not be determined.

6.4.5 Predictive value of SVV

Values of the SVV in responders and non-responders were compared by unpaired t-test for unequal variances, according to which mean values of the two groups have a statistically significant difference.

Mean values (means) of SVV for responders and non-responders are as follows: 14.6% (SD +/- 5.1) and 7.1% (SD +/- 2.7) (Fig. 24).

Predictive value of SVV was assessed by means of ROC curve analysis, constructed by binary response to a fluid challenge and the baseline value of SVV in the studied patients. The ROC curve thus obtained is presented in Fig. 25

Thus, the obtained AUC ROC value of 0.91 indicates a high predictive value of SVV for fluid responsiveness. Obtained value of $p < 0.05$ shows that AUC ROC differs from 0.5 with statistical significance.

Using the method of maximum sum of sensitivity and specificity - 1 (Youden's Index), an optimal threshold value of 8.5% was determined (sensitivity: 95%, specificity: 82 %).

Therefore patients with SVV at least 8.5% have a high probability of a positive response to fluid.

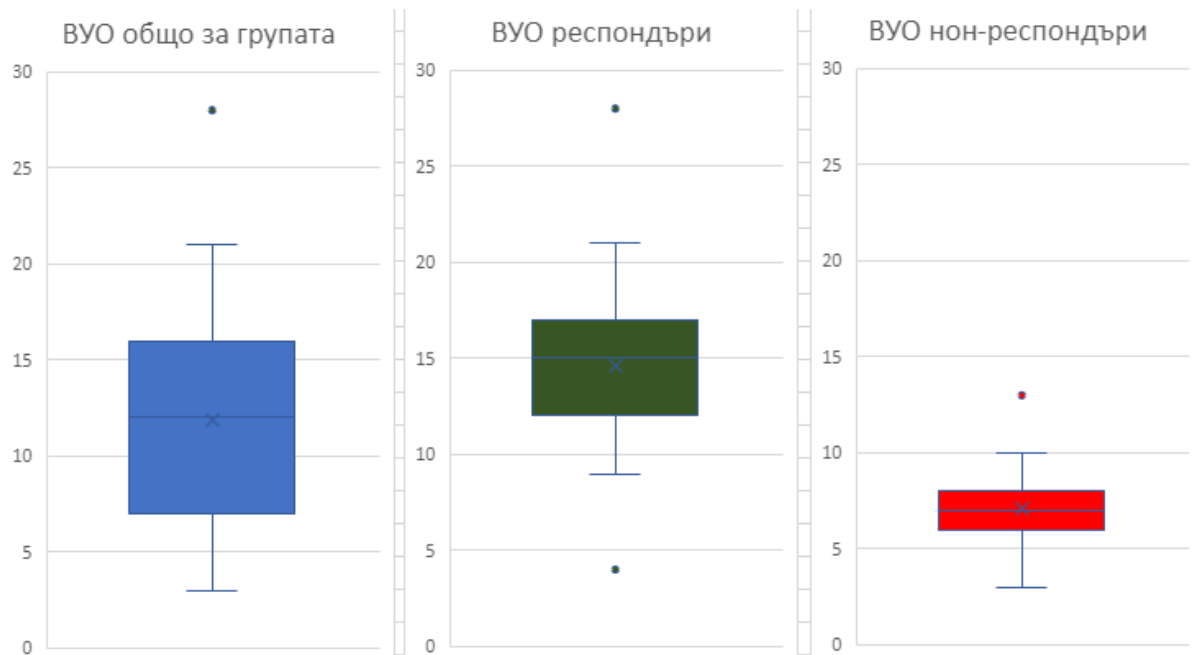


Fig. 24 Values of SVV₁ for the group, for responders and non-responders

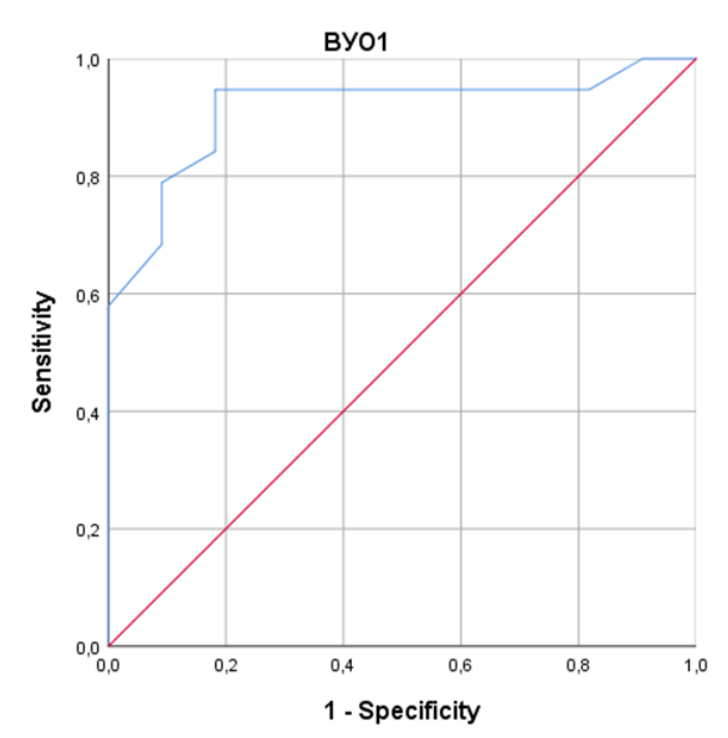


Fig. 25 ROC curve for SVV₁ and response to fluid

Predictive value of mini fluid challenge

For data analysis after mini fluid challenge Jarque-Bera normality test was applied to the CO₂ values, which showed a normal distribution of data.

Student's t-test was applied to prove a difference in the values of CO_1 and CO_2 for the studied population. The results showed a statistically significant difference in mean values for both parameters. Fig. 26 shows the CO values before and after mini fluid challenge.

Analysis of the correlation between ΔCO_1 and ΔCO_2 showed a correlation coefficient (r) of 0.91. Correlation between the two variables is presented in Fig. 27.

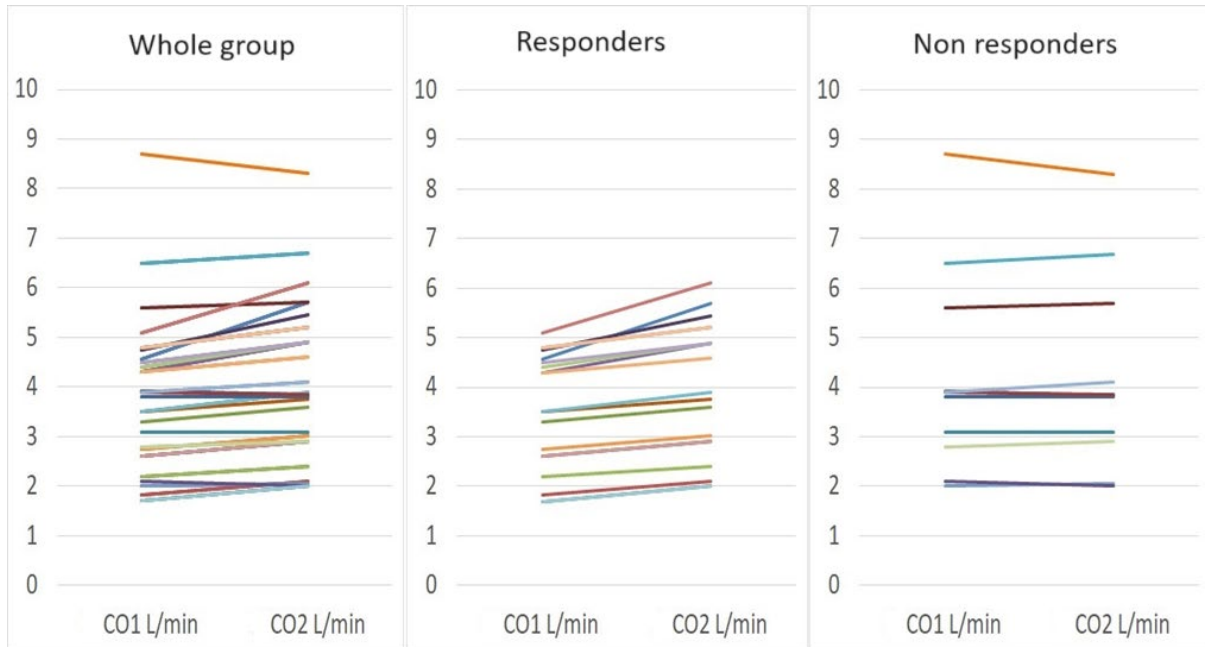


Fig. 26 CO before and after mini fluid challenge

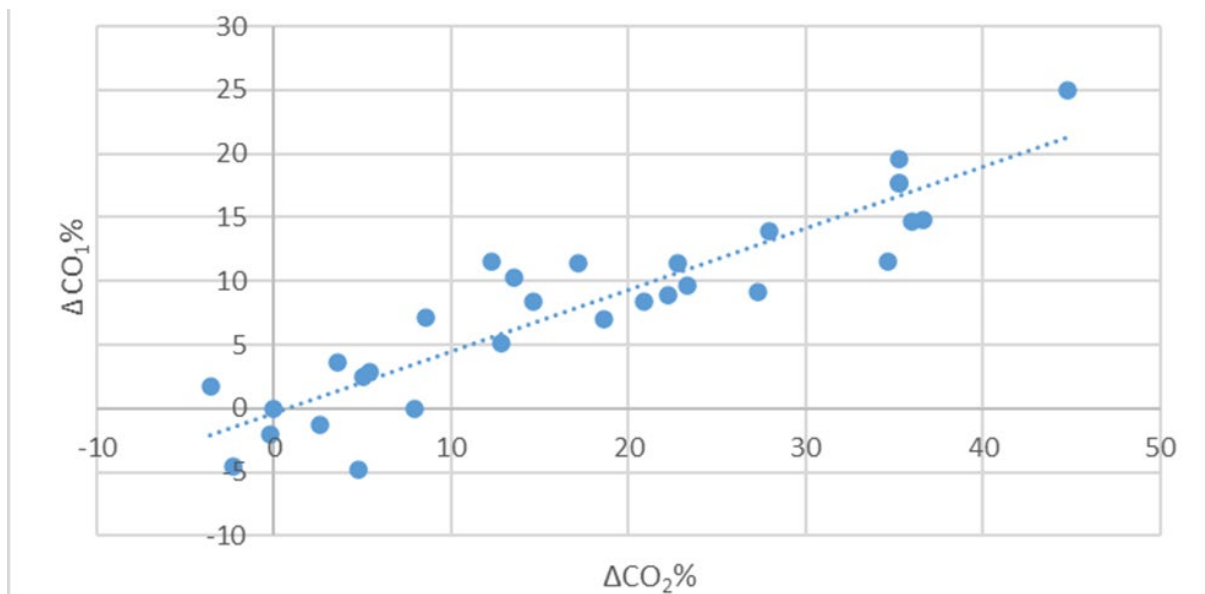
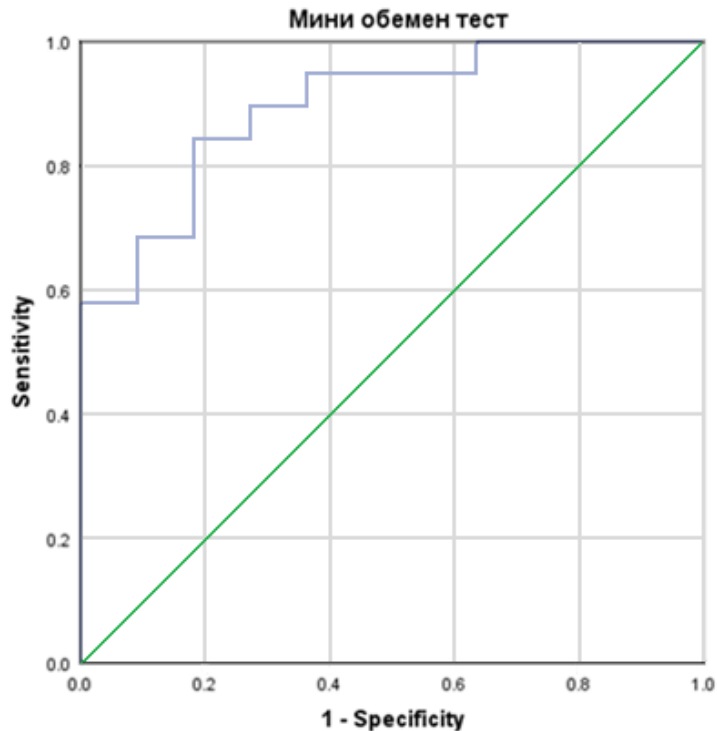


Fig. 27 Correlation of ΔCO_1 and ΔCO_2

A ROC curve was constructed based on the binary response of a 6 mL/kg fluid challenge and ΔCO_1 . The latter is presented in Fig. 28.

Fig. 28 ROC curve of the response to mini fluid challenge and the response to 6 ml/kg fluid challenge



The obtained AUC ROC value of 0.90 indicates a high predictive value of mini fluid challenge for the response to fluid. Obtained value of $p < 0.05$ shows that AUC ROC differs from 0.5 with statistical significance.

Using the method of maximum sum of sensitivity and specificity - 1 (Youden's index), an optimal threshold value for an increase in CO after a mini fluid challenge of 7.7% was determined (sensitivity: 84%, specificity: 82%). Therefore, patients with an increase in CO of at least 7.7% after a mini fluid challenge have a high probability of a positive response to fluid.

Predictive value of EEOT

Values of ΔCO -Vigileo in responders and non-responders were compared by unpaired t-test for unequal variance, the result of which showed that there was no statistically significant difference between the mean values for the two groups. Means for both groups were 2.41 (SD +/- 6.95) and 3.10 (SD +/- 4.15) for responders and non-responders, respectively.

ROC curve for EEOT was constructed based on the change in CO values measured by the Vigileo monitor before and after the end of a 15 second end-expiratory occlusion (Fig. 29).

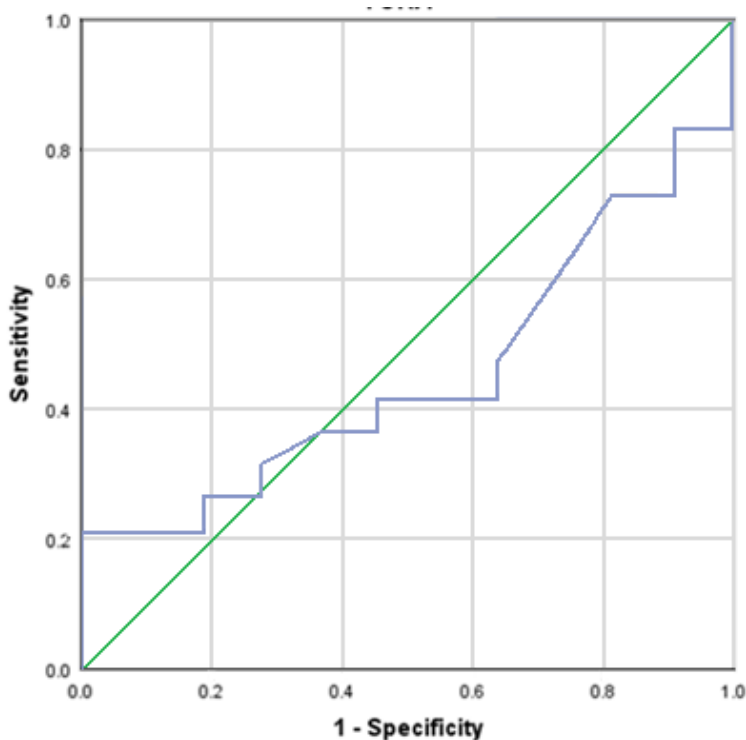


Fig. 29 ROC curve of EEOT response and fluid responsiveness

The resulting AUC ROC of 0.46 indicates a low predictive value of EEOT for response to fluid. Value of $p=0.70$ does not allow rejecting the null hypothesis that the AUC ROC is 0.5. A threshold value of ΔCO Vigileo could not be determined.

Analysis of the resulting ROC curves

The ROC curves based on experimental data in the study were interpreted by relevant indicators. First of all, value of “asymptotic significance” “p” was taken into account. A “p” value of less than 0.05 was deemed necessary to reject the null hypothesis, H_0 : “area under the curve does not differ from 0.5” (coin toss). Of the ROC curves obtained, only two showed $p < 0.05$ - the ROC curves for SVV and mini fluid challenge.

Second, area under the AUC ROC curve was considered. For SVV and mini fluid challenge this value showed a very good predictive value (0.91 and 0.90, respectively). For the remaining predictors, AUC ROC was significantly lower. AUC ROC for CVP_1 , $PAWP_1$, ΔCVP_2 , EEOT shows a low predictive value of the studied parameter/test. For these predictors no threshold value could be identified.

Determining the best predictor of fluid responsiveness in patients with IABP after cardiac surgery

Two methods with a very good predictive value according to the results obtained are SVV and mini fluid challenge. They have very similar area under the ROC curve - 0.91 (95% CI 0.81 - 1.00) and 0.90 (95% CI 0.78 - 1.00) respectively.

Binary outcomes of SVV and mini fluid challenge tests for the respective specified thresholds were compared by Student's t-test, which showed no statistically significant difference for the mean values. A comparison of "true positive" and "true negative" values showed the same. This justified the conclusion that there was no statistically significant difference between the two tests for predicting the response to fluid loading, despite the experimentally determined slightly higher AUC ROC value for SVV.

A comparison of the threshold values for SVV and mini fluid challenge showed equal specificity but a higher sensitivity for SVV (0.95 and 0.84, respectively). For this reason, it was determined that at a threshold of 8.5 for SVV and 7.7% for an increase in CO in mini fluid challenge, SVV has a better predictive value.

Discussion

The proposed study analyzed predictors of fluid responsiveness from all major groups in patients with IABP in the early period after cardiac surgery - static, dynamic parameters and functional tests. Our results show a low predictive value of static hemodynamic parameters and a high predictive value of dynamic parameters and functional tests. This data confirm results from studies cited in the literature review that were conducted in other patient groups and in a different clinical context. An exception is the data we obtained for EEOT, for which the predictive value for fluid responsiveness was measured as low, possibly due to methodological shortcomings of the experimental protocol.

When comparing results of the presented study with available literature, it should be kept in mind that the literature review, in addition to the lack of data on prediction of fluid responsiveness in patients with IABP, lacks studies in patients with such a severe condition as those included here. This applies in particular to studies in the field of cardiac surgery, which almost without exception were conducted in elective low-risk cases, mainly coronary surgery. Patients in these studies were not in a state of circulatory shock.

Discussion of materials and methods

Chosen experimental data collection period was determined with respect to the relatively low frequency of IABP implantation in the study center, which in previous periods was between 5 and 10%. On the other hand, the minimum set number of participants in the study – thirty people – was taken into account. It was inferred from the total annual average number of CPB operations at UMBAL St. Ekaterina that the required number of cases would be collected in approximately an year.

Inclusion criteria were carefully refined in order to comply with requirements for the maximum predictive value of the predictors of the fluid responsiveness and, in particular, to the most "fragile" of them - SVV. A review of key studies on the topic served to selected criteria outlined in the Materials and Methods section.

Closed chest condition dictates a number of methodological considerations - measurements cannot be performed before the chest is closed. Complying with the defined algorithm of measurements and interventions, estimated to last about half an hour, it was deemed not rational to perform it intraoperatively. This would mean a delay at the end of the operation, after fixing the sternum, and keeping the patient in theater for measurements. It was concluded that the time most suitable to perform the experimental part is after transfer to intensive care, in the initial hours when sedation is maintained.

Sedation was required to meet another important criterion for the validity of SVV – controlled mechanical ventilation with no spontaneous respiratory activity. For an optimal predictive value of SVV tidal volume needs to be the same in separate breaths, thus controlling for uniformity of microbolus blood volume to the left ventricle induced by lung inflation as a result of cardiopulmonary hemodynamic interactions. This is why SVV should not be used in spontaneously breathing patients, where tidal volume varies tremendously between respiratory cycles.

One more condition was considered critical for the validity of SVV - regular heart rhythm. In the presence of different time intervals between heart contractions, stroke volume is affected, and this does not allow predicting fluid responsiveness by dynamic hemodynamic parameters. The most common rhythm disturbance in the perioperative period in heart surgery is atrial fibrillation. Fortunately, even with chronic atrial fibrillation, after separation from CPB and restoring cardiac activity, a regular heart rhythm is very often achieved - sinus or supraventricular lead, which is maintained for several hours to days after the operation. This is why no patients with atrial fibrillation were noticed in our patient selection.

Another reason favoring patient recruitment is that post-CPB patients have temporary pacing electrodes implanted intraoperatively. This allows for irregular heart rhythm to be paced over with one- or two-chamber stimulation above the intrinsic rate. This was not actually required, as per protocol, cardiac surgery patients in the study center were paced at 90-100 beats per minute in the early postoperative period. Thus, regular heart rhythm was established in all examined patients.

A state of circulatory shock with criteria for tissue hypoperfusion, such as elevated serum lactate or low mixed venous saturation, low cardiac index, or low mean perfusion or systolic arterial pressure, was added to the inclusion criteria. The reason for this is that the state of circulatory shock serves as a trigger for administration of fluid bolus, rather than simply infusing boluses indiscriminately. However, this can be pointed out as a drawback of most studies on fluid responsiveness from the literature review – they used fluid loading in patients who had no indications for it.

During patient recruitment patients were excluded due to a veno-arterial extracorporeal membrane oxygenation (ECMO) system implanted intraoperatively. The heart is effectively bypassed by ECMO so it was decided to exclude such patients from the study. Four such patients were identified during data collection.

Another exclusion criterion - high-grade tricuspid regurgitation - was set in order to obtain a reliable value when measuring CO with pulmonary thermodilution. Due to the nature of the technique CO measured in high-grade tricuspid regurgitation is falsely elevated due to prolongation of the transit time of the thermal tracer injected for the measurement through the proximal lumen of the Swan-Ganz catheter. Some of the patients included in the study had high-grade tricuspid regurgitation preoperatively, but this was corrected during the operative intervention. Therefore, no high-grade tricuspid regurgitation was observed in the follow-up echocardiographic examination in the first hours after surgery in any of the included patients.

The used algorithm of measurements and interventions was carefully refined so that the conditions for a good predictive value of the studied predictors are met. Many of the authors of studies in the literature review performed experimental measurements in a similar way in order to utilize multiple predictors in one study group and compare predictive value [47, 84, 95, 126, 135, 140].

It was preferred to avoid testing different groups of patients who would differ in their characteristics. Instead, one group is used in which baseline measurements of hemodynamic variables are performed, undergo interventions in an order that does not interfere with the validity of the predictors being studied, and then measure the same variables as at baseline to determine the hemodynamic effect of fluid administration.

The algorithm of measurements and interventions generally looks like this:

1. Measurement of initial values of hemodynamic parameters - CVP, PAWP, SVV, CO.
2. Performing EEOT.
3. Performing mini fluid challenge test.
4. Performing a fluid challenge.
5. Measurement of final values of hemodynamic parameters.

Regarding the implementation of EEOT, some theoretical assumptions were taken into consideration. When an end-expiratory occlusion is applied to a mechanically ventilated patient, mean intrathoracic pressure decreases, causing an increase in venous return. Thus, a

bolus of blood volume is shifted towards the heart, and by measuring CO before and after the occlusion the heart response to volume can be assessed. The occlusion at the end of exhalation is short-lived for obvious reasons. In a critically ill patient, hypercarbia, hypoxemia, and an associated increase in pulmonary vascular tone may rapidly occur with the risk of hemodynamic decompensation.

The hemodynamic response to EEOT is also transient. In order to detect the expected increase in CO with EEOT, a methodology for rapid measurement of CO in real time is required. The thermodilution method used to evaluate the response to fluid takes a few minutes according to the described methodology. The expected duration of a change in CO after EEOT is several seconds. For this reason, it was decided that thermodilution cannot be relied upon in EEOT. It was estimated that this transient change in CO could be accounted for by CO measured in real time by the arterial pulse contour analysis method. The Vigileo system offers such an indicator, called for the purposes of the study the Vigileo CO. It should be noted that this is an uncalibrated CO value.

A mini-fluid challenge was performed with 2 ml/kg fluid infused over 5 minutes. Mini fluid challenge studies are characterized by significant heterogeneity in methodology. The specified volume was chosen in order to infuse a significant amount of fluid, moreover, 2 ml/kg is a relatively common dose in other studies in the field. The duration of the intervention is dictated by the need to monitor the hemodynamic response with the aim of patient safety and timely termination of the infusion in case of acute hemodynamic decompensation. When conducting the experimental part of the study, there were no such registered cases.

A fluid challenge was performed with 4 ml/kg fluid infused over 10 minutes. The same considerations as for a mini fluid challenge test were taken into account. The dose was determined based on a cumulative fluid bolus of 6 ml/kg, which was judged to be sufficient and comparable to other studies in the field. A major concern in conducting the experimental part was safe infusion of fluid and strict monitoring of hemodynamic parameters.

The use of fluid therapy in cardiac surgery patients should be extremely careful. This was the reason to monitor CVP and arterial pressure values in the experimental protocol in order to identify hemodynamic decompensation in a timely manner. If such occurred, there was readiness to stabilize hemodynamics by applying inotropic agents or a vasodilator at discretion.

Calculation of SVR and SVRI was dictated by the need to diagnose the type of circulatory disorder. Calculation of SVR and SVRI is needed as a criterion for severe pulmonary hypertension, which would jeopardise the predictive value of SVV.

Discussion of study population characteristics

The studied patient population represents nearly 4% of all patients operated on with CPB during the study period. This result is relevant to data from scientific literature. In one study, the rate of IABP implantation was 3.9% of patients undergoing coronary surgery [223].

Patients in the studied group present the highest risk group in cardiac surgery. The high values of ASA Class and Euroscore, the presence of regional wall motion abnormalities of the left ventricle, as well as the high class of CHF and CKD for the group serve to emphasize this fact. The need for IABP implantation further increases the operative risk and most likely explains the difference between ES-predicted and observed mortality, 22.8% and 50%, respectively. It needs to be emphasized that the study center normally has a lower mortality rate than predicted by ES.

Patients with large volume and complexity of surgical intervention predominate. In two people, the operation is single-valve, in five - two or three aortocoronary bypasses. The remaining 23 people underwent an operation with a very large volume and complexity. On the other hand, the total duration of CPB and crossclamp time were not correspondingly high taking into account the severe condition of the patients after surgery.

All patients studied had at least one sign of shock. The study population had high serum lactate values (mean value 4.2 mmol/L), with two thirds of the studied patients having a serum lactate value above 3 mmol/L. Elevated lactate values indicate that a significant proportion of patients experienced a period of tissue hypoperfusion during cardiac surgery, and most likely some of them were in a state of persistent tissue hypoperfusion in the early postoperative period.

The majority of the examined cases (73%) had normal systolic arterial and mean perfusion pressure values. Stabilization of the macrocirculation is due to the favorable influence of the implanted IABP. Even with stabilized hemodynamics, it is evident, however, that 60% of patients have a low measured cardiac index value.

One third of the cases have ScvO₂ values <50%, which also points to ongoing tissue hypoperfusion. It is noteworthy that arterial blood oxygenation is adequate. There is no presence of low values of partial pressure of oxygen in arterial blood, as well as a low PaO₂/FiO₂ ratio. This is relevant to the clinical evaluation of patients with low ScvO₂. One possible cause of low venous saturation is arterial hypoxemia, and in its absence, tissue hypoperfusion. Therefore, patients with low venous saturation are correctly judged to be in a state of circulatory shock.

In addition to the implanted IABP, the stabilized hemodynamic status of the patients also occurs at the cost of high values of catecholamine infusion. The mean catecholamine index for the study group was 16, which is an extremely high value, equating to a dopamine infusion average of 16 µg/kg/min.

When reviewing the values from the baseline set of hemodynamic measurements, it is striking that only one patient had a hyperdynamic circulation, with low SVRI and high CI, characteristic of distributive shock. Thirteen patients had a hemodynamic constellation typical of cardiogenic shock with low CO syndrome, with a high SVRI and significantly decreased CI < 2 L/min/m². In the remaining 16 people, CI was normal or slightly decreased, with a value between 2.2 and 2.0 L/min/m², and catecholamine infusion in high doses. Therefore, the hemodynamic profile is stabilized in slightly more than half of the patients, in

approximately 40% there is a persistent low-flow syndrome, and in only one person - a hyperdynamic hemodynamic constellation.

Severe pulmonary hypertension, defined as PAM ≥ 35 mmHg or PVR ≥ 6 Wood units ($480 \text{ dyn/s/cm}^{-5}$), respectively PVRI $\geq 960 \text{ dyn/s/cm}^{-5}/\text{m}^2$ was not reported in any patient of the study group. There were no patients with severe tricuspid regurgitation, as well as with extremely high CVP values. This finding may be related to the high predictive value of SVV obtained as a result of the study. In severe right ventricular dysfunction, SVV has a low predictive value for fluid responsiveness. SVV is an indicator that examines the reserve of preload of the left ventricle, but in right-sided heart failure it must be interpreted with particular care, because the left ventricle may actually respond to fluid, but after a volume bolus, the expected increase in CO may not be obtained due to failure of the right ventricle to respond to fluid. In such circumstances when predicting fluid responsiveness the number of false positive cases increases.

The size of the study group ($n=30$) is comparable to leading studies in the field. In 17 of 56 (30%) of the studies in the literature review in non-cardiac surgery patients study group was smaller than 30 people. The average group size in the cited studies was 39 people. In 18 of 33 (55%) of the studies in cardiac surgery patients cited in the literature review study group was smaller than 30 people. The average number of patients in the cited cardiac surgery studies was 36. Based on this it can be argued that the number of patients examined in the present study was small but sufficient.

Frequency of positive response to fluid

The positive response rate fluid was measured to be 63% of cases. This number is supported by data available in scientific studies and generally varies between 50% and 70%. [108, 109]. It can be concluded that in the absence of specialized equipment for hemodynamic monitoring, for instance in a low-resource environment, in the absence of trained personnel and other obstacles for prediction of fluid responsiveness, empiric administration of a volume bolus leads to a significant increase in CO in 63% of patients with IABP.

Predictive value of CVP, PAWP, ΔCVP

The predictive value of CVP was determined to be low with an AUC ROC of 0.65 (95% CI 0.44-0.85) and a high "p" value (0.19) for the ROC curve. This shows that the null hypothesis "the area under the curve is equal to 0.5" cannot be rejected. According to the obtained results, there is no statistically significant difference between the use of CVP and throwing of a coin as a predictor of fluid responsiveness. This result is in agreement with data obtained in other patient populations. Three large meta-analyses on the subject reported AUC ROC for CVP close to 0.5 (0.54, 0.56 and 0.56) [40, 32, 39]. All three meta-analyses included studies

with very large total number of patients. No statistically significant difference was found in baseline values of CVP in responders and non-responders.

When analyzing the fluid responsiveness in patients with marginal CVP values, it is evident that at values <4 mmHg (four patients) all patients were fluid responders. On the other hand, the only patient with CVP above 18 mmHg was a non-responder. These data serve to confirm an opinion given in the article by DeBacker et al. [50] that a positive fluid responsiveness can be expected at very low values of CVP and accordingly a negative response at very high values.

Mean CVP for the study group was 9 mmHg, with no statistically significant difference between responders and non-responders. This intermediate CVP value serves to confirm data from studies in the literature review, according to which intermediate CVP values prevail in intensive care patients, and they are non-informative with regard to fluid responsiveness.

Changes in baseline CVP after a fluid challenge appear to be of little value for the prediction of fluid responsiveness. The constructed ROC curve with area 0.48 (95% CI 0.27 - 0.68) has a "p" value of 0.83, therefore there is an 83% probability that the area under the curve is equal to 0.5. A similar result was essentially presented in a study cited in the literature review [12]. It is noteworthy that in the patients with a large increase in CVP after a fluid challenge (three with ΔCVP_2 over 6 mmHg), a positive response to fluid with more than 20% increase in cardiac output was observed. However, the opposite is not observed at low ΔCVP_2 .

Pulmonary artery wedge pressure, analogous to CVP, has a ROC curve with a high "p" value: 0.67. The measured area under the curve 0.45 is close to the 0.56 reported by Keller et al. in cardiac surgery patients [68]. At very low values of PAWP <3 mmHg (only in two subjects) only positive response to fluid was observed. There was no trend, however, for a low fluid responsiveness at high values above 18 mmHg.

PAWP as a static hemodynamic indicator and as a surrogate marker for left ventricular filling pressure has a low predictive value for fluid responsiveness, as proven in other patient populations, evidenced by data from the literature review.

Predictive value of EEOT

While the results for static hemodynamic parameters are corroborative of data from multiple clinical trials and meta-analyses in other patient populations, the EEOT data obtained in the current study differ from most publications in the field. The studies cited in the literature review had a mean AUC ROC (adjusted for the number of patients in each study) of 0.88. Of the 13 studies cited in the literature review, only three are negative. The AUC ROC of 0.46 with $p = 0.7$ measured in the current study is among the lowest that can be found in the scientific literature. This relatively low value can be explained by methodological pitfalls in the study measurements.

Studies on EEOT most commonly use measurement of CO based on calibrated pulse contour analysis or sonographically measured difference in left ventricular outflow tract blood flow velocity. Measurement of CO in the present study was done by uncalibrated arterial pulse contour analysis. Several scientific papers have described inaccurate CO values measured with uncalibrated pulse contour analysis in patients with alterations in vascular tone and high dose of catecholamine support [228, 229]. It is possible that the measured CO by the Vigileo monitor was not correct. Another drawback of the methodology is that the duration of the expiratory occlusion is 15 seconds, while the value update interval of the Vigileo system is 20 seconds [230, 231]. The updated value is an average for the elapsed interval and does not reflect the current value of the CO at the end of the EEOT. The CO value measured immediately after the end of EEOT reflects the CO from before the start of the test, as well as at its beginning, when the hemodynamic effect of expiratory occlusion is not evident. Given these limitations, perhaps a more appropriate method for measuring changes in CO within EEOT is left ventricular outflow tract velocity (LVOT VTI) sonography. CO is equal to the product of the area of the left ventricular outflow tract and the LVOT VTI. Thus, differences in left ventricular SV are measured in real time. In addition, there is scientific evidence that sonographic determination of LVOT VTI has insufficient sensitivity to accurately measure small differences in VTI resulting from EEOT. A study by Jozwiak et al. showed that transthoracic echocardiography could not reliably detect a change in LVOT VTI below 10% [232]. Alternatively, an esophageal Doppler system may be used. Other authors use echographic Doppler measurements of blood flow through large arterial vessels, which also makes it possible to read differences in real time. It is important to note that ultrasound methods have less accuracy compared to the thermodilution method.

Transpulmonary or pulmonary thermodilution with calibrated analysis of the arterial pulse loop can be pointed out as a good method for measuring CO during EEOT - which gives a good opportunity to accurately measure differences in CO in real time. Alternatively, a single injection of a thermal tracer could be used instead of five consecutive as in the current study protocol. This, in turn, can reduce the accuracy of the CO measurement, but allows for a quick measurement within 10-15 seconds.

In general, it can be stated that due to the considerable precision and timing of CO measurement required to reliably perform EEOT, it is a relatively difficult test in clinical routine.

Predictive value of SVV

The measured predictive value of SVV is high. An area under the ROC curve of 0.91 (95% CI 0.81 - 1.00) with $p < 0.05$ is a value that is among the high values measured in other patient populations.

In comparison, Zhang et al. reported an AUC ROC of 0.84 [89]. An AUC ROC of 0.90 was reported by Sanchez et al. in their systematic review and meta-analysis of ICU patients, although their patients were ventilated with low tidal volumes [90]. It is debatable whether a

higher predictive value of SVV should be expected in patients ventilated with conventional tidal volume. In the studied patients after cardiac surgery, due to their inherent hemodynamic specificities and problems, there are factors contributing to a lower predictive value of the dynamic hemodynamic parameters compared to patients in the general population. These are high catecholamine index, shock state, low contractility.

Mean ROC AUC was calculated for the non-cardiac surgery studies included in the literature review, adjusted for the number of patients in each study. The resulting AUC ROC value was 0.78. Upon careful analysis, the studies by Angappan et al. and Huang et al., in which patients were ventilated with a low tidal volume were excluded from analysis. Recalculation of AUC revealed ROC 0.85 for non-cardiac surgery patients.

Studies in cardiac surgery have resulted in AUC ROC between 0.76 [12] and 0.97 [109] - median AUC ROC = 0.87.

Mean ROC AUC was calculated for the studies on cardiac surgery patients included in the literature review, adjusted for the number of patients in each study. The result was an area under the curve of 0.90. This value is very close to the result of the present study. This shows that when an IABP is placed on stand-by for one minute, the predictive value of SVV is comparable to that in patients undergoing cardiac surgery in whom no IABP is implanted.

The CO threshold used to distinguish between responders and non-responders is different between studies. In some studies it is 10%, in others 15%. No clear relationship could be demonstrated between the area under the curve for AUC determined by the authors and the threshold value of CO used.

For the purposes of the comparative analysis, a ROC curve was also constructed for the predictive value of SVV₁ for an increase in CO by at least 15% after a fluid challenge with 6 ml/kg of fluid. The resulting AUC ROC was 0.88 (95% CI 0.74 - 1.00) and $p < 0.05$. The best cut-off value of SVV with the highest Youden index was determined to be 11% (sensitivity 0.87, specificity 0.80). In spite of this we decided to use CO threshold of 10%. The reason for this is the clinical significance of such an increase in CO. For comparison, this is roughly the coronary blood flow required for two hearts.

Our results show a best threshold value of SVV 8.5% with a sensitivity of 0.95 and a specificity of 0.82. This means that SVV identifies 95% of patients with an increase in CO of at least 10% and 82% of patients who do not have an increase in CO of at least 10%.

It should be noted that SVV is an indicator that is misused extremely often in clinical practice. There is a common misunderstanding that a high SVV is a pathological manifestation of hypovolemia and this is very often interpreted as a need for the administration of fluid. This practice is unwarranted and leads to excessive fluid load, as well as criticism towards the use of SVV to predict fluid responsiveness.

It is more reasonable to say that SVV above the threshold value for a positive fluid responsiveness reflects a normovolemic state, as in healthy volunteers. This means that the heart has a reserve of preload and would respond with an increase of CO after a fluid bolus. An above-threshold value of SVV does not in any case give reason to apply fluid by itself. The

judgment of whether a fluid bolus needs to be infused is dictated by additional considerations such as adequacy of tissue oxygen delivery and evidence of large circulatory volume loss for instance. However, extremely high values of SVV on the magnitude of 20% and more point to the presence of hypovolemia.

On the other hand, sub-threshold values of SVV may be a good reason to refrain from fluid loading. Low values of SVV are associated with a position of the heart in the flat part of the Frank-Starling curve, therefore fluid unresponsiveness. Such circulatory state is pathological and points to the presence of hypervolemia. The heart cannot increase CO in response to volume loading. There is a high likelihood of an increase in the filling pressures of the heart and therefore high likelihood of pulmonary congestion, splanchnic edema, etc. – all negative effects of volume overload.

SVV is a very good hemodynamic index, easily applicable in daily practice. Of course, a good understanding of cardiovascular physiology is required as a prerequisite. In this way, an incorrect interpretation of the readings of the SVV, as well as of the other dynamic hemodynamic indicators, is avoided.

Predictive value of mini fluid challenge test

Mini fluid challenge test demonstrated high predictive value for fluid responsiveness with AUC ROC 0.90 (95% CI 0.78 - 1.00) and $p < 0.05$.

The area under the ROC curve for the mini fluid challenge test ranges between 0.83 and 0.97 according to different authors [152, 154], median AUC ROC = 0.90.

Mean AUC ROC for mini fluid challenge studies in the general population, adjusted for the number of patients in each study, was calculated. The result showed an AUC ROC of 0.93. This value is comparable to that obtained in the present study 0.90. The fact that it is slightly higher can be explained by the higher rate of infusion of the mini-fluid bolus, usually 1-2 minutes.

Of note, only two studies have addressed mini fluid challenge as a predictor of fluid responsiveness in cardiac surgical patients [157, 158]. Average area under the ROC curve, adjusted for the number of patients in the studies, was 0.87, which is comparable to the value obtained in the present study of 0.90.

Given the size of the study groups in the two studies mentioned ($n=21$ in both), the study presented in the dissertation is the largest in the field of cardiac surgery involving mini fluid challenge.

The determined best threshold value for CO increase after mini fluid challenge of 7.7% is close to that obtained by Guinot et al. 7% [150] and is the highest of all studies included in the literature review. In the majority of scientific data, the threshold for increasing CO is 5-6%. This high value (7.7%) can be explained by the severe condition of the studied patients,

high frequency of left ventricular dysfunction preoperatively and myocardial injury caused during cardiac surgery.

A mini-fluid challenge threshold value of 7.7% has an estimated sensitivity of 0.84 and specificity of 0.82. Therefore, an increase in CO of at least 7.7% after a mini fluid challenge predicted a positive fluid responsiveness in 84% of patients. In patients with an increase in CO below 7.7%, a fluid unresponsiveness is predicted in 82% of cases.

One limitation of the present study is related to the way in which the predictive value of the mini fluid challenge was determined. According to the algorithm for measurements and interventions, it was determined to perform a baseline measurement of CO, a mini fluid challenge with 2 ml/kg fluid bolus, a second measurement of CO, a fluid challenge with 4 ml/kg and a final measurement of CO. The calculated difference between the first and second and between the first and third CO measurements was used to define responders. The described methodology allows for statistical inaccuracy. A study by Enevoldsen revealed that the results thus obtained may not be reliable [233]. The authors recommend that in addition to one CO value at the end of the mini fluid challenge, one more should be measured before the start of the fluid challenge. Then, the difference between the first and second CO values on the mini fluid challenge response and the difference between the third and fourth CO values on the fluid challenge response should be used. Otherwise, the predictive value of a mini fluid challenge test is falsely elevated. This methodological flaw of the study was identified after the implementation of the experimental protocol, after the necessary data had already been collected from the participants, and may be related to the high determined predictive value of the mini fluid challenge.

Determining the best predictor of fluid responsiveness in patients with IABP after cardiac surgery

The two methods with a very good predictive value according to the results obtained are SVV and mini fluid challenge test. The predictive value of the two tests was estimated to be very close, slightly better for SVV, mostly in terms of sensitivity of the method.

SVV is more easily applicable in clinical practice because cardiac output monitoring is not required. Only invasive blood pressure monitoring is necessary.

However, it should be emphasized that mini-fluid challenge is applicable to a wider range of patients, due to the possibility of its use in patients with rhythm disorders, with an open chest, with the presence of spontaneous respiratory efforts, spontaneous breathing, etc. Therefore, in the early postoperative period, in a mechanically ventilated, deeply sedated patient with a correct rhythm, the SVV may be more accurate for predicting fluid responsiveness, while mini fluid challenge is more reliable in patients with IABP, in whom the strict criteria for SVV are not fulfilled.

Advantages of the survey

The proposed study has certain advantages. To our knowledge, this is the first study of fluid responsiveness in patients with IABP.

As far as we know, this is the first study in Bulgaria focused on the predictors of fluid responsiveness SVV and mini volumetric test in patients with IABP.

The methodology of the study (and in particular the algorithm for measurements and interventions) was refined in order to adequately measure the predictive value of the studied parameters.

Another strength of the study is that CO was measured by pulmonary thermodilution, the gold standard for measurement.

Limitations of the study

The present study has a number of limitations. First of all, the size of the study group (n=30), although it is comparable to a many other studies on "fluid responsiveness" in the scientific literature, is small and is a prerequisite for statistical error. It is mainly due to the low incidence of IABP implantation in the study center (4%).

This is a single-center study and it is possible that factors influencing clinical practice at the site of conduct may have influenced the results.

The present study did not cover some validated methods for predicting fluid responsiveness such as PPV and PLR test.

Compromise of EEOT may be related to an inability to quickly and accurately measure CO in real time.

Due to pitfalls of methodology for calculating the predictive value of a mini fluid challenge test, the value obtained may be falsely elevated [233].

Conclusion

Main conclusions

Based on the obtained results and data analysis the following conclusions were drawn:

1. The frequency of positive response to fluid in patients with IABP early after cardiac surgery is 63%.
2. Static hemodynamic parameters CVP, PAWP and changes in CVP have a low predictive value for fluid responsiveness in patients with IABP early after cardiac surgery.
3. The dynamic index SVV has a high predictive value for fluid responsiveness in patients with IABP early after cardiac surgery. Best threshold value for differentiating responders and non-responders is 8.5% (sensitivity: 95%, specificity: 82%)
4. Mini fluid challenge has a high predictive value for fluid responsiveness in patients with IABP early after cardiac surgery. Best threshold value for differentiating responders and non-responders was a 7.7% increase in MCR (sensitivity: 84%, specificity: 82%)
5. EEOT in the present study has a low predictive value for fluid responsiveness, most likely due to methodological shortcomings of the used protocol. Accurate real-time monitoring of CO in EEOT is very difficult in clinical practice.
6. The best predictor of fluid responsiveness in patients with IABP early after cardiac surgery is SVV with a threshold value of 8.5%.

Contributions

Original contributions

1. Frequency of positive response to fluid in patients with IABP is described for the first time.
2. Predictive value of hemodynamic parameters and tests in patients with IABP regarding the response to fluid is assessed for the first time.
3. A dynamic hemodynamic parameter is used to predict fluid responsiveness in patients with IABP after placing the pump on standby for 1 minute for the first time.
4. An algorithm for fluid responsiveness evaluation in patients with IABP in circulatory shock is presented.
5. A fluid responsiveness study on IABP patients is being carried out using SVV and a mini fluid challenge for the first time in Bulgaria.

Cinfirmation contributions

1. Low predictive value of static hemodynamic indices (CVP, Δ CVP, PAWP) proven in other patient populations is confirmed.
2. High predictive value of the dynamic hemodynamic index of SVV described in other patient populations is confirmed.
3. High predictive value of the mini fluid challenge described in other patient populations is confirmed.

Recommendations

Based on studied data from the scientific literature and the results of the present study following recommendations for clinical practice are stated:

1. Use of "trigger" to initiate a fluid bolus (elevated lactate, hypotension, low venous saturation, etc.)
2. Careful assessment of the patient's tolerance to infusions and the benefit/risk ratio of a fluid bolus in the clinical context, not only based on prediction of fluid responsiveness (assessing the risk of deterioration of respiratory function, occurrence of hemodilution etc.) [243].
3. Routine prediction of fluid responsiveness in patients with implanted IABP *
 - a. Use of a dynamic hemodynamic index to predict fluid responsiveness when appropriate.
 - b. Use of mini fluid challenge in patients in whom the conditions for dynamic hemodynamic parameters are not met.

* except in emergency situations with an obvious need for a massive infusion of fluid (severe hemorrhage, initial phase of septic shock, severe dehydration, etc.)

Recommendations for future research:

It is evident from the literature review that studies in the field of prediction of fluid responsiveness have relatively small study groups and have considerable heterogeneity among them. This makes it difficult to draw definitive conclusions even in the existing meta-analyses. There is a need for large-scale, multicenter studies of fluid responsiveness in patients subject to surgery and intensive care. International recommendations need to be produced to standardize the approach for prediction of fluid responsiveness.

There is an urgent need for studies predicting fluid responsiveness in different contexts, for example timing of termination of renal replacement therapy in patients with hypervolemia.

There is a certain effort to study the patient's tolerance to fluid (fluid tolerance) as a natural extension of the field of fluid responsiveness. In this scientific field data is very recent and really scarce until now.

Another direction for future studies could be the issue of introducing new methods for prediction of fluid responsiveness with better predictive value and easier to apply in daily practice than those established so far. An important development in the field would be the invention of fluid responsiveness prediction devices that are more easily accessible and cost effective than the current ones. What needs to be identified are surrogate measures of cardiac output that can be used to accurately monitor the response to infusions without the need for specialized, highly invasive equipment.

Algorithm for fluid responsiveness prediction in patients with IABP

Based on the obtained results an algorithm was prepared regarding prediction of fluid responsiveness in patients with IABP after cardiac surgery.

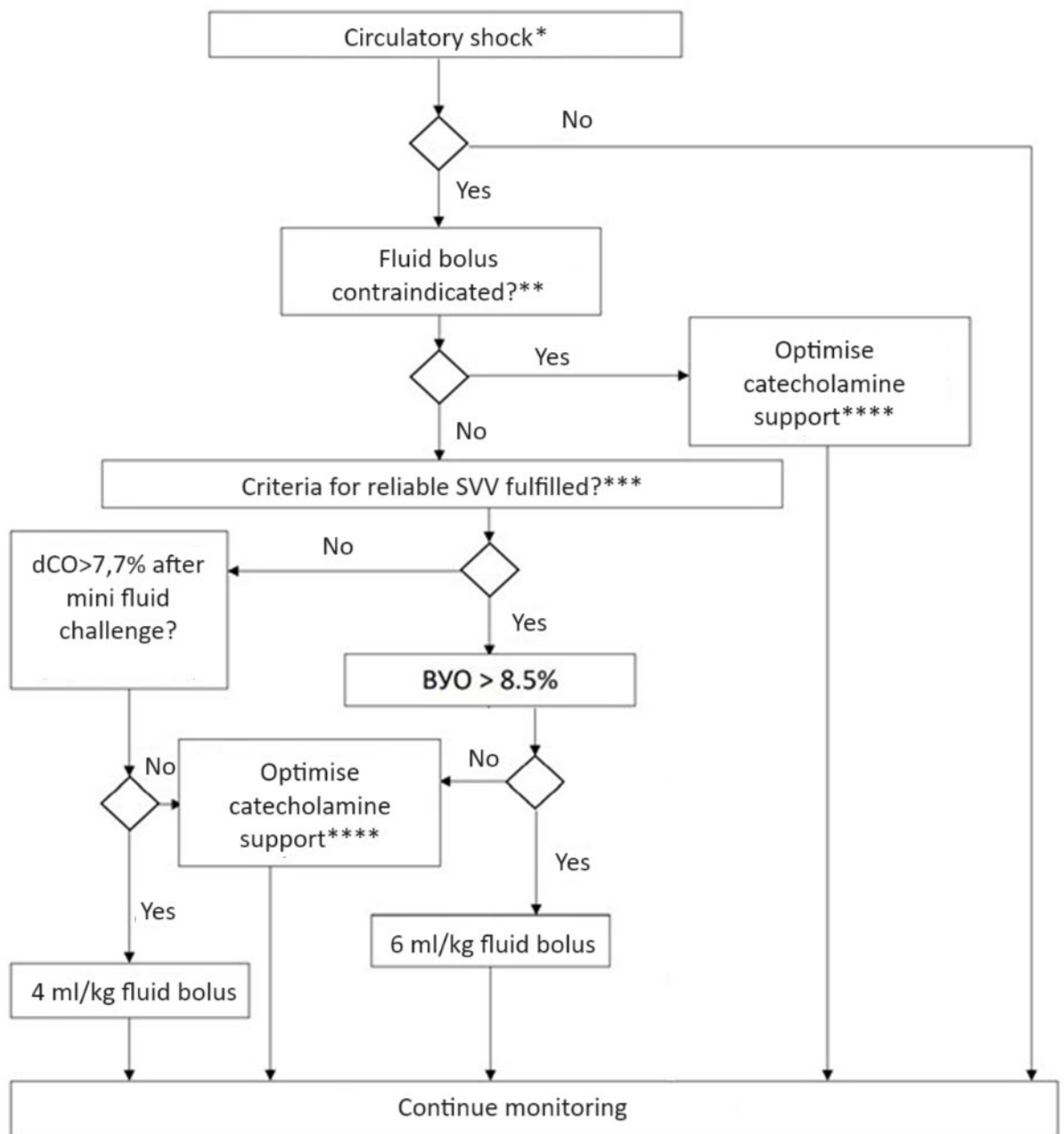


Fig. 30 Algorithm for fluid responsiveness prediction in patients with IABP early after cardiac surgery

- *Presence of at least one of the listed
- SBP < 90 mmHg

- MPP < 60 mmHg
- $S_{cv}O_2$ < 50%
- Lact > 3 mmol/L
- CI < 2.2 L/min/m²

****Contraindications for fluid bolus**

- Critically low oxygenation level (PaO_2 < 60 mmHg)
- Very high systolic blood pressure or systolic blood pressure (> 18 mmHg)
- Others based on clinical benefit/risk judgment (significantly increased cumulative fluid balance, hemodilution, postoperative paralytic ileus, etc.)

*****Criteria for accuracy of SVV**

- controlled mechanical ventilation
- lack of spontaneous breathing efforts
- Tidal volume 8 ml/kg
- correct heart rhythm
- closed chest

******** And unloading of the circulation at discretion (diuretics, RRT, vasodilators)

List of scientific publications related to the dissertation work

1. Enev R., Abedinov F., Bakalova N., Atanasova M., Chilingirova N., and Krastev P., 2023, "Stroke Volume Variation is a Good Predictor of Fluid Responsiveness in Cardiac Surgery Patients with Implanted Intra-aortic Balloon Pump", CR Acad. Bulgaria Sci. , 76:4, 612–621. - impact factor 0.329
2. Enev R.; Mini Fluid Challenge for Prediction of Fluid Responsiveness in Patients with Intra-Aortic Balloon Pump after Cardiac Surgery; 2021; Sys Rev Pharm, 12:11: 611-614, E-ISSN 0976-2779 P-ISSN 0975-8453
3. Enev E., Krastev P., Abedinov F.; Prediction of fluid responsiveness: a review, Biotechnology & Biotechnological equipment; 2021; 35:1, 1147–1155 - impact factor 1.762