PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Dynamic Arterial Elastance for Weaning Vasopressor Support in Septic Shock Patients: A Randomized Controlled Trial Protocol
AUTHORS	Alvarado Sánchez, Jorge Iván; Montañez-Nariño, Andrea; Cárdenas-Bolivar, Yenny; Stozitzky-Ríos, Maria; Mora Salamanca, Andrés Felipe

VERSION 1 – REVIEW

REVIEWER	Monaco, Fabrizio Scientific Institute San Raffaele, Cardiothoracic and Vascular Anesthesia
REVIEW RETURNED	04-Apr-2024

GENERAL COMMENTS	The authors present their protocol for evaluating Dynamic Elastance in patients with septic shock. However, the manuscript exhibits several shortcomings and fails to meet the rigorous standards of BMJ Open. Below are my considerations: Abstract: The methods section of the abstract should clarify how Edyn is assessed and which device is used. Objectives with endpoints should be relocated to the materials and methods section. Consider PICO Lines 168-171 can be omitted as a Spanish version of the protocol may not be necessary. Line 177: The meaning of "public involvement" should be elucidated. Line 221: Specify which echocardiographic parameters are collected. Line 223: The authors need to explain the criteria for initiating weaning from vasopressors. Additionally, SVV validation requires a closed chest and ventilation at 6 ml/kg, yet ventilation settings are not reported in the paper. Consideration should be given to excluding EF% and right ventricular dysfunction among the exclusion criteria.

REVIEWER	Zhou, Xiaoyang
REVIEW RETURNED	21-Apr-2024

GENERAL COMMENTS	Thanks very much for the opportunity to review this study protocol entitled “Efficacy and Safety of Dynamic Arterial Elastance for Vasopressor Support Weaning in Septic Shock Patients: A Randomized Controlled Trial Protocol”. The authors declared that they plan to enroll 114 septic shock patients to conduct a

	pragmatic single-center randomized controlled trial (RCT) to compare the efficacy and safety of the Eadyn-based vasopressor weaning algorithm against the MAP-based usual weaning procedure. I appreciate the authors' efforts and their great work on this interesting topic that may bring changes to the management concept of septic shock. To improve the quality of this manuscript, I have some major and minor comments that the authors need to address. Major comments 1. In the INTRODUCTION section, the authors write a large amount of content to describe the theoretical relationship between the Eadyn and arterial load (including pulsatile and steady components). In my opinion, this content does not help to explain the purpose of this RCT and the length of this part of the content should be reduced in half. The authors should discuss the significance of the Eadyn in the management of septic shock (norepinephrine weaning and fluid expansion). More importantly, the authors should add a paragraph to describe why they plan to conduct an RCT to explore the efficacy of the Eadyn-based vasopressor weaning algorithm. 2. In the ELIGIBILITY CRITERIA section, the authors pre-established a series of inclusion criteria. However, the study protocol has no clear inclusion or exclusion criteria for patients with mechanical ventilation or spontaneous breathing. The measurement of Eadyn will be inevitably affected by spontaneous breathing during the vasopressor weaning process which is a relatively long period. Furthermore, in a recent meta-analysis regarding Eadyn in the vasopressor weaning process, all patients received mechanical ventilation (doi: 10.3389/fcvm.2024.1350847). Thus, I suggest that patients with spontaneous breathing should be excluded. By the way, please clearly indicate which type of vasopressor it is in your protocol. 3. In lines 221-222, the authors stated that patients sustaining a MAP ≥ 75 mmHg for 30 minutes or more will begin weaning from vasopressor support. Whether these patients are suitable for vasopressor withdrawal? In clinical practice, vasopressor withdrawal generally occurs in the stabilization and de-escalation phases of septic shock. If these patients who have maintained a MAP ≥ 75 mmHg for more than 30 minutes were in the optimization phase, vasopressor withdrawal is more likely to fail and lead to the unnecessary occurrence of hypotension and hypoperfusion. In my opinion, such a standard can not ensure these patients are in the stabilization and de-escalation phases. Please explain. 4. In the study protocol, vasopressor weaning will be discontinued as long as the Eadyn is less than 0.90. As I know, the cutoff value of Eadyn is 0.94 in a previous RCT (doi: 10.1007/s00134-016-4666-z). Can you explain why you chose 0.90 as the cutoff value? Furthermore, the norepinephrine dose will be gradually reduced at 0.02 mcg/kg/min every 30 minutes. Whether the time interval (30 minutes) for evaluating hemodynamic changes is too long? which may lead to prolonged hypotension. 5. Why the authors will assess the preload dependence before vasopressor weaning? Whether the preload will impact the outcomes of vasopressor weaning and the measurement of Eadyn? 6. In Figure 2, the authors indicated that in the experimental group, the preload dependence will be reassessed before measuring MAP in those patients who have a measured Eadyn of greater than 0.90 after reducing the norepinephrine dose. Why?

	7. Why the authors will exclude those patients whose MAP falls below 50 mmHg after reducing the norepinephrine dose in both groups? How to handle the missing data regarding these patients? In my opinion, the data on this cohort of patients are very important for assessing the effect of the Eadyn-based norepinephrine weaning algorithm on the duration of vasopressor support. Excluding this cohort of patients might cause potential bias in the final results. 8. More importantly, as shown in Figure 2 which depicts the Eadyn-based norepinephrine weaning algorithm in the experimental group, deciding whether to continue reducing the dose of norepinephrine ultimately depends on the mean arterial pressure, but not the measured Eadyn, which means a similar process with the MAP-based weaning strategy in the control group. What is the significance of the Eadyn-based norepinephrine weaning algorithm? Minor comments 1. Please provide a unified abbreviation for dynamic arterial elastance, Eadyn or EaDyn? 2. In lines 150-154, the authors stated “The objective of this study is to ……. Secondary objectives include to compare the following variables between ……, including the duration of vasopressor support”. However, in the ABSTRACT section, their primary outcome is the difference in the duration of vasopressor support. Please clearly indicate what are the primary and secondary objectives. 3. Please carefully check the grammar and spelling errors throughout the entire text. For example, in line 58, “…… will be include”; in lines 60-62, “Our primary outcome is the difference between the duration of vasopressor support between the EaDyn and MAP groups”, etc. 4. In line 185, mean arterial pressure should be written in the form of “MAP”. 5. In the first row in Table 1, the timepoint “Completion of VS weaning (T3)” is different from that in Figure 2 (described as data collection after weaning VS).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Fabrizio Monaco, Scientific Institute San Raffaele
Comments to the Author:
Summary:
The authors present their protocol for evaluating Dynamic Elastance in patients with septic shock. However, the manuscript exhibits several shortcomings and fails to meet the rigorous standards of BMJ Open. Below are my considerations:

Abstract:
The methods section of the abstract should clarify how Edyn is assessed and which device is used.

The definition of EaDyn was included. We will use a Pulse index Continuous Cardiac Output device (PiCCO ®, PULSION Medical Systems SE, Feldkirchen, Germany) connected to a PulsioFlex Monitoring Platform (Reference PC4000, PULSION Medical Systems SE, Feldkirchen, Germany) through a PiCCO module (Reference PC4510, PULSION Medical Systems SE, Feldkirchen, Germany). This information was included in the abstract and the eligibility criteria.

Objectives with endpoints should be relocated to the materials and methods section.

Thank you for the recommendation. This paragraph has been moved to the Methods section.

Consider PICO

Our study's aim has been adjusted following your recommendation. We add our PICO strategy as the online supplementary material 3.

Lines 168-171 can be omitted as a Spanish version of the protocol may not be necessary.

Thank you for your recommendation; this statement has been deleted.

Line 177: The meaning of "public involvement" should be elucidated.

The requested changes have been implemented in the manuscript. The public involvement is a section required by BMJ Open, which is the reason why we include this information.

Line 221: Specify which echocardiographic parameters are collected.

Thank you for your suggestion. The echocardiographic variables to be collected included stroke volume and cardiac output. This information was added in lines 210-213.

Line 223: The authors need to explain the criteria for initiating weaning from vasopressors.

The initiation of vasopressor weaning coincides with the onset of the optimization phase, which occurs when patients achieve a mean arterial pressure (MAP) > 75 mmHg, a cardiac index (CI) > 2.5 L/min/m2, and a lactate level < 2 mmol/L. This statement has been included in our manuscript.

Additionally, SVV validation requires a closed chest and ventilation at 6 ml/kg, yet ventilation settings are not reported in the paper.

Thank you for your important recommendation. The ventilation settings are described in the intervention subsection with the following statement:

“All patients will undergo daily echocardiographic evaluation, measuring variables including stroke volume and CO using the Mindray TE5 Ultrasound System (Mindray North America, Mahwah, NJ, USA), following widely used formulas. All patients will be ventilated with a tidal volume of 6-8 ml/kg of predicted body weight (PBW) to maintain a plateau pressure greater than 30 cmH2O and a driving pressure lower than 15 cmH2O. The respiratory rate will be adjusted to achieve a target CO2 level of 30-35 mmHg, and PEEP and FiO2 will be adjusted to maintain SpO2 between 90-94%..”

Consideration should be given to excluding EF% and right ventricular dysfunction.

Our exclusion criteria was updated to exclude patients with a left ventricular ejection fraction (LVEF) less than 50% and right ventricular dysfunction.

Reviewer: 2
Dr. Xiaoyang Zhou

Comments to the Author:
Dear Editor,
Thanks very much for the opportunity to review this study protocol entitled “Efficacy and Safety of Dynamic Arterial Elastance for Vasopressor Support Weaning in Septic Shock Patients: A Randomized Controlled Trial Protocol”. The authors declared that they plan to enroll 114 septic shock patients to conduct a pragmatic single-center randomized controlled trial (RCT) to compare the efficacy and safety of the Eadyn-based vasopressor weaning algorithm against the MAP-based usual weaning procedure. I appreciate the authors’ efforts and their great work on this interesting topic that may bring changes to the management concept of septic shock. To improve the quality of this manuscript, I have some major and minor comments that the authors need to address.
Major comments
1. In the INTRODUCTION section, the authors write a large amount of content to describe the theoretical relationship between the Eadyn and arterial load (including pulsatile and steady components). In my opinion, this content does not help to explain the purpose of this RCT and the length of this part of the content should be reduced in half. The authors should discuss the significance of the Eadyn in the management of septic shock (norepinephrine weaning and fluid expansion). More importantly, the authors should add a paragraph to describe why they plan to conduct an RCT to explore the efficacy of the Eadyn-based vasopressor weaning algorithm.

We appreciate the feedback from the reviewer and have revised the introduction accordingly to provide readers with more context and a better understanding of the aim of our study.

2. In the ELIGIBILITY CRITERIA section, the authors pre-established a series of inclusion criteria. However, the study protocol has no clear inclusion or exclusion criteria for patients with mechanical ventilation or spontaneous breathing. The measurement of Eadyn will be inevitably affected by spontaneous breathing during the vasopressor weaning process which is a relatively long period. Furthermore, in a recent meta-analysis regarding Eadyn in the vasopressor weaning process, all patients received mechanical ventilation (doi: 10.3389/fcvm.2024.1350847). Thus, I suggest that patients with spontaneous breathing should be excluded. By the way, please clearly indicate which type of vasopressor it is in your protocol.

Thank you for your accurate comment. I have added 'Patients spontaneously breathing' as an exclusion criterion.

3. In lines 221-222, the authors stated that patients sustaining a MAP ≥ 75 mmHg for 30 minutes or more will begin weaning from vasopressor support. Whether these patients are suitable for vasopressor withdrawal? In clinical practice, vasopressor withdrawal generally occurs in the stabilization and de-escalation phases of septic shock. If these patients who have maintained a MAP ≥ 75 mmHg for more than 30 minutes were in the optimization phase, vasopressor withdrawal is more likely to fail and lead to the unnecessary occurrence of hypotension and hypoperfusion. In my opinion, such a standard can not ensure these patients are in the stabilization and de-escalation phases. Please explain.

Thank you for your insightful comment. While the terms "stabilization" and "de-escalation" were coined to guide fluid therapy in critically ill patients, we respectfully believe that this concept may not directly apply to vasopressor weaning in all aspects. However, we agree with the reviewer's suggestion that vasopressor weaning should commence once the "optimization phase" begins. Therefore, we have clarified the definition of vasopressor weaning as follows: "The initiation of vasopressor weaning will coincide with the onset of the stabilization phase, which occurs when patients achieve a mean arterial pressure (MAP) > 75 mmHg, cardiac index (CI) > 2.5 L/min/m2, and lactate levels < 2 mmol/L."

4. In the study protocol, vasopressor weaning will be discontinued as long as the Eadyn is less than 0.90. As I know, the cutoff value of Eadyn is 0.94 in a previous RCT (doi: 10.1007/s00134-016-4666-z). Can you explain why you chose 0.90 as the cutoff value? Furthermore, the norepinephrine dose will be gradually reduced at 0.02 mcg/kg/min every 30 minutes. Whether the time interval (30 minutes) for evaluating hemodynamic changes is too long? which may lead to prolonged hypotension.

Thank you for your comment. Following an analysis of five published studies, we estimated an average threshold of 0.89. Therefore, we chose 0.9 as the EaDyn threshold to guide vasopressor weaning.

The five studies analyzed were:

1. https://ccforum.biomedcentral.com/articles/10.1186/s13054-014-0732-5
2. https://www.yiigle.com/LinkIn.do?linkin_type=pubmed&issn=0578-1426&year=2017&vol=56&issue=5&fpage=344
3. https://www.bjanaesthesia.org/article/S0007-0912(18)30094-1/fulltext
4. https://www.nature.com/articles/s41598-021-82408-9
5. https://www.mdpi.com/2075-1729/13/1/28

5. Why the authors will assess the preload dependence before vasopressor weaning? Whether the preload will impact the outcomes of vasopressor weaning and the measurement of Eadyn?

Thank you for your insightful comment. Since EaDyn was initially proposed to be a predictor of a mean arterial pressure increase secondary to fluid challenge, we believe that it is necessary to administer a fluid load in patients with EaDyn >0.9 and a MAP of 50-70 mmHg. The term "preload fluid assessment" has been omitted to avoid misunderstanding. Additionally, it is important to highlight that a secondary aim of our study will be to evaluate the cumulative fluid dose administered to each study group during vasopressor weaning, with the objective of determining whether vasopressor weaning based on EaDyn influences the cumulative fluid dose administered. This clarification has been added to the manuscript.

6. In Figure 2, the authors indicated that in the experimental group, the preload dependence will be reassessed before measuring MAP in those patients who have a measured Eadyn of greater than 0.90 after reducing the norepinephrine dose. Why?

Thank you for your comment. The inclusion of the MAP in our algorithm aims to evaluate whether a patient requires a fluid load when the EaDyn is >0.9 and the MAP is within the range of 50-75 mmHg. This decision is based on previous studies suggesting a high likelihood of MAP increase following a fluid load in this context. We originally used the term "preload dependence" to convey this concept. However, upon reflection, we acknowledge the potential for misunderstanding and have thus removed the term to enhance clarity.

7. Why the authors will exclude those patients whose MAP falls below 50 mmHg after reducing the norepinephrine dose in both groups? How to handle the missing data regarding these patients? In my opinion, the data on this cohort of patients are very important for assessing the effect of the Eadyn-based norepinephrine weaning algorithm on the duration of vasopressor support. Excluding this cohort of patients might cause potential bias in the final results.

Our aim was to evaluate the efficacy and safety of dynamic arterial elastance for vasopressor support weaning in septic shock patients. Safety will be assessed by comparing differences between the experimental and control groups in terms of hypotension (defined as MAP ≤ 50 mmHg), cardiac arrhythmias leading to hemodynamic instability, and deterioration in neurological or respiratory patterns.
In terms of data management, we will utilize an intention-to-treat approach, ensuring that all patients are included and analysed with respect to the safety objective. This methodology will enable us to identify the safest weaning strategy based on our safety outcomes.

These claims have been comprehensively detailed and emphasized within the manuscript, as evidenced in the Outcomes and Data Collection and Management sections.

8. More importantly, as shown in Figure 2 which depicts the Eadyn-based norepinephrine weaning algorithm in the experimental group, deciding whether to continue reducing the dose of norepinephrine ultimately depends on the mean arterial pressure, but not the measured Eadyn, which means a similar process with the MAP-based weaning strategy in the control group. What is the significance of the Eadyn-based norepinephrine weaning algorithm?

Thank you for highlighting this important aspect. Measuring MAP in the experimental group has to purposes: to administer a fluid load when the MAP falls within the range of 50-70 mmHg or to remove the patient from our study if the MAP is less than 50 mmHg. In all other cases, the weaning of vasopressors will continue. To clarify this concept, we have removed the expression "Weaning is paused, and vasopressor is returned to previous value."

Minor comments
1. Please provide a unified abbreviation for dynamic arterial elastance, Eadyn or EaDyn?

We have thoroughly reviewed the entire manuscript to ensure consistency in the use of abbreviations. EaDyn was used in the whole manuscript.

2. In lines 150-154, the authors stated “The objective of this study is to ……. Secondary objectives include to compare the following variables between ……, including the duration of vasopressor support”. However, in the ABSTRACT section, their primary outcome is the difference in the duration of vasopressor support. Please clearly indicate what are the primary and secondary objectives.

Thank you for bringing up this important point. We have refined our objectives to ensure alignment with our primary and secondary outcomes.

3. Please carefully check the grammar and spelling errors throughout the entire text. For example, in line 58, “…… will be include”; in lines 60-62, “Our primary outcome is the difference between the duration of vasopressor support between the EaDyn and MAP groups”, etc.

We have reviewed our work to ensure that there are no spelling errors.

3. In line 185, mean arterial pressure should be written in the form of “MAP”.

Thank you for pointing out our mistake. This word has been corrected.

4. In the first row in Table 1, the timepoint “Completion of VS weaning (T3)” is different from that in Figure 2 (described as data collection after weaning VS).

The recommended changes have been incorporated into Table 1.

Reviewer: 1
Competing interests of Reviewer: None

Reviewer: 2
Competing interests of Reviewer: I have no competing interests to declare.

VERSION 2 – REVIEW

REVIEWER	Zhou, Xiaoyang
REVIEW RETURNED	22-May-2024

GENERAL COMMENTS	Thank you for allowing me to review the revised version of this study protocol. I still have some concerns about this study protocol. 1. Lines 102-103, the authors stated that EaDyn is now recognized as an index reflecting the overall functioning of the cardiovascular system. I respectfully disagree with the authors' viewpoint. According to the calculation formula of EaDyn (the ratio of PPV to SVV), EaDyn defines the changes in the arterial pulse pressure caused by the changes in left ventricular stroke volume related to the intrathoracic pressure changes during a respiratory cycle. Thus, EaDyn describes the dynamic interaction between changes in pressure and flow and evaluates the dynamical changes in arterial tone. It can reflect a part of cardiovascular function, but cannot reflect the overall function. 2. Line 188, “Patients requiring mechanical ventilation” should be revised to “Patients received invasive mechanical ventilation” 3. Lines 212-214, why the plateau pressure should be maintained above 30 cmH2O? 4. Although the authors have explained why they chose 0.9 as the cutoff value, they did not explain why the norepinephrine dose will be reduced at 0.02 mcg/kg/min every 30 minutes. In my opinion, the time interval (30 minutes) for evaluating hemodynamic changes is relatively too long, which may lead to prolonged hypotension. By the way, the recent publication (doi: 10.3389/fcvm.2024.1350847) should be referenced because it provides the optimal cutoff value of EaDyn for the study protocol. 5. I agree with the authors' viewpoint that the preload status should be assessed if hypotension occurs after reducing the norepinephrine dose. However, I disagree with the behavior that preload dependence should be evaluated in all patients before starting norepinephrine weaning (as indicated in Figures 2 and 3). In clinical practice, it is not a routine behavior to evaluate volume responsiveness before norepinephrine weaning, because the patients at the de-escalation stage have generally received adequate fluid expansion before norepinephrine weaning. This study protocol is unlike those previous studies that assessed the performance of EaDyn in predicting the arterial response to fluid expansion. In the previous studies, the included patients were at the early rescuing stage of septic shock, they usually are more likely to have insufficient volume status, thus requiring volume responsiveness assessment. 6. I agree with using the MAP < 50 mmHg as a safety indicator in the study protocol, but these patients with a MAP < 50 mmHg after

	reducing the norepinephrine dose should not be excluded from the study, because their blood pressure can still be recovered after appropriate interventions, and timely correction of hypotension usually does not lead to serious consequences. Excluding these patients from the study will inevitably have an impact on the primary outcome (the duration of norepinephrine use), and retaining these patients in the study will not have an impact on the safety evaluation. 7. I suggest that volume responsiveness should be assessed if hypotension occurs after reducing the norepinephrine dose, irrespective of whether the MAP is within 50-70 mmHg or less than 50 mmHg. If volume responsiveness is present, fluid expansion should be given; if is not present, the norepinephrine dose should be returned to the previous value. Please clearly indicate in Figures 2 and 3.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Xiaoyang Zhou

Comments to the Author:

Dear editor,

Thank you for allowing me to review the revised version of this study protocol. I still have some concerns about this study protocol.

1. Lines 102-103, the authors stated that EaDyn is now recognized as an index reflecting the overall functioning of the cardiovascular system. I respectfully disagree with the authors' viewpoint. According to the calculation formula of EaDyn (the ratio of PPV to SVV), EaDyn defines the changes in the arterial pulse pressure caused by the changes in left ventricular stroke volume related to the intrathoracic pressure changes during a respiratory cycle. Thus, EaDyn describes the dynamic interaction between changes in pressure and flow and evaluates the dynamical changes in arterial tone. It can reflect a part of cardiovascular function, but cannot reflect the overall function.

Thank you for your valuable feedback on our manuscript. We appreciate your insight regarding the description of EaDyn. We have revised the text to better reflect the nuanced role of EaDyn in evaluating cardiovascular function. We have updated description as follows:

"However, it is now recognized as a variable that describes the dynamic interaction between changes in arterial pressure and left ventricular stroke volume related to intrathoracic pressure changes during a respiratory cycle. Thus, EaDyn evaluates the dynamic changes in arterial tone, reflecting a part of the cardiovascular function."

We hope this clarification addresses your concern and enhances the accuracy of our manuscript.

2. Line 188, “Patients requiring mechanical ventilation” should be revised to “Patients received invasive mechanical ventilation”

Thank you for your recommendation. We have now implemented your suggestion.

3. Lines 212-214, why the plateau pressure should be maintained above 30 cmH2O?

Thank you for highlighting our mistake. We have corrected the statement to indicate that patients will be ventilated to maintain a plateau pressure below 30 cmH2O.

4. Although the authors have explained why they chose 0.9 as the cutoff value, they did not explain why the norepinephrine dose will be reduced at 0.02 mcg/kg/min every 30 minutes. In my opinion, the time interval (30 minutes) for evaluating hemodynamic changes is relatively too long, which may lead to prolonged hypotension. By the way, the recent publication (doi: 10.3389/fcvm.2024.1350847) should be referenced because it provides the optimal cutoff value of EaDyn for the study protocol.

Thank you for your accurate comment. However, the studies that have evaluated EaDyn have assessed the outcome (MAP decreases) 30 minutes after norepinephrine doses were reduced [1–4]. For this reason, we selected this time interval. Additionally, we have added the study as a reference.

5. I agree with the authors' viewpoint that the preload status should be assessed if hypotension occurs after reducing the norepinephrine dose. However, I disagree with the behavior that preload dependence should be evaluated in all patients before starting norepinephrine weaning (as indicated in Figures 2 and 3). In clinical practice, it is not a routine behavior to evaluate volume responsiveness before norepinephrine weaning, because the patients at the de-escalation stage have generally received adequate fluid expansion before norepinephrine weaning. This study protocol is unlike those previous studies that assessed the performance of EaDyn in predicting the arterial response to fluid expansion. In the previous studies, the included patients were at the early rescuing stage of septic shock, they usually are more likely to have insufficient volume status, thus requiring volume responsiveness assessment.

Assessment of Fluid Responsiveness Before Weaning: Based on your argument, we have deleted the step of assessing fluid responsiveness before starting norepinephrine weaning. We recognize that in clinical practice, patients at the de-escalation stage have generally received adequate fluid expansion before norepinephrine weaning, making this step unnecessary.

6. I agree with using the MAP < 50 mmHg as a safety indicator in the study protocol, but these patients with a MAP < 50 mmHg after reducing the norepinephrine dose should not be excluded from the study, because their blood pressure can still be recovered after appropriate interventions, and timely correction of hypotension usually does not lead to serious consequences. Excluding these patients from the study will inevitably have an impact on the primary outcome (the duration of norepinephrine use) and retaining these patients in the study will not have an impact on the safety evaluation.

Protocol for Patients with MAP < 50 mmHg: We agree with your point regarding the inclusion of patients with a MAP < 50 mmHg. These patients will not be excluded from the study, as their blood pressure can often be recovered after appropriate interventions. We have adjusted our protocol to reflect this change, ensuring that these patients are retained in the study and properly managed.

7. I suggest that volume responsiveness should be assessed if hypotension occurs after reducing the norepinephrine dose, irrespective of whether the MAP is within 50-70 mmHg or less than 50 mmHg. If volume responsiveness is present, fluid expansion should be given; if is not present, the norepinephrine dose should be returned to the previous value. Please clearly indicate in Figures 2 and 3.

Thank you for your thorough review and valuable comments. We have carefully considered your feedback and made the following adjustments to our study protocol:

Assessment of Volume Responsiveness: We have incorporated your suggestion to assess volume responsiveness if hypotension occurs after reducing the norepinephrine dose, regardless of whether the MAP is within 50-70 mmHg or less than 50 mmHg. If volume responsiveness is present, fluid expansion will be administered. If it is not present, the norepinephrine dose will be returned to the previous value. This has been clearly indicated in Figures 2 and 3.

We believe these changes will enhance the clarity and accuracy of our protocol and align it more closely with clinical practice standards. Thank you once again for your insightful suggestions.

references:

1 Persona P, Tonetti T, Valeri I, et al. Dynamic Arterial Elastance to Predict Mean Arterial Pressure Decrease after Reduction of Vasopressor in Septic Shock Patients. Life. 2022;13:28. doi: 10.3390/life13010028

2 Bar S, Leviel F, Abou Arab O, et al. Dynamic arterial elastance measured by uncalibrated pulse contour analysis predicts arterial-pressure response to a decrease in norepinephrine. Br J Anaesth. 2018;121:534–40. doi: 10.1016/j.bja.2018.01.032

3 Guinot P-G, Bernard E, Levrard M, et al. Dynamic arterial elastance predicts mean arterial pressure decrease associated with decreasing norepinephrine dosage in septic shock. Crit Care. 2015;19:1–7. doi: 10.1186/s13054-014-0732-5

4 Nguyen M, Abou-Arab O, Bar S, et al. Echocardiographic measure of dynamic arterial elastance predict pressure response during norepinephrine weaning: an observational study. Sci Rep. 2021;11:2853. doi: 10.1038/s41598-021-82408-9

VERSION 3 – REVIEW

REVIEWER	Zhou, Xiaoyang
REVIEW RETURNED	09-Jul-2024

GENERAL COMMENTS	Thanks to the authors for making extensive revisions. I have no more comments on this study.