UNIVERSITY OF MEDICINE AND PHARMACY

„CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

CONTRIBUTIONS TO THE HEMODYNAMIC MONITORING OF THE CRITICALLY ILL PATIENT

Summary of the PhD Thesis

PhD Coordinator

PROF. DR. POPESCU BOGDAN ALEXANDRU

PhD Student:

ANDREI ȘTEFAN

2023

Content

1 Introduction

The critically ill patient admitted to the intensive care unit requires a multidimensional therapeutic approach and comprehensive monitoring (1-2). All hemodynamically-targeted therapies that may be administered to the critically ill patient carry potential serious adverse effects (3). Therefore, careful selection of patients who may benefit from a particular therapeutic intervention is necessary (4). Hemodynamic monitoring methods should be capable of accurately addressing this question.

The overall objective of this work is to explore and evaluate new hemodynamic parameters of interest in the hemodynamic monitoring of critically ill patients. This research endeavor will rely on minimally or non-invasive hemodynamic evaluation methods (such as echocardiography) to minimize the iatrogenic impact on patients who are already in a critical state. The clinical interest would be to describe relatively simple parameters that can be used in day-to-day practice.

In addition to the traditional cardio-centric approach, other parameters of circulatory energetics (the integrative concept of ventriculo-arterial coupling) or venous circulation may be of interest by exploring new hemodynamic models and paradigms in cardiology or sports medicine. This could contribute to better patient selection for those who would benefit from hemodynamic treatment, while avoiding its undesirable effects (e.g. venous congestion).

Another objective of this work is to individualize appropriate temporal moments for the utilization of these parameters, with studies so far traditionally focusing on the acute phase of hemodynamic treatment. The hemodynamic de-escalation phase is less studied, and it is uncertain whether data from the acute phase can be extrapolated. Withdrawal of inotropic-vasopressor support, initiation and continuation of diuretic treatment for the purpose of volume depletion require attention and monitoring. Additionally, early identification of patients who may be suitable for hemodynamic de-escalation could reduce the duration of intensive care unit hospitalization (faster vasopressor weaning, accelerated recovery, earlier intensive care unit discharge).

2 General part

2.1 Problems and perspectives in hemodynamic monitoring of the critically ill patient

The current approach in intensive care medicine is towards reducing the use of invasive procedures and devices and simplifying patient management (5). There is a preference for a dynamic and multimodal approach (6-7). The historical gold-standard method, represented by the pulmonary artery catheter - Swan-Ganz, has gradually fallen out of use in the last decade due to associated complications and even suspected increased mortality(8-9). At the same time, general ultrasound and transthoracic and transesophageal echocardiography have gained an increasingly important role in the critically ill patient (10). Interest is given to its diagnostic role, less invasive character, but also the possibility of evaluating therapeutic means dynamically: titration of intravenous fluid administration, introduction of vasopressors and/or inotropes, being a complementary method to other devices (10-11).

Hemodynamic treatments are not without undesirable effects. The use of inotropic and vasopressor medications may be associated with the onset of arrhythmias or microcirculatory dysfunction, and should be used with caution, for a specific purpose, and for a well-defined duration (3). Excessive intravenous fluid administration can also lead to congestion, respiratory dysfunction, and is a known negative prognostic factor for mortality (12). Additionally, while diuretics cannot be used liberally in hemodynamically unstable patients, they may have a benefit if introduced early in patients with volume excess in stabilized patients (13).

In recent years, there has been a growing scientific interest in the diagnosis and treatment of hypervolemia and congestion in critically ill patients (14-15). Venous congestion and hypervolemia are important factors with an impact on morbidity and mortality in intensive care (16-17), but the diagnosis remains challenging. While there is ample data on the acute management of shock, the therapeutic de-escalation phase of hemodynamic support is much less studied and is beginning to be increasingly discussed (18-19). Although it is believed that hemodynamic therapeutic interventions should be administered titrated and for the minimum necessary time, it is not precisely known when to switch to the opposite approach, especially regarding the initiation of depletion (20).

Several echo(cardio)graphic parameters, studied in sports medicine or in cardiac patients, may be of interest in optimizing the hemodynamic evaluation of critically ill patients, both in the acute phase and during de-escalation(6),(21-22).

2.2 The clinical utility of measuring and monitoring ventriculo-arterial coupling for anaesthesia and ICU patients (23)

Within these parameters of interest, ventriculo-arterial coupling holds a special place, as it has been studied in cardiology for over 30 years. Ventriculo-arterial coupling is a physiological concept that presupposes the cardiac pump and arterial system function in an integrated manner. Ventriculo-arterial coupling is described by the pressure-volume relationship between the left ventricle and the arterial vascular system (24-25). The heart and arteries adapt to each other throughout the cardiac cycle to optimize cardiac output, cardiac performance and efficiency (23).

Ventriculo-arterial coupling is defined as the ratio of two elastances, arterial elastance (E_A) and ventricular elastance (E_V) (23) (Ventriculo-arterial coupling = E_A/E_V). E_V is a characteristic of cardiac function (contractility and morphology), independent of preload and afterload, and can be derived from the pressure-volume ventricular curve (26). E_A represents a cumulative parameter of the entire arterial system, a representation of arterial function, which can be assimilated to net arterial load, characterized by total peripheral resistance, specific impedance, and systolic and diastolic time intervals (26-27). For the human heart, the normal value of E_V is 2.3 +/- 1 $mmHg.ml^{-1}$, of E_A is 2.2 +/- 0.8 $mmHg.ml^{-1}$, and the mean value of the E_A/E_V ratio 1+/-0.36 (23). The energetic balance of cardiovascular function is optimal when the E_A/E_V ratio is 1, and the maximum cardiac efficiency is achieved when the E_A/E_V ratio is 0.5 (28). The alteration of this ratio is both a severity indicator and an independent predictor of worse outcomes in cardiovascular diseases (29).

Several non-invasive methods have been proposed and validated compared to the standard invasive method, making it possible to evaluate ventriculo-arterial coupling in daily clinical practice (30). Some studies have already suggested the potential of monitoring ventriculo-arterial coupling in the acute phase of circulatory failure (23),(31-32).

3 Special part

3.1 Study no. I. New ultrasound parameters in patients' selection and hemodynamic interventions titration: the role of the evaluation of the electro-mechanical dyssynchrony in acute circulatory failure and its relation to ventriculo-arterial coupling (33)

Among the determinants of ventriculo-arterial coupling, E_V is closely correlated with various time periods of the cardiac cycle (34). A correlation between cardiac time intervals and systolic function indicators has been documented in patients admitted to cardiovascular ICU (35). Another indicator of cardiac time efficiency (an indirect indicator of electromechanical efficiency), which is correlated with cardiac performance, is the total isovolumic time (t-TIV) (36). Increased t-TIV is predictive of subsequent cardiac events after cardiac surgery (37), while reducing t-TIV has led to increased cardiac output and improved cardiac energetics (38-39). A t-TIV greater than 12 s/min has been considered as systolic electromechanical inefficiency (intraventricular dyssynchrony) (35). However, the clinical role of intraventricular dyssynchrony is not known in polyvalent intensive care patients, although it may have therapeutic interest (38). This opens an interesting research niche in the direction of investigating the relationship between ventriculo-arterial coupling and electromechanical coupling, a parallel paradigm in hemodynamic research that has not been studied in intensive care patients before.

The primary objective of this study was to investigate the relationship between electromechanical dyssynchrony and acute circulatory failure, depending on the administered hemodynamic treatment. The secondary objective was to evaluate the relationship between electromechanical coupling and ventriculo-arterial coupling.

3.1.1 Methods

This study conducted a retrospective analysis of a prospectively collected database from a cardiovascular intensive care unit. Adult patients with hemodynamic instability who were deemed to require hemodynamic treatment (intravenous fluids, noradrenaline or dobutamine infusions) by the ICU physician were included. Exclusion criteria were low echogenicity, pacemaker presence, bundle branch block, permanent atrial fibrillation, moderate or severe valvulopathy, and right-sided heart dysfunction. Hemodynamic data (including echocardiography) were collected before and after treatment. The relationship

between electromechanical dyssynchrony (defined as t-TIV > 12 s) and hemodynamic parameters in acute circulatory failure before and after treatment was analyzed, including ventriculo-arterial coupling determined by the Chen method (34)). T-TIV was calculated using the formula t-TIV = 60 - (t-TE + t-TF), where t-TE is the total ejection time and t-TF is the total filling time (36).

3.1.2 Results

Fifty-four patients were included in the study. The mean age was 66 ± 12 years, predominantly male (78%), with a mean SAPS II severity score at admission of 42 ± 14. The median length of stay in the intensive care unit was 3 [2-6] days, and the mortality rate was 6/54 (11.1%). The most common type of surgical intervention was valve surgery (52%), followed by aorto-coronary bypass surgery (19%). Approximately 43% of patients received fluid expansion, 37% received norepinephrine, and 20% received dobutamine.

Thirty-nine (72%) of the 54 patients had a t-TIV above 12 s, being classified as having intraventricular dyssynchrony. Logistic regression analyses did not find an association between demographic or initial hemodynamic data, type of circulatory failure (hypovolemia, vasoplegia, cardiogenic), and intraventricular dyssynchrony.

Patients with intraventricular dyssynchrony at baseline improved their t-TIV from 18 ± 4 s to 14 ± 6 s (p = 0.001), E_V from 1.1 (0.72-1.52) to 1.33 (0.84-1.67) mmHg mL^{-1} (p = 0.001), and ventriculo-arterial coupling from 2 (1.67-2.59) to 1.80 (1.40-2.21) (p = 0.001). In contrast, patients without intraventricular dyssynchrony at baseline showed an increase in t-TIV after hemodynamic treatment, with no statistically significant change in the other parameters. The type of hemodynamic treatment showed no effect on t-TIV changes (p = 0.906).

3.2 Study no II. Challenges in monitoring hemodynamic de-escalation and congestion prevention: arterial hypotension following norepinephrine decrease in septic shock patients is not related to preload dependence (40)

Due to its action on two types of adrenergic receptors, alpha and beta adrenergic receptors, norepinephrine can modulate several components of the cardiovascular equilibrium, including venous return, cardiac preload, inotropism, and afterload (41). Because of these effects, the intuitive but still incompletely demonstrated corollary would be

that reducing the dose of norepinephrine during de-escalation would lead to a decrease in venous return and cardiac preload, and therefore cardiac output (42),(43). As acute circulatory failure is frequently associated with altered preload and vasomotor tone, and because norepinephrine can have effects similar to volume expansion (through venoconstriction), clinicians may decide to administer fluids haphazardly to wean off norepinephrine in order to improve or expedite this process. The main objective of this study was to evaluate the association between preexisting preload dependence and the decrease in arterial pressure after norepinephrine withdrawal.

3.2.1 Methods

This prospective observational study included adult patients diagnosed with septic shock and treated with continuous noradrenaline infusion, for whom the treating physician decided to decrease the noradrenaline dose, and who were monitored using a PiCCO® device. Patients treated with adrenaline and/or dobutamine, patients with arrhythmias and intra-abdominal hypertension were excluded.

The included patients were hemodynamically evaluated in three consecutive stages: (i) at the initial time point; (ii) after reducing the noradrenaline dose by 0.04 µg kg-1 min-1; patients were classified as responsive if they recorded a decrease of more than 10% in mean arterial pressure (MAP) after the reduction of noradrenaline dose. (iii) the third set of measurements was performed after achieving volume expansion with 500 ml of saline solution administered intravenously over a period of 10 minutes; patients were classified as responsive if they recorded an increase of more than 10% in MAP.

3.2.2 Results

Forty-five patients were included in the study. The median age was 67 [60-78] years, 36% were female, and the SAPS II score at admission had a median of 55 [45-63]. At the initial hemodynamic evaluation, 6/45 (13%) patients had a positive passive leg raising (PLR) test (preload dependence). No statistically significant association was found between the initial positive PLR test and pressure responsiveness after weaning from noradrenaline (p=1.0). With an AUC of 0.42 (95% CI 0.25-0.59, p=0.395), the change in stroke volume variation during PLR did not demonstrate adequate predictive ability for pressure response after noradrenaline weaning.

The prevalence of positive PLR was not different between the two subgroups of responsive and non-responsive patients (14% versus 13%, p=1) after IV fluid administration.

Pressure responsiveness after reducing the dose of noradrenaline was not associated with pressure responsiveness after volume repletion (14 (40%) versus 8 patients (23%), p=0.211).

Ventriculo-arterial coupling values (determined by PiCCO®) were not statistically significantly different between responsive and non-responsive patients, either at the initial evaluation (3.39 [2.99-4.75] versus 4.19 [3.42-5.69], p=0.197), after reducing the dose of noradrenaline (3.49 [3.00-4.65] versus 4.07 [3.47-5.36], p=0.252), or after volume repletion (3.15 [2.71-4.6] versus 3.93 [3.4-5.6], p=0.145).

3.3 Study no III. The potential of the new parameters in hemodynamic de-escalation: early diuretic initiation was associated with cardiac index and ventriculo-arterial coupling improvement in resuscitated congestive patients

Venous congestion is commonly treated with diuretics, which are an important part of the therapeutic de-escalation phase in intensive care (12). Several clinical studies have demonstrated the benefits of volume depletion in mechanically ventilated patients, but have excluded patients on vasopressor treatment or in the initial acute phase of shock (13),(44). In clinical practice, early administration of diuretics is not a straightforward decision, considering the risks of hemodynamic instability and impaired renal function (45). More data is needed on the macro- and microcirculatory effects of volume depletion in congestive patients in intensive care, especially in the initial phases of therapeutic de-escalation.

The primary objective of this study was to describe the hemodynamic effects of volume depletion (on cardiac index and ventriculo-arterial coupling) with diuretic treatment in the de-escalation phase of acute circulatory shock in ICU patients.

3.3.1 Methods

This study is a post-hoc analysis of a prospectively collected database from a cardiovascular intensive care unit in a university hospital. Inclusion criteria were consecutive adult patients for whom the attending physician decided to administer a loop diuretic. The indication for diuretic administration was at the discretion of the attending physician (clinical signs of hypervolemia, congestion, oliguria in the context of positive fluid balance). In the intensive care unit where the data were collected, diuretic treatment is standardized in accordance with international guidelines (46). Exclusion criteria were diuretic treatment administered in the intensive care unit prior to study inclusion, permanent arrhythmia, renal

replacement therapy, patients with hemodynamic instability (variation in arterial pressure >10% despite hemodynamic treatment and/or need for increased hemodynamic support), and incomplete echocardiographic data. Patients were evaluated clinically and hemodynamically immediately before the initiation of diuretic treatment (baseline) and 24 hours later. Patients with a central venous pressure (CVP) greater than 12 mmHg were classified as congestive (17).

3.3.2 Results

Seventy patients were included in this study, with a median age of 71 [63-76] years and a severity score at admission (Simplified Acute Physiology Score II) of 46 [33-58], of whom 43/70 (61%) were male. 26/70 (37%) patients were admitted to the intensive care unit for non-surgical causes. The median length of stay in the intensive care unit prior to diuretic administration was 2 [1-3] days. At baseline, 51/70 (73%) patients were classified as congestive. 19 congestive patients (27%) and 4 non-congestive patients (21%) were under treatment with norepinephrine. The norepinephrine dose was 0.13 [0.06-0.31] mcg kg^{-1} min^{-1} in the congestive group and 0.09 [0.03-0.33] mcg kg^{-1} min^{-1} in the non-congestive group (p=0.596). Following diuretic administration, the cardiac index increased in the congestive group from 2.5 ± 0.8 2.5 ± 0.8 L min^{-1} m^{-2} to 2.7 ± 0.8 L min^{-1} m^{-2} (p=0.042), but not in the non-congestive group (from 2.7 ± 0.8 L min^{-1} m^{-2} to 2.7 ± 0.7 L min^{-1} m^{-2} , p=0.968). A decrease in arterial lactate was observed in the congestive group (from 2.1 ± 2 mmol L^{-1} to 1.3 ± 0.6 mmol L^{-1}, p=<0.001), but not in the non-congestive group (1.2 ± 0. mmol L^{-1} vs 1.1 ± 0.4 mmol L^{-1}, p= 0.444). Diuretic treatment was also associated with an improvement in ventricular-arterial coupling compared to baseline values in the congestive patient group (from 1.92 ± 1.5 to 1.69 ± 1, p=0.031), without significant effects for the other group (1.28 ± 0.8 vs 1.23 ± 0.6, p=0.937).

3.4 Study no IV. New echographic parameters and diuretic treatment monitoring: Doppler evaluation of portal and renal veins predicts the adequate response to diuretics in ICU (47)

Monitoring diuretic treatment is challenging in practice, as the natriuretic response to a standard diuretic test dose, as suggested in the literature, may not always adequately predict decongestion due to intra- and inter-individual variability (48). Among the novel parameters proposed in studies, portal pulsatility index appears to be the most promising, as it is

associated with venous congestion and hypervolemia (49). Case studies have suggested an association between portal pulsatility index and renal venous impedance and clinical response to diuretic-induced volume depletion (50). However, there are no studies in intensive care regarding the usefulness of portal pulsatility index in identifying patients who will respond to volume depletion with diuretic administration.

The primary objective of this study was to evaluate the ability of portal pulsatility index to detect an adequate response to diuretic-induced volume depletion.

3.4.1 Methods

We conducted a prospective, observational, single-center study in a cardiovascular mixed ICU. Consecutive adult patients with clinical signs of hypervolemia without preload dependence (negative passive leg raising test) and for whom the intensivist decided to introduce furosemide treatment for several days were included. Exclusion criteria were diuretic treatment in the immediate period prior to study inclusion, permanent atrial fibrillation, renal replacement therapy, and unstable hemodynamic shock. Patients were evaluated immediately before diuretic treatment, after 2 hours, after 24 hours, and on the last day of intensive care. The portal pulsatility index was determined by evaluating PW Doppler of the portal vein at the hepatic hilum (51).

Taking into account published literature, a congestion score was constructed based on various clinical and paraclinical indicators of congestion(52-54). Adequate volume depletion under diuretic therapy was considered achieved if the congestion score decreased to below 3 at the end of the study, for patients with significant clinical congestion at the initial time point (54).

3.4.2 Results

81 patients were included. In this study cohort, the mean age was 68 ± 11 years, 51 (63%) were male, and the mean SAPS II score was 46 ± 18. 43 (53%) patients had an initial congestion score ≥ 3. 34 patients (42%) had an adequate response to diuretics. Left and right cardiac echocardiographic parameters were similar between the two response groups.

The portal pulsatility index at the initial time point demonstrated a very good ability to predict an adequate response to diuretic treatment (AUC = 0.80, 95%CI 0.70-0.92, p = 0.001). In multivariate logistic regression analysis, the portal pulsatility index (OR = 20.9, 95%CI 2.8-158.9, p = 0.003), cardiac index (OR = 6.9, 95%CI 17-28.5), and renal venous

impedance pattern (OR = 6.3, 95%CI 2.2-18.2) were statistically significantly associated with an adequate response to diuretics.

3.5 Study no V. Role of ultrasound femoral vein evaluation: a pulsatile Doppler flow pattern is associated with congestion in ICU patients

Diagnosis of venous congestion is difficult in critically ill patients due to false positive signs. Recent case studies have observed a pulsatile pattern of femoral venous flow in right heart failure (55), severe ARDS patients (56), as well as in non-pathological contexts (57). These observations suggest that pulsatility of femoral venous flow may be associated with venous congestion in cases of heart failure and problematic cardio-respiratory interactions in critically ill patients. To date, no study has evaluated the association between pulsatility of femoral venous flow and cardio-respiratory variables in critically ill patients. Pulsatile femoral venous flow may be an independent indicator of venous congestion. The objective of this study was to evaluate the association between pulsatile pattern of femoral venous flow and ultrasound indicators of venous congestion.

3.5.1 Methods

The study had a retrospective design, analyzing an ultrasound database from three medical-surgical intensive care units. Patients who were evaluated by ultrasound at multiple time points during their intensive care unit stay were included: at baseline (within the first 24 hours of intensive care unit admission) and/or daily during intensive care unit stay (day 1, day 2, day 5, and/or in the last 24 hours before intensive care unit discharge). The common femoral vein was evaluated with Doppler at the femoral triangle level, using a high-frequency (5-13 MHz) vascular mode transducer. Venous flow was considered pulsatile when it showed cyclic retrograde increase and decrease, inversely correlated with the cardiac cycle(58).

3.5.2 Results

A total of 108 patients who underwent a total of 400 ultrasound evaluations, with an average of 3.7 ± 1 ultrasound evaluations per patient during their stay in the intensive care unit, were included in the study. A pulsatile femoral venous flow was observed at least once in 79/108 (73%) of patients.

Multivariate logistic regression analysis with mixed effects demonstrated an association between pulsatile femoral venous flow and body mass index (OR 0.91, 95%CI 0.85-0.96,

p=0.002), inferior vena cava diameter (OR 2.35, 95%CI 1.18-4.66, p=0.014), portal venous pulsatility (OR 2.3, 95%CI 1.2-4.4, p=0.012), and renal venous pulsatility (OR 4.02, 95%CI 2.01-8.03, p<0.001).

3.6 Conclusions and personal contributions

The study no. I established, for the first time, a link between patients with intraventricular dyssynchrony (prolonged total isovolumic time, an indicator of electromechanical coupling inefficiency) and those with ventriculo-arterial decoupling, determined by ultrasound. The results suggest that patients with intraventricular d dyssynchrony and ventriculo-arterial coupling impairment may specifically benefit from hemodynamic treatment (intravenous fluid administration, vasopressor support, or inotropic support).

The study no. II focused on the hemodynamic peculiarities of the hemodynamic de-escalation phase (vasopressor weaning). Contrary to intuition, no association was found between the hypotension induced by the decrease in norepinephrine dose and the previous preload dependency. Additionally, the intravenous fluid administration to hypotensive patients after the decrease in norepinephrine dose did not lead to an increase in arterial pressure. This study suggests caution in the use of hemodynamic parameters validated in the acute phase during the de-escalation phase and provides important data against the liberal administration of intravenous fluids in this context.

The study no. III analyzed the hemodynamic response to early diuretic treatment in the therapeutic de-escalation phase (some patients were still under vasopressor support and with abnormal arterial lactate levels). Congestive patients recorded a marked hemodynamic response towards normalization of hemodynamic parameters, including ventriculo-arterial coupling, regardless of the presence or absence of vasopressor support. The results suggest that in selected patients, hemodynamic de-escalation could be initiated even earlier than previously believed.

The study no. IV presented original data in favor of the portal pulsatility index in predicting a positive response to volemic depletion during the therapeutic de-escalation phase, compared to other echocardiographic indices. The results suggest that the portal pulsatility index could be successfully used to guide diuretic treatment.

The study no. V showed the important association between venous congestion and a pulsatile femoral vein flow pattern, for the first time in a general population of ICU patients. The results suggest that ultrasound evaluation of the femoral vein could be useful in diagnosing venous congestion.

The results of this thesis demonstrated in a multifaceted approach the importance of ultrasound evaluation for the hemodynamic monitoring in ICU. The evaluation of peripheral and splanchnic venous circulation, integrative quantification of the relationship between the heart and the arterial system (by determining ventriculo-arterial coupling), can be useful approaches in identifying congestive patients and guiding decongestive diuretic or other hemodynamic treatments, as suggested by the results of this thesis.

List of articles published within the doctoral research:

1. Guinot PG, **Andrei S***, Longrois D. Ventriculo-arterial coupling: from physiological concept to clinical application in perioperative care and ICU. European Journal of Anaesthesiology and Intensive Care April 2022 - Volume 1 - Issue 2 - p e004 https://doi.org/10.1097/EA9.0000000000000004
2. **Andrei S***, Popescu BA, Caruso V, Nguyen M, Bouhemad B, Guinot PG. Role of Electromechanical Dyssynchrony Assessment During Acute Circulatory Failure and Its Relation to Ventriculo-Arterial Coupling. Frontiers in Cardiovascular Medicine. 21 June 2022 | https://doi.org/10.3389/fcvm.2022.907891
3. **Andrei S***, Nguyen M, Abou-Arab O, Bouhemad B, Guinot PG. Arterial Hypotension Following Norepinephrine Decrease in Septic Shock Patients Is Not Related to Preload Dependence: A Prospective, Observational Cohort Study. Frontiers in Medicine, 22 February 2022 Sec. Intensive Care Medicine and Anesthesiology https://doi.org/10.3389/fmed.2022.818386
4. Guinot PG, Bahr PA, **Andrei S*[1],** Popescu BA, Caruso V, Mertes PM, Berthoud V, Nguyen M, Bouhemad B. Doppler study of portal vein and renal venous velocity predict the appropriate fluid response to diuretic in ICU: a prospective observational echocardiographic evaluation. Crit Care. 2022 Oct 5;26(1):305. https://doi.org/10.1186/s13054-022-04180-0

List of other submitted articles related to the doctoral research:

1. **Andrei S***, Bahr PA, Berthoud V, Popescu BA, Nguyen M, Bouhemad B, Guinot PG. Diuretics depletion improves cardiac output and ventriculo-arterial coupling in congestive resuscitated ICU patients – submitted
2. **Andrei S***, Bahr PA, Alissant M, Saccu M, Berthoud V, Nguyen M, Martin A, Popescu BA, Bouhemad B, Guinot PG. Pulsatile femoral vein Doppler flow is associated with congestion in general ICU patients: an observational study – submitted
3. **Andrei S***, Bahr PA, Nguyen M, Bouhemad B, Guinot PG. Systemic venous congestion assessed by ultrasound is not associated with acute kidney injury in a general ICU cohort: a prospective multicentric study – submitted

*corresponding author

[1] first-author equal contribution

Selective references

1. Aseni P, Orsenigo S, Storti E, Pulici M, Arlati S. Current concepts of perioperative monitoring in high-risk surgical patients: a review. Patient Saf Surg. 2019;13:32.

2. Michard F, Biais M, Lobo SM, Futier E. Perioperative hemodynamic management 4.0. Best Pract Res Clin Anaesthesiol. 2019 Jun;33(2):247–55.

3. Guinot PG, Martin A, Berthoud V, Voizeux P, Bartamian L, Santangelo E, et al. Vasopressor-Sparing Strategies in Patients with Shock: A Scoping-Review and an Evidence-Based Strategy Proposition. J Clin Med. 2021 Jul 18;10(14):3164.

4. De Backer D, Aissaoui N, Cecconi M, Chew MS, Denault A, Hajjar L, et al. How can assessing hemodynamics help to assess volume status? Intensive Care Med. 2022 Aug 10;

5. Jozwiak M, Monnet X, Teboul JL. Less or more hemodynamic monitoring in critically ill patients. Curr Opin Crit Care. 2018 Aug;24(4):309–15.

6. Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. Crit Care. 2014 Oct 28;18(5):584.

7. Messina A, Romano SM, Ozdemirkan A, Persona P, Tarquini R, Cammarota G, et al. Multivariable haemodynamic approach to predict the fluid challenge response: A multicentre cohort study. Eur J Anaesthesiol. 2021 Jan;38(1):22–31.

8. Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD003408.

9. Cooper AS. Pulmonary Artery Catheters for Adult Patients in Intensive Care. Critical Care Nurse. 2016 Apr 1;36(2):80–2.

10. Vieillard-Baron A, Millington SJ, Sanfilippo F, Chew M, Diaz-Gomez J, McLean A, et al. A decade of progress in critical care echocardiography: a narrative review. Intensive Care Med. 2019 Jun;45(6):770–88.

11. Cemaj S, Visenio MR, Sheppard OO, Johnson DW, Bauman ZM. Ultrasound and Other Advanced Hemodynamic Monitoring Techniques in the Intensive Care Unit. Surg Clin North Am. 2022 Feb;102(1):37–52.

12. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016 Aug 2;17:109.

13. Cinotti R, Lascarrou JB, Azais MA, Colin G, Quenot JP, Mahé PJ, et al. Diuretics decrease fluid balance in patients on invasive mechanical ventilation: the randomized-controlled single blind, IRIHS study. Crit Care. 2021 Mar 10;25:98.

14. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. Crit Care Med. 1990 Jul;18(7):728–33.

15. Miller WL. Fluid Volume Overload and Congestion in Heart Failure: Time to Reconsider Pathophysiology and How Volume Is Assessed. Circ Heart Fail. 2016 Aug;9(8):e002922.

16. Okazaki K, Fu Q, Martini ER, Shook R, Conner C, Zhang R, et al. Vasoconstriction during venous congestion: effects of venoarteriolar response, myogenic reflexes, and hemodynamics of changing perfusion pressure. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2005 Nov;289(5):R1354–9.

17. Vellinga NA, Ince C, Boerma EC. Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis. BMC Anesthesiology. 2013 Aug 7;13(1):17.

18. Bissell BD, Donaldson JC, Morris PE, Neyra JA. A narrative review of pharmacologic de-resuscitation in the critically ill. J Crit Care. 2020 Oct;59:156–62.

19. Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018 May 22;8(1):66.

20. Vincent JL, Pinsky MR. We should avoid the term "fluid overload". Crit Care. 2018 Sep 11;22:214.

21. Vignon P, Repessé X, Bégot E, Léger J, Jacob C, Bouferrache K, et al. Comparison of Echocardiographic Indices Used to Predict Fluid Responsiveness in Ventilated Patients. Am J Respir Crit Care Med. 2017 Apr 15;195(8):1022–32.

22. Beaubien-Souligny W, Benkreira A, Robillard P, Bouabdallaoui N, Chassé M, Desjardins G, et al. Alterations in Portal Vein Flow and Intrarenal Venous Flow Are Associated With Acute Kidney Injury After Cardiac Surgery: A Prospective Observational Cohort Study. J Am Heart Assoc. 2018 Oct 2;7(19):e009961.

23. Guinot PG, **Andrei S**, Longrois D. Ventriculo-arterial coupling: from physiological concept to clinical application in peri-operative care and ICUs. European Journal of Anaesthesiology and Intensive Care. 2022 Apr;1(2):e004.

24. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure/volume ratio: a new index of ventricular contractility. Am J Cardiol. 1977 Nov;40(5):748–53.

25. Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. Ann Biomed Eng. 1984;12(2):163–89.

26. Chantler PD. Arterial Ventricular Uncoupling With Age and Disease and Recoupling With Exercise. Exerc Sport Sci Rev. 2017 Apr;45(2):70–9.

27. Magder S. The meaning of blood pressure. Crit Care. 2018 Oct 11;22(1):257.

28. Chirinos JA. Ventricular-arterial coupling: Invasive and non-invasive assessment. Artery Res. 2013 Mar;7(1).

29. Ky B, French B, May Khan A, Plappert T, Wang A, Chirinos JA, et al. Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure. J Am Coll Cardiol. 2013 Sep 24;62(13):1165–72.

30. Ikonomidis I, Aboyans V, Blacher J, Brodmann M, Brutsaert DL, Chirinos JA, et al. The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association. Eur J Heart Fail. 2019 Apr;21(4):402–24.

31. **Andrei S**, Nguyen M, Longrois D, Popescu BA, Bouhemad B, Guinot PG. Ventriculo-Arterial Coupling Is Associated With Oxygen Consumption and Tissue Perfusion in Acute Circulatory Failure. Front Cardiovasc Med. 2022;9:842554.

32. Zhou X, Zhang Y, Pan J, Wang Y, Wang H, Xu Z, et al. Optimizing left ventricular-arterial coupling during the initial resuscitation in septic shock - a pilot prospective randomized study. BMC Anesthesiol. 2022 Jan 21;22(1):31.

33. **Andrei S**, Popescu BA, Caruso V, Nguyen M, Bouhemad B, Guinot PG. Role of Electromechanical Dyssynchrony Assessment During Acute Circulatory Failure and Its Relation to Ventriculo-Arterial Coupling. Front Cardiovasc Med. 2022;9:907891.

34. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol. 2001 Dec;38(7):2028–34.

35. Tavazzi G, Dammassa V, Corradi F, Klersy C, Patel B, Pires AB, et al. Correlation Between Echocardiographic and Hemodynamic Variables in Cardiothoracic Intensive Care Unit. Journal of Cardiothoracic and Vascular Anesthesia. 2020 May 1;34(5):1263–9.

36. Duncan AM, Francis DP, Henein MY, Gibson DG. Limitation of cardiac output by total isovolumic time during pharmacologic stress in patients with dilated cardiomyopathy:

Activation-mediated effects of leftbundle branch block and coronary artery disease. Journal of the American College of Cardiology. 2003 Jan 1;41(1):121–8.

37. Bajraktari G, Duncan A, Pepper J, Henein M. Prolonged total isovolumic time predicts cardiac events following coronary artery bypass surgery. Eur J Echocardiogr. 2008 Nov;9(6):779–83.

38. Tavazzi G, Kontogeorgis A, Bergsland NP, Price S. Resolution of Cardiogenic Shock Using Echocardiography-Guided Pacing Optimization in Intensive Care: A Case Series. Crit Care Med. 2016 Aug;44(8):e755-761.

39. Tavazzi G, Kontogeorgis A, Guarracino F, Bergsland N, Martinez-Naharro A, Pepper J, et al. Heart Rate Modification of Cardiac Output Following Cardiac Surgery: The Importance of Cardiac Time Intervals*. Critical Care Medicine. 2017 Aug 1;45(8):e782–8.

40. **Andrei S**, Nguyen M, Abou-Arab O, Bouhemad B, Guinot PG. Arterial Hypotension Following Norepinephrine Decrease in Septic Shock Patients Is Not Related to Preload Dependence: A Prospective, Observational Cohort Study. Front Med (Lausanne). 2022;9:818386.

41. Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther. 2015 May;20(3):249–60.

42. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. Crit Care Med. 2011 Apr;39(4):689–94.

43. He H, Yuan S, Long Y, Liu D, Zhou X, Ince C. Effect of norepinephrine challenge on cardiovascular determinants assessed using a mathematical model in septic shock: a physiological study. Ann Transl Med. 2021 Apr;9(7):561.

44. Hua Z, Xin D, Xiaoting W, Dawei L. High Central Venous Pressure and Right Ventricle Size Are Related to Non-decreased Left Ventricle Stroke Volume After Negative Fluid Balance in Critically Ill Patients: A Single Prospective Observational Study. Front Med (Lausanne). 2021;8:715099.

45. McCoy IE, Chertow GM, Chang TIH. Patterns of diuretic use in the intensive care unit. PLoS One. 2019;14(5):e0217911.

46. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 Feb;21(2):137–55.

47. Guinot PG, Bahr PA, **Andrei S**, Popescu BA, Caruso V, Mertes PM, et al. Doppler study of portal vein and renal venous velocity predict the appropriate fluid response to diuretic in ICU: a prospective observational echocardiographic evaluation. Crit Care. 2022 Oct 5;26(1):305.

48. Kenig A, Kolben Y, Asleh R, Amir O, Ilan Y. Improving Diuretic Response in Heart Failure by Implementing a Patient-Tailored Variability and Chronotherapy-Guided Algorithm. Front Cardiovasc Med. 2021;8:695547.

49. Abou-Arab O, Beyls C, Moussa MD, Huette P, Beaudelot E, Guilbart M, et al. Portal Vein Pulsatility Index as a Potential Risk of Venous Congestion Assessed by Magnetic Resonance Imaging: A Prospective Study on Healthy Volunteers. Front Physiol. 2022 Apr 29;13:811286.

50. Argaiz ER, Rola P, Gamba G. Dynamic Changes in Portal Vein Flow during Decongestion in Patients with Heart Failure and Cardio-Renal Syndrome: A POCUS Case Series. Cardiorenal Med. 2021;11(1):59–66.

51. Huette P, Guinot PG, Haye G, Moussa MD, Beyls C, Guilbart M, et al. Portal Vein Pulsatility as a Dynamic Marker of Venous Congestion Following Cardiac Surgery: An Interventional Study Using Positive End-Expiratory Pressure. J Clin Med. 2021 Dec 12;10(24):5810.

52. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013 Mar;34(11):835–43.

53. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012 Apr;38(4):577–91.

54. Caravaca Pérez P, Nuche J, Morán Fernández L, Lora D, Blázquez-Bermejo Z, López-Azor JC, et al. Potential Role of Natriuretic Response to Furosemide Stress Test During Acute Heart Failure. Circulation: Heart Failure. 2021 Jun;14(6):e008166.

55. Denault AY, Aldred MP, Hammoud A, Zeng YH, Beaubien-Souligny W, Couture EJ, et al. Doppler Interrogation of the Femoral Vein in the Critically Ill Patient: The Fastest Potential Acoustic Window to Diagnose Right Ventricular Dysfunction? Critical Care Explorations. 2020 Oct;2(10):e0209.

56. Malinovska A, Arslani K, Zellweger N, Gebhard C, Beaubien-Souligny W, Calderone A, et al. Femoral and popliteal venous Doppler during prone and supine position in COVID-19 patients: a potential diagnostic tool to detect abnormal right ventricular function. Can J Anaesth. 2021;68(5):737–9.

57. Schroedter WB, White JM, Garcia AR, Ellis ME. Presence of Lower-Extremity Venous Pulsatility is not always the Result of Cardiac Dysfunction. Journal for Vascular Ultrasound. 2014 Jun 1;38(2):71–5.

58. Kim ES, Sharma AM, Scissons R, Dawson D, Eberhardt RT, Gerhard-Herman M, et al. Interpretation of peripheral arterial and venous Doppler waveforms: A consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. Vasc Med. 2020 Oct;25(5):484–506.