

ASSESSMENT OF RIGHT VENTRICULAR HEART FUNCTION IN POLYTRAUMATIZED PATIENTS WITH PULMONARY CONTUSIONS WITH AND WITHOUT NEED FOR MECHANICAL VENTILATION: A MULTICENTER STUDY PROTOCOL

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Abstract

Introduction: Pulmonary contusions are the most common form of chest trauma (25-80%) with a mortality rate of 10-20% in severely injured patients, while ARDS has been observed in 78% of polytraumatized patients with pulmonary contusions. Right ventricular function has already been evaluated in patients with acute respiratory failure and ARDS, with studies demonstrating a clear association between lung injury and the development of right heart dysfunction.

Study Objective: The aim of this study is to examine the relationship of right ventricular dysfunction and the usage of mechanical ventilation in patients with pulmonary contusions.

Material and Methods: In this prospective cohort study, right ventricular function will be evaluated by echocardiography at 4 examination points. Measurements will include RV diameters, tricuspid regurgitation velocity, TAPSE, RV Fractional Area Change, RV diastolic function and Inferior Vena Cava collapsibility or distensibility. Pulmonary circulation pressures will be calculated in both groups using established equations based on echocardiography-derived measurements. All patients included in the study must be polytraumatized with radiologically confirmed existence of pulmonary contusions and will be divided into two groups depending on the need for mechanical ventilation.

Rationale: Beyond the primary objective of the study, this detailed explanation of the protocol, originally developed as part of a completed and defended PhD thesis, is intended facilitate multicenter collaboration and further research into the effects of mechanical ventilation on right ventricular function.

Keywords: Echocardiography; Lung ultrasound; Mechanical ventilation; Pulmonary contusions; POCUS; Right ventricular dysfunction.

Introduction

Pulmonary contusions are defined as destruction of the lung parenchyma with the occurrence of alveolar hemorrhage as a result of blunt thoracic trauma without pleural laceration and are present in 17-75% of blunt thoracic trauma (1). The presence of pulmonary contusion in polytraumatized patients is a serious predictor of mortality in up to 10-25% (1). According to Hosseini M. and colleagues, lung contusions are the most common form of chest trauma (25-80%) with a high mortality rate of 10-20% in severely injured patients (2). Following trauma involving the transfer of kinetic energy on the lung, the secondary lung injury occurs, which is considered to be immunologically mediated due to activation of defensive immune mechanisms. The systemic inflammatory response is marked by the secretion of IL-6, which is a mediator of lung injury after the occurrence of trauma. Kurt A. et al. found that IL-6 levels are significantly higher in patients with lung contusions compared to the control group (3). The occurrence of lung contusions disrupts gas exchange at the level of the alveolo-capillary membrane, an increase in pulmonary vascular resistance, and a decrease in lung compliance in the first 24 hours after injury (4). Lung contusions are considered as an independent risk factor for the occurrence of Acute Lung Injury - ALI and Acute Respiratory Distress Syndrome – ARDS. ARDS has been observed in 17% of patients with an isolated lung contusion and in 78% of patients with lung contusion accompanied by polytrauma. (5). Impaired gas exchange resulting from lung injury leads to hypoxemia, which triggers defense mechanisms such as hypoxic pulmonary vasoconstriction, thereby increasing pulmonary circulation resistance. In addition, an immunologically mediated increase in vascular permeability promote transmigration of fluid and leukocytes into the interstitium, and subsequently into the alveoli, contributing to an increase in right ventricular afterload. In an experimental animal study, where oxygen delivery was reduced with a fall in FiO_2 from 0.3 to 0.15, a 100% increase in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), confirmed that hypoxemia can lead to an increase in right ventricular (RV) afterload (6). Hypoxic vasoconstriction and the need for mechanical ventilation with high PEEP can compromise RV function in individuals with acute respiratory failure, where excessive alveolar distension can occur due to the application of high tidal volumes, which can lead to an increase in RV afterload (7). An increase in RV afterload due to an increase in pulmonary vascular resistance (PVR) as a form of right ventricular pressure load leads to a series of adaptive or maladaptive structural and functional changes in the right ventricle, which is why mechanical ventilation and lung injury are thought to play an important role in the development of right ventricular dysfunction (RVD) (8).

Right Ventricular Dysfunction: Definition and Clinical Significance in Critically Ill Patients

Right ventricular dysfunction refers to impaired RV systolic and/or diastolic performance resulting from the inability of the right ventricle to adequately adapt to changes in preload, afterload, or myocardial contractility. Progression to right ventricular failure occurs when the RV is unable to maintain sufficient pulmonary blood flow and adequate left ventricular filling (11). A high mortality rate of 32-61% was found in patients diagnosed with right ventricular failure. An acute increase in RV afterload is considered the most frequently recorded reason for RVD development, and the transition from RVD to RV failure depends on the RV ability to adapt to the increased RV afterload (11). RVD is the result of disturbed RV mechanics that cannot deliver blood in the pulmonary circulation against the increased RV afterload (12). When, for any reason, there is an increase in pressure in the pulmonary circulation, a pressure load occurs on the right ventricle, which activates the adaptive mechanisms that aim to ensure an adequate stroke volume. However, when the pressure load exceeds the adaptive

capacities of the right ventricle, right heart dysfunction occurs. When the pressures in the pulmonary circulation are elevated, myocardial cell growth is activated in RV, initiating the process of hypertrophy of the free wall of the right ventricle, which, according to Laplace's law, should resist the right ventricular afterload and provide an adequate stroke volume (12). When this compensatory mechanism is worn out and the right ventricle is not able to achieve an adequate stroke volume against the pressure in the pulmonary circulation, the next adaptive mechanism occurs, i.e., the right ventricular dilatation and thinning of the septal wall, leading to echocardiographic signs of right heart dysfunction with elevated dimensions. Because of its design and function to generate stroke volume against a pulmonary circulation with low pressures and high compliance, the right ventricle tolerates volume than pressure load more easily. If right ventricular afterload increases gradually over an extensive period, the ventricle can hypertrophy, remodel and adapt to the increased pressure load, and it will successfully tolerate higher values of sPAP (systolic pulmonary artery pressure). However, an acute increase in the right ventricular afterload without previous right ventricular hypertrophy will prevent the right ventricle from generating sPAP higher than 50-60mmHg, leading to the development of signs of RVD (13,14). According to Chen et al., as many as 43% of examined 1879 critically ill patients had RV dysfunction (15); while Grignola JC and Domingo E consider that RVD occurs in as many as 30-56% of patients with ARDS even when protective modes of mechanical ventilation are used, and the occurrence of RVD is directly influenced by the severity of lung injury and the ventilatory strategy (16). The $\text{PaO}_2/\text{FiO}_2$ ratio below 150, $\text{PaCO}_2 > 48\text{mmHg}$ (6.4 kPa), and driving pressure greater than 18 in critically ill patients, are identified as risk factors for the occurrence of RVD (16). Lanspa et al., reported that the development of RVD is an indicator of the severity of lung disease and is associated with increased 28-day mortality and lower values for the $\text{PaO}_2/\text{FiO}_2$ ratio in critically ill patients, but not with the need for mechanical ventilation (17). RVD in this research will be defined as the existence of abnormal values for at least one of the following markers for the assessment of right ventricular function: for TAPSE values less than 17mm, RV FAC < 35% and/or RV/LV ratio > 1.

Rationale for the Use of Ultrasonography in the Diagnosis and Monitoring of Pulmonary Contusions

Given the fact that chest x-ray can underestimate the severity of blunt thoracic trauma and the presence of pulmonary contusions, computed tomography is considered the gold diagnostic standard. Computed tomography, in addition to exposure to high doses of X-rays, carries the risk of complications that may occur during the transport of critically ill patients, especially those needing mechanical ventilation. Therefore, ultrasonography can be an adequate alternative for diagnosing lung contusions and detecting their extent (18). In their study, Mohamed SS. et al. examined the accuracy of ultrasound in detecting lung contusions and assessing their extent compared to CT, as well as the predictive power of the ultrasonographic findings for the development of ARDS. LUS study, performed within 72 hours from injury can accurately indicate a high risk for the development of ARDS in patients with lung contusions. Also, the LUS findings on the extent of pulmonary contusions correlated with the findings of the performed CT examinations (18), which points to the fact that LUS can be used for the diagnosis and monitoring of the evolution of pulmonary contusions as well as the assessment of their extent. In a study, Jahanshir A. and colleagues examined the LUS accuracy, and found that lung contusions can be diagnosed with PoCUS with a sensitivity of 58, 1% and a specificity of 100% with a positive predictive value of 100% and a negative predictive value of 86.3% (19). According to Zhao Z. et al., LUS performed early in the course of hospitalization, after the first 24 hours, is a more reliable diagnostic indicator of ALI than subsequent follow-up examinations (20). LUS not only has

a positive correlation with the level of EVLW and $\text{PaO}_2/\text{FiO}_2$, but it is also considered a diagnostic marker and predictor of mortality in patients with ARDS (20). Another study by D. Huang et al., which included 55 patients treated in ICU with suspected ARDS, showed that LUS findings on the first, second and third days of hospitalization correlated with CT findings in patients with ARDS, but also in patients where ARDS was not present (21). The study by Lei Li et al. found that LUS findings on the first day positively correlate with the height of SOFA Score and APACHE II, while there is a negative correlation with $\text{PaO}_2/\text{FiO}_2$ (22). Therefore, as the lung injury progresses over the following days, the LUS score increase while the $\text{PaO}_2/\text{FiO}_2$ ratio decreases. This suggests that LUS with a 12-field view and a 0-36-point score represents a semiquantitative tool in lung injury monitoring. Baseline LUS Score is an independent risk factor for 28-day mortality in patients with ALI, as well as SOFA score, APACHE II score, and $\text{PaO}_2/\text{FiO}_2$ (22). LUS Score, APACHE II, SOFA, and $\text{PaO}_2/\text{FiO}_2$ combined together can predict the prognosis of patients with ALI with 88.9% sensitivity and 95.5% specificity (22). LUS as a diagnostic method for the etiology of respiratory failure is superior to radiography and clinical examination (23-25). Findings obtained from LUS can be compared with those obtained from computed tomography (26, 27). Costamagna Andrea et al compared CT and LUS results at admissions and one week later to determine whether LUS can adequately monitor the developmental dynamics of lung changes. They concluded that LUS results correlate with CT results at admission, and one week later, suggesting that LUS can be used to monitor the evolution of lung changes in patients with ARDS (28). Stengel D. et al performed a meta-analysis that included a total of 34 studies with 8635 subjects on the use of POCUS in the diagnosis of blunt thoracoabdominal trauma and found that this method can diagnose chest injuries with a sensitivity and specificity of 96%. and 99% respectively (29). The European Society of Intensive Care Medicine (ESICM) issued a strong recommendation regarding the use of ultrasound in ICU, identifying the detection of B-lines as indicators of interstitial syndrome. Therefore, consolidation as a form of lung aeration disorders should be considered as a basic competency for every intensivist (30), justifying the use of LUS in this study.

Rationale for the Use of Echocardiography in Assessing Right Ventricular Function in Critically Ill Patients with Lung Injury

The ESICM strongly recommends the use of echocardiography as a method for evaluating right ventricular function and diagnosing right ventricular failure, by measuring right ventricular diameter, RV/LV ratio, right ventricular free wall thickness, and right ventricular chamber end-diastolic diameter. These should be basic competencies of the intensivist, necessary for the diagnosis of right heart failure in critically ill patients (30). According to Riishede M, POCUS leads to rapid rejection of presumptive diagnoses in the first 4 hours of hospitalization, and increases the chances of receiving adequate treatment in the first 4 hours by 13.5% (31). C. Lazzeri and colleagues also favor the use of combined ultrasound of the heart and lungs. This conclusions corresponds with the findings of their study in which 47 patients with ARDS due to COVID-19 were examined, where in addition to LUS, the patients were examined echocardiographically with special reference to the right ventricular function with increased right ventricular afterload. RV/LV ratio, right ventricular end-diastolic diameters, right ventricular free wall thickness, tricuspid annular systolic excursion (TAPSE), and systolic pulmonary arterial pressure (sPAP) were monitored. It was determined that non-survivors had higher LUS values at admission, increased RV/LV ratio, and higher sPAP values compared to survivors. In addition, this study demonstrated a correlation between the value of LUS score and the measured sPAP, supporting the routine combined assessment of cardiac and pulmonary function in critically

ill patients. The development of ARDS and pulmonary deaeration increase the pulmonary vascular resistance, which, together with the mechanical ventilation, increases RV afterload and precipitates RVD (32). Vignon P et al. also recommend the combined use of lung ultrasound and echocardiography in critically ill patients with ARDS, as increased pulmonary arterial pressure from lung injury and the need for mechanical ventilation can compromise RV function (33). The risk of developing acute right heart failure in patients with ARDS is highest in the first three days after being placed on mechanical ventilation (34). The first echocardiographic examination in patients with ARDS on mechanical ventilation should be performed within the first 24 hours after admission (33). The rationale behind the use of echocardiography as a method in this study and in daily clinical practice is confirmed by the results of a study performed on 700 patients with ARDS, who were divided into two groups: patients who had no signs of right heart disease and were hemodynamically stable; and hemodynamically unstable patients who did not necessarily have echocardiographic signs of right heart disease. Echocardiography was repeated at least once a day in the second group of patients, but also in patients who will developed hemodynamic instability and/or hypoxia de novo (35).

Study Objective

According to C. Chen et al., up to 43% of the 1879 examined critically ill patients had ventricular dysfunction (36). So far, right ventricular function has been evaluated in patients with acute respiratory failure and ARDS, and a clear relationship between lung injury or ARDS and the development of right heart dysfunction has been established (7,37,38,39). RVD has also been detected in patients with sepsis (8,40,41). The literature has analyzed the association between right heart failure and acute respiratory failure in general, without considering blunt traumatic lung injury as a separate entity. Traumatic chest injury occurs in almost 60% of all polytrauma patients and has a high mortality rate of 20-25% (42). Lung contusions occur in 17-75% of blunt chest injury cases followed by rib fracture (43). The rationale for evaluating right ventricular function in polytraumatized patients with pulmonary contusions arises from the fact that lung injury and hypoxemia lead to pulmonary hypoxic vasoconstriction, which, together with the use of mechanical ventilation, can have deleterious effects on the RV. The association between the occurrence of right ventricular dysfunction in polytraumatized patients with pulmonary contusions and the need for mechanical ventilation could influence the therapeutic approach and the course of treatment in regards to timely diagnosis and treatment of RVD by applying protective modes of ventilation. Therefore, it is crucial to evaluate the right ventricular function in patients with pulmonary contusions because the lung injury by itself, and often the therapeutic strategies involving mechanical ventilation, can generate greater afterload due to the increase in pulmonary circulation pressures. Pressure overload caused by the above-mentioned causes can lead to right ventricular adaptation or maladaptation resulting in altered right ventricular function. Due to its structural characteristics, the right ventricle cannot maintain optimal function when faced with increased afterload, which in 48 hours will change the structural and functional echocardiographic parameters (44), justifying the evaluation of right ventricular function in patients with a traumatic model of lung injury. Hence, we hypothesize that the use of mechanical ventilation in polytraumatized patients with pulmonary contusions is associated with the development of right ventricular dysfunction. In addition to the primary hypothesis, this study has several other objectives, which are discussed below:

- To determine the association between the usage of mechanical ventilation and the development of right ventricular dysfunction

- To determine the overall prevalence of RVD in polytraumatized patients with pulmonary contusions, and the prevalence of RVD in patients who are treated with mechanical ventilation versus those who are not treated with mechanical ventilation
- To determine the time frame of myocardial vulnerability when the risk of developing RVD is the highest in both groups.
- To determine the length of hospital stay (Length of stay-LOS), the length of stay in the intensive care unit (ICU Length of stay - ICU LOS) in both studied groups
- To determine the number of days spent without the need for mechanical ventilation (VFD– Ventilator free days) in the group of patients treated with mechanical ventilation who will develop RVD, compared to those who will not develop RVD
- To determine mortality in both study groups as well as in patients who will develop RVD versus those who will not develop RVD
- To analyze the parameters of mechanical ventilation in patients who will develop RVD versus those who will not develop RVD and thereby reveal the existence of a possible association between the development of RVD and any of the analyzed parameters
- To evaluate the correlation of measured LUS and the sPAP levels
- To evaluate echocardiographically estimated pulmonary arterial pressures in both groups and compare them between patients who develop RVD and those who do not
- To evaluate the association of LUS, TAPSE, pulmonary pressures with development of RVD, mortality and LOS
- To evaluate the utility of combined bedside lung and cardiac ultrasonography (POCUS) and its potential integration into routine clinical practice

As this protocol was originally developed as part of a completed PhD thesis, its publication is intended to encourage further multicenter research involving institutions across the country and the wider region. The study has already been conducted using this protocol, with 81 patients enrolled over a two-year period. Since the study's specific inclusion and exclusion criteria limit the number of eligible patients, we believe that involving other research centers may significantly contribute in recruiting another 100 patients in a timeframe of another 2 years. Multicentric involvement is expected to include a significant number of patients so that its statistical significance may increase. Apart from the call for multicentric involvement in this study, researchers are encouraged to use this protocol when evaluating the effect of mechanical ventilation over the right ventricle in critically ill patients, even if they experience different kind of underlying condition demanding mechanical ventilation, other than pulmonary contusions.

Materials and Methods

Study Design

This study is prospective, cohort, and observational in design. Written informed consent for participation in the original single-center study was obtained from the patients or their legally authorized representatives, as applicable. The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje and the Ethics Commission at the Department of Anesthesiology, Reanimation and Intensive Care, as relevant institutional Ethics Committees. Any future multicenter implementation of this protocol should be conducted following approval by the respective local Ethics Committees and according to applicable requirements for informed consent at each participating center.

Sample

The original study was already conducted at the University Clinic for Traumatology, Orthopedics, Anesthesiology, Reanimation, Intensive Care, and Emergency Department and included 81 patients who met the predefined inclusion criteria. For future multicenter application of this protocol, eligible patients will be allocated to the MV and non-MV groups, based on the need for mechanical ventilation. Patients initially enrolled in the non-MV group who subsequently require mechanical ventilation for any reason during hospitalization are excluded from the study.

Inclusion Criteria:

- patients must be older than 18 years
- patients where the existence of pulmonary contusions is determined by a radiologist using a CT scan before admission in the ICU
- patients for whom signed informed consent is provided by a family member

Exclusion Criteria:

- patients with pneumothorax due to the inadequacy of examining the lung with ultrasound.
- patients with a history of stent placement or CABG
- patients with previously echocardiographically proven pulmonary arterial hypertension and/or reduced left ventricular systolic function, i.e. previously diagnosed right heart disease
- patients with a history of COPD or idiopathic pulmonary fibrosis
- patients who were resuscitated prior to admission in the ICU
- patients with elevated levels of Troponin suggesting cardiac contusion
- pregnant women.

Methods

All patients included in the study will be examined in four unified time points, the first examination will be performed within 24 hours after the patient's admission, the second on the 4th day of hospitalization, the third examination will be done on the 7th day from the hospitalization, and the fourth examination will be performed on the 14th day of the patient's admission. In all patients, an ultrasonographic examination of the lungs, echocardiography, standard laboratory analyses, acid-base status will be performed, and vital parameters and mechanical ventilation parameters will be noted identically as it was done in the first cohort of 81 patients. Placing patients on mechanical ventilation will be performed based on the generally accepted criteria for intubation and mechanical ventilation such as: presence of hypoxia with SpO_2 below 90%, i.e. $\text{PaO}_2 < 60 \text{ mmHg}$, presence of hypercapnea with $\text{PaCO}_2 > 55 \text{ mmHg}$, respiratory rate > 35 per minute, hemodynamic instability with systolic pressure lower than 90 mmHg accompanied by signs of shock, as well as the presence of impaired consciousness with $\text{GCS} \leq 8$. To avoid bias, the author of this research will not participate in setting the indication for starting mechanical ventilation nor will he participate in ordination of the parameters of mechanical ventilation. All patients with elevated levels of troponins measured 4 hours after ICU admission will not be included in the study because of possible cardiac contusion.

Ultrasonographic Examination of the Lungs

All patients that will be recruited in this study after the first 24 hours of patient admission, on days 4, 7, and 14, will undergo ultrasonographic examination of the lungs. Lung ultrasound examination will include standardized assessment of pulmonary aeration using a 12-region Lung Ultrasound Score (LUS), with each region scored from 0 to 3 in line with the degree of aeration loss. Where clinically appropriate, elements of the BLUE protocol may additionally be used for bedside assessment of acute respiratory abnormalities (45). Lung injury will be stratified according to the Lung Ultrasound Score (LUS). Both of the patients' lungs will be evaluated, by dividing them into 12 segments: anterior-upper, anterior lower segment left and right, lateral upper, lateral lower segment left and right, and posterior upper and posterior lower segment left and right. The ultrasound finding of the lung parenchyma will be interpreted and classified as follows: the presence of A-lines indicating a normally aerated lung will be scored 0 points, the presence of 3-5 B-lines described as laser light or sunlight that extend from the surface to the bottom of the screen and are clearly defined by the surrounding parenchyma will be scored with 1 point, the presence of multiple B-lines or their confluence will be scored with 2 points, the existence of clearly circumscribed pulmonary consolidations where lung parenchyma resembling a liver will be scored with 3 points (46). Examination of the lung will be made with positioning of the probe perpendicularly to the ribs where the lung parenchyma in between two ribs will be visualized and examined. All previously mentioned regions will be scored as it was already explained and each of their points will provide the total number of the LUS Score. The minimum number of the total LUS Score will be 0 points, indicating a completely preserved lung aeration and structure, while the maximum number of points for the LUS Score can reach 36 points, indicating a serious lung injury leading to its deaeration. For scanning of the lungs, a convex probe with a frequency of 2.5-7.5MHz will be used.

Echocardiographic Examination

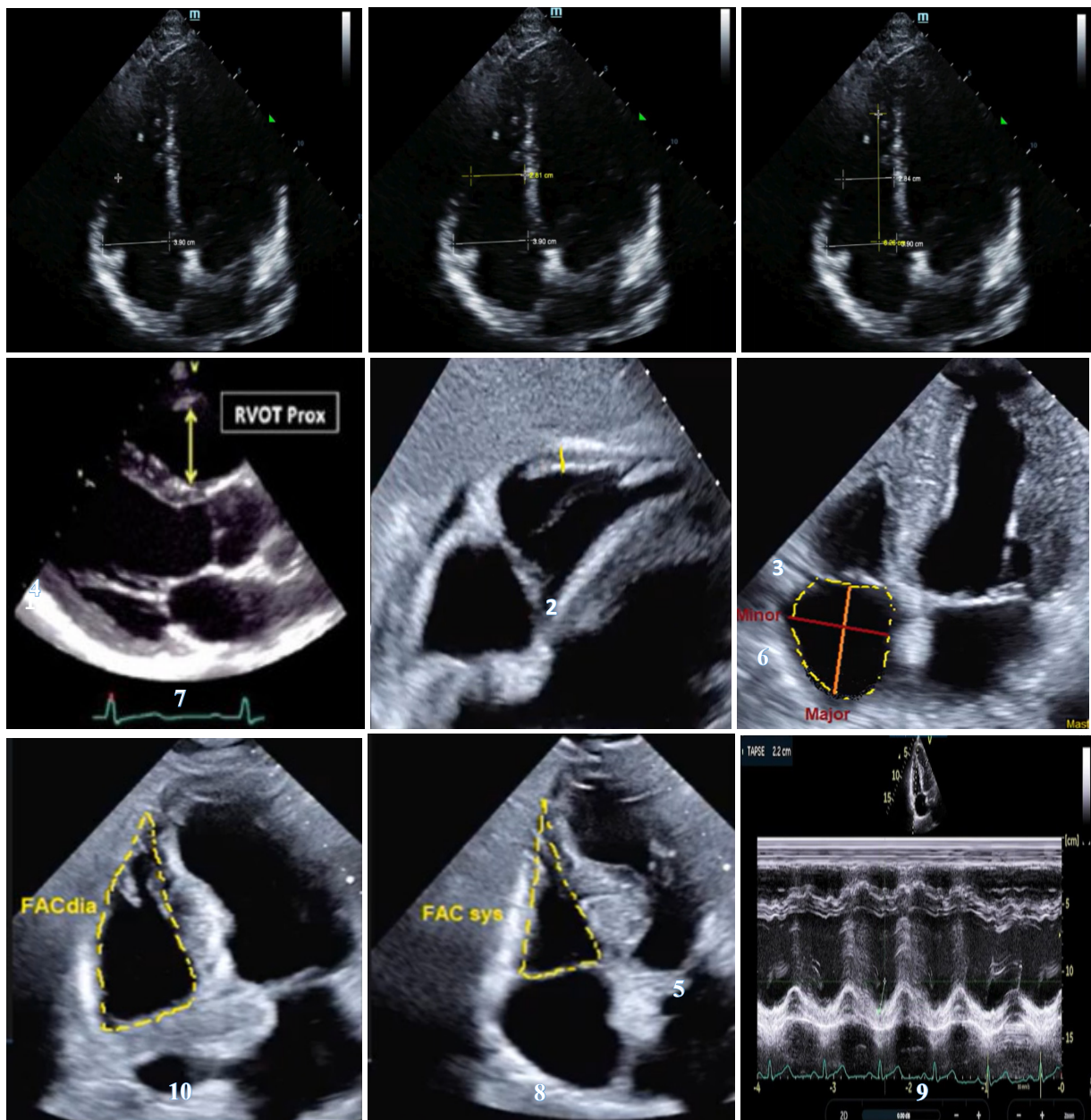
All patients that will be recruited in the future will have an echocardiographic examination focusing

on right heart function after the first 24 hours of admission, on the 4th day of admission, on the 7th day of admission, and on the 14th day of admission. The evaluation of right ventricular dimensions, systolic and diastolic function will be performed following the recommendations for echocardiographic evaluation of cardiac cavities issued in 2015 by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (47). In order to rule out pre-existing left ventricular dysfunction before inclusion in the study, the left ventricular surface in end diastole and end systole (LVEDA and LVESA) will be measured and the area of fractional change of the left ventricle (LV FAC) will be calculated according to formula $LVEDA-LVESA/LVEDA \times 100$, whereby patients with LV FAC less than 35% will be excluded from the study. During each echocardiographic examination, the dimensions of the right ventricle in end diastole will be measured as: basal RVD (diameter of the RV at the base of the heart), midRVD (dimension of the RV at the middle segment), longRVD (longitudinal diameter of the RV) measured in an apical 4 chamber view of the heart where values for bRVD > 41mm, values for midRVD > 35mm and lRVD > 83mm suggest right ventricular dilatation (47,48). The diameter of the RV outflow tract (RVOT) in end diastole, as well as the free wall thickness of the right ventricle will be measured in the long parasternal axis, and measured values for RVOT > 35mm will suggest dilatation, while values for the free wall greater than 5mm will be considered as hypertrophic (47,48). Furthermore, using the apical 4-chamber view of the heart, the area of RV in end diastole (RVEDA) and in end systole (RVESA) will be measured, whereas the value for the fractional change of RV surface (RV FAC) will be calculated according to the following formula: $RVEDA-RVESA/RVEDA \times 100$ as an indicator of the radial function of the RV and it will be expressed in percent; while values for RV FAC < 35% will define the existence of RVD (47,48). Evaluation of the longitudinal systolic function of the RV will be performed using the apical four-chamber window in which the tricuspid transannular excursion in systole (TAPSE) will be evaluated in M-mode with the cursor positioned in the direction of the tricuspid lateral annulus with values for TAPSE less than 17 mm suggesting the existence of RV systolic dysfunction (47,48). During the echocardiographic examination, the presence of tricuspid regurgitation will be detected with color Doppler, and its quantification of peak tricuspid regurgitant velocity will be done with CW Doppler. The systolic pulmonary pressure will be calculated according to the modified Bernoulli equation where sPAP is equal to $\text{peak tricuspid regurgitant velocity}^2 \times 4 + \text{right atrial pressure (RAP)}$ (48,49). Using CW Doppler Pulmonary artery regurgitant flow, the velocity will be measured. Its maximal value will be used for dPAP calculation according to this equation: $\text{peak pulmonary valve regurgitant velocity}^2 \times 4 + \text{right atrial pressure (RAP)}$. Mean PAP (mPAP) should be calculated by using the following equation: $\text{sPAP} \times 0.61 + 2$. RAP should be measured by standard central venous line or it may be calculated when measuring the maximal and minimal values of the Inferior Vena Cava used for calculating the IVC collapsibility or distensibility depending of the need of mechanical ventilation. At each examination, the diastolic function of both ventricles will be evaluated using PW Doppler and the result will be recorded as the E/A ratio. The E' wave will be monitored with tissue Doppler. The obtained values for the left ventricular E wave and the E' wave will provide their ratio, which will be calculated according to the following formula E/E' . The result will be considered as the left preload pressure (LAP) whose value corresponds to the pulmonary capillary wedge pressure (PCWP), which can be corrected according to Nagueh's formula where $\text{PCWP} = 1.9 + 1.24(E/E')$ (50). The regurgitant jet from the pulmonary artery (PR Vmax) PA regurgitant peak velocity with CW Doppler will also be evaluated and from the obtained values the diastolic pressure in the pulmonary circulation (dPAP) will be calculated according to the following formula: $\text{PRVmax}^2 \times 4 + \text{RAP}$. The mean pressure in the pulmonary circulation will be calculated according to the following formula $\text{sPAP} \times 0.61 + 2$ (48,49). Dimensions, collapsibility or distensibility of the inferior vena cava, and the

dimensions of the right atrium will also be measured (47,48).

Remaining Investigations

In addition to the ultrasonographic parameters of the patients included in the study, the following will also be monitored: mortality, length of hospital stay (LOS - length of stay), length of ICU stay (ICU LOS) and number of days without mechanical ventilation (ventilator free days). Basic vital parameters such as systolic and diastolic arterial pressure, mean arterial pressure (MAP), heart rate and blood oxygen saturation (SpO_2) will be monitored in all patients. Central venous pressure (CVP) will be measured in each patient, and if direct measurement is not possible, it will be indirectly calculated by the values of the dimensions of the inferior vena cava and its collapsibility (47,48). Acute Physiology and Chronic Health Evaluation II (APACHE II) Score, Sequential Organ Failure will be evaluated in each patient enrolled in the study.



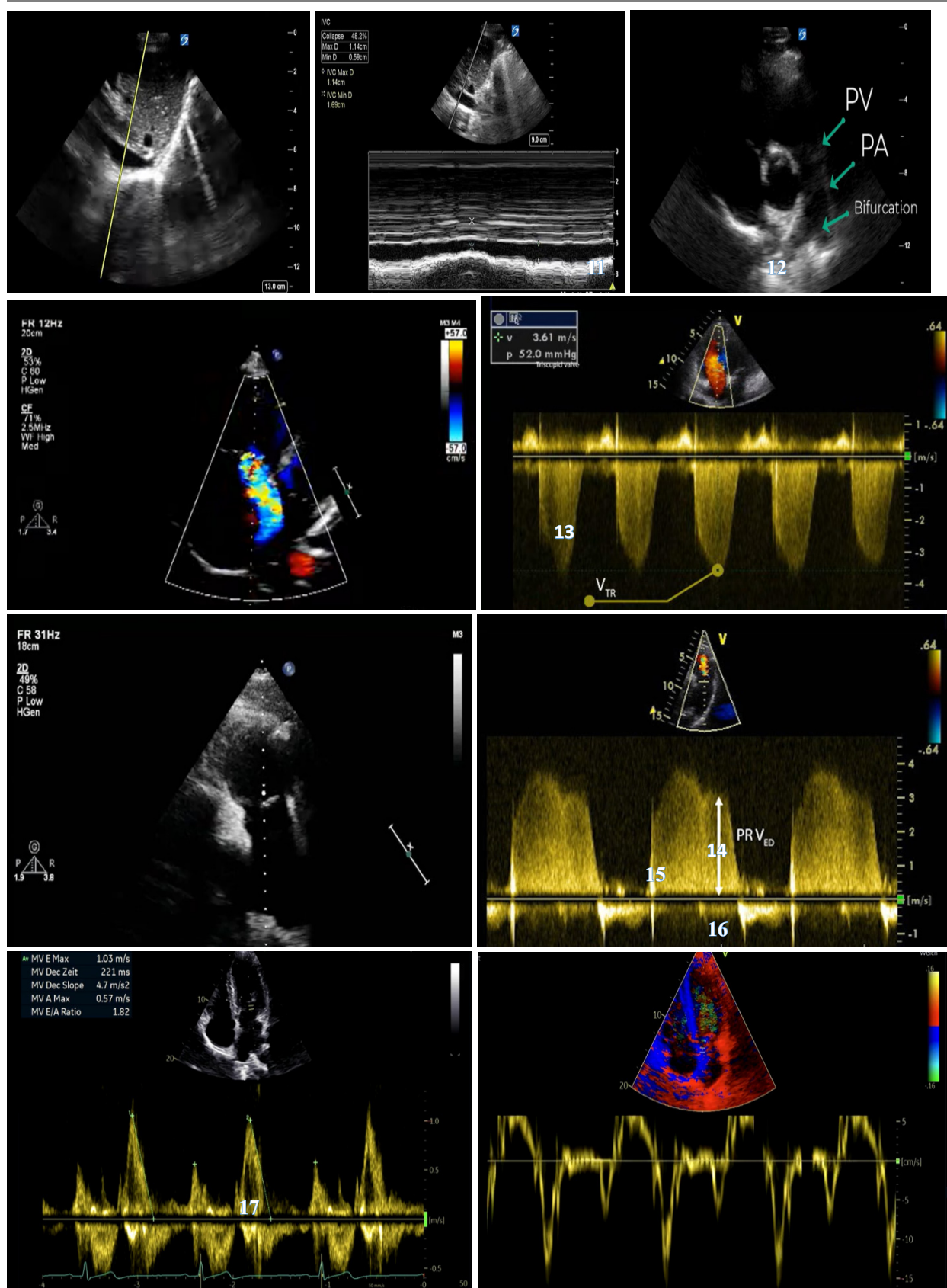


Fig. Illustration of echocardiographic measurements; (1) Measurement of RV basal diameter, (2) Measurement of RV mid-diameter, (3) Measurement of RV longitudinal diameter, (4) Measurement of right ventricular outflow tract diameter, (5) Measurement of RV free wall thickness, (6) Measurement of right atrial diameters, (7) Measurement of RV end-diastolic area (RVEDA), (8) Measurement of RV end-systolic area (RVESA), (9) Measurement of TAPSE, (10) Visualization of the inferior vena cava, (11) Measurement of maximum and minimum inferior vena cava diameters, (12) Measure-

ment of pulmonary artery diameter, (13) Color Doppler visualization of tricuspid regurgitation, (14) Measurement of tricuspid regurgitation using CW and determination of the numerical value for TR Vmax, (15) Detection of pulmonary regurgitation, (16) Measurement of pulmonary regurgitation (PR Vmax), (17) Measurement and display of E/A ratio using PWD, (18) Measurement of e' using TDI.

Statistical Processing

When analyzing the data, the descriptive statistical model will be used for gender, age and distribution of patients with detected RVD in both studied groups. For each of the obtained values from the measurements, the mean value and standard deviation will be derived, and for the parameters with a normal distribution, the Student's T test will be used. The Mann Whitney U test will be used with the obtained values with deviations from the normal distribution. To determine the existence of the need for mechanical ventilation with the development of right ventricular dysfunction based on the definition mentioned above, the Chi square test will be used. The overall prevalence of RVD in all patients included in the study, as well as the RVD prevalence in one group versus the other, will be determined. Determination of differences in parameters used during mechanical ventilation in patients who developed RVD versus those who did not develop RVD will be done using the Mann Whitney U test. Correlation between variables will be evaluated with the Spearman Test, while identification of independent risk factor for development of RVD will be conducted by using a multivariate regression analysis. The mortality and survival rates will be calculated and expressed graphically with the Kaplan Meyer curve. Multivariable logistic regression analysis will be used for identifying possible nondependent predictors for development of RVD in all patients included in the study. Linear regression model for mechanical ventilation settings will be performed for patients exposed to mechanical ventilation in order to identify their possible relationship with RVD. The calculations of the confidence interval (CI-confidence interval) will be performed at a value of 95%, and the values for $p < 0.05$ will be considered statistically significant, while the values for $p < 0.01$ will be considered highly significant.

Limitations

The subjectivity of the physician performing the exam may be a potential limitation in conducting this study, although well experienced and trained echocardiographer performing the examination is a must in order to avoid measurement errors. Inclusion of small number of patients could also be a possible limitation related to the statistical significance of the measured and calculated variables.

Further Possibilities and Applications

This article provides a detailed explanation on the usage and importance of the study protocol explanation, already developed within a PhD thesis. Its publishing is intended to make this protocol available to other researchers who can use it in their practice, or its modulation in further research in the area of the Intensive Care. We recommend that the application of this study protocol in further research is not reserved only to polytraumatized patients, but in many other different cohorts of critically ill patients receiving mechanical ventilation.

Declarations

Ethics approval and consent to participate: Conduction of this study was approved by the Ethical

Committee for Human Research of the Faculty of Medicine in Skopje, at University of SS. Cyril and Methodius – Skopje on 1 February 2023, with approval number 03-300/3.

For the publication of this article, written informed consent was obtained from the patients included in the study until present moment, as well as accompanying data and images. Signing a written informed consent is strongly advised in further inclusion of patients in ongoing research when following this study protocol.

Availability of data and materials: All data are available from the corresponding author upon reasonable request.

Conflict of interest: The authors declare no conflict of interest.

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Authors contributions: All authors have contributed in the design of the study, whereas author A has thoroughly researched existing literature.

Use of Artificial Intelligence (AI) tools: No AI tools were used in the preparation of this manuscript.

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