Editorial

ATHOS-3 and the knights of the round table—the search for the holy grail of vasopressors

Michael Hessler[1], Philip-Helge Arnemann[1], Laura Seidel[1], Tim Kampmeier[1], Sebastian Rehberg[2], Christian Ertmer[1]

[1]Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital of Muenster, Muenster, Germany; [2]Department of Anaesthesiology, University Hospital of Greifswald, Greifswald, Germany

Correspondence to: Priv.-Doz. Dr. med. Christian Ertmer, MD, PhD. Department of Anaesthesiology, Intensive Care and Pain Medicine, University Hospital of Muenster, Albert-Schweitzer-Campus 1, Building A1, 48149 Muenster, Germany. Email: ertmer@anit.uni-muenster.de.

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The international, multicentre, double-blinded, randomized, controlled ATHOS-3 trial by Khanna and colleagues (1) was conducted from May 2015 to January 2017 in nine countries across Europe, North America, and Australia. ATHOS-3 was designed to answer two primary endpoints within a study period of 48 h.

First, in the initial 3 h, a "vasopressor" trial was conducted to test the hypothesis, that mean arterial pressure (MAP) of patients who already receive more than 0.2 µg/kg/min norepinephrine or the equivalent dose of another conventional vasopressor in vasodilatory shock states can be raised by angiotensin II. Therefore, angiotensin II was titrated to increase MAP to at least 75 mmHg (starting at 20 ng/kg/min to max 200 ng/kg/min) in the intervention group while standard of care vasopressors were held constant. The primary endpoint was defined as vasopressor response due to the infusion of angiotensin II or placebo (MAP ≥75 mmHg, or an increase in MAP from baseline ≥10 mmHg).

Second, in the period between 3 and 48 h, a clinically more relevant study design was used to test the ability of angiotensin II in maintaining MAP levels between 65–75 mmHg and reducing catecholamine doses. Therefore, an infusion of angiotensin II equivalent to 1.25 to 40 ng/kg/min was compared to placebo; both in combination with the respective standard of care vasopressors. The study protocol included a non-binding adjustment scheme for vasopressors: briefly, the attending physician could choose between standard of care vasopressors and angiotensin II (in doses between 1.25 and 40 ng/kg/min) to maintain a MAP between 65–75 mmHg.

Overall, 321 patients were included in the analysis: 163 received angiotensin II, and 158 received placebo. There were no statistically significant differences between groups in baseline characteristics and demographics. Patients in both treatment groups were severely ill, as suggested by high vasopressor doses [median (interquartile range): angiotensin II group 0.33 µg/kg/min (0.23–0.56), and placebo group 0.34 µg/kg/min (0.23–0.56)] and high disease severity scores {e.g., APACHE II Score, ranging from 0–71 with higher scores indicating greater disease severity, was 28 [22–33] in all patients}.

At the end of the initial 3-h period significantly more patients met the criteria for a positive vasopressor response in the angiotensin II group compared to the placebo group (70% *vs.* 23%, P<0.001) corresponding to a significantly greater increase in MAP in the angiotensin II group (12.5 *vs.* 2.9 mmHg, P<0.001). Regarding the second major endpoint, mean dosages of the standard of care vasopressors were consistently lower in the angiotensin II group compared to the placebo group. In addition, at the end of the 48-h interventional period, the improvement of the cardiovascular sequential organ failure assessment score (SOFA) was more pronounced in the angiotensin II group

than in the placebo group (–1.75 *vs.* 1.28, P=0.01); however, the total SOFA change at the end of the interventional period did not differ between groups. In addition, there were no statistical significant differences in serious adverse events (angiotensin II group 60.7% *vs.* placebo group 67.1%) and 28-day mortality rates [angiotensin II: 75 of 163 patients (46%); placebo: 85 of 158 patients (54%), P=0.12] between both study groups.

The authors concluded that angiotensin II was able to increase MAP and allowed dose reductions of catecholamines in patients with vasodilatory shock states requiring high-dose vasopressor therapy.

Khanna and colleagues devote themselves to a noble objective: the search for the holy grail of vasopressors. It should be potent, but with a non-adrenergic mechanism of action to contribute to the de-catecholamination of intensive care therapy (2). To date, catecholamines still are the first line vasopressors for vasodilatory shock. But it is also known that especially high doses are associated with several deleterious side effects (2,3) and are independently associated with increased mortality rates (3-5). For example, patients receiving more than 0.2 μg/kg/min norepinephrine or equivalent have a mortality risk of >50% (6). Thus, the optimal vasopressor for patients in vasodilatory shock states still needs to be identified. Currently, the only evidence-based alternative to catecholamines are vasopressin receptor agonists with arginine vasopressin (AVP) representing the most intensively studied compound. The discussed phase III study by Khanna *et al.* was the first step to pave the way to introduce angiotensin II in clinical practice (1,7). Indeed, their findings are very promising and at first glance, both major endpoints were reached. However, there are several issues, which need to be considered when interpreting the findings.

First, the study claimed to investigate the safety and efficacy of angiotensin II in vasodilatory shock states. Vasodilatory shock was defined as high dosages of norepinephrine or equivalent (>0.2 μg/kg/min), cardiac index of greater than 2.3 L/min/m^2 or a central venous oxygen saturation of >70% coupled with central venous pressure of more than 8 mmHg, and a MAP of 55–70 mmHg. Notably, the causes of vasodilatory shock in the study were sepsis, other (potentially sepsis), pancreatitis, postoperative vasoplegia and a condition referred to as multifactorial. Summarizing all these conditions under one generic term is quite problematic, as there are differences in the pathophysiology of each condition. Whereas the reasons for the catecholamine-resistant vasodilatory shock in sepsis are well known (8), the aetiology for postoperative vasoplegia, for example after cardiac surgery, remains unclear and various factors are discussed to contribute to this condition (9,10). This issue becomes even more relevant considering the high rate of non-responders of 30% suggesting that angiotensin II is not effective in all conditions causing vasodilatory shock. Indeed, most of the study patients suffered from sepsis (259 of 321) and in 31 of the 62 remaining patients, sepsis was likely. Therefore, the study investigated the efficacy and safety rather in vasodilatory septic shock than in other shock states. Thus, generalization of the results to other vasodilatory shock conditions should be avoided.

Second, angiotensin II is known to increase heart rate by influencing the baroreceptor control of heart rate and due to withdrawal of cardiac vagal tone (11). In the current study (1), patients receiving angiotensin II had higher heart rates during the 48-h interventional period. Especially in the first 3 h, during the "vasopressor" trial, heart rates were considerably increased. Although not discussed by the authors, an increase in heart rate in patients with septic shock is of utmost importance, because tachycardia increases myocardial oxygen consumption, shortens diastolic filling time, and compromises coronary perfusion (12). Especially in critically ill patients a higher heart rate is associated with an increase in mortality (13,14). As a consequence current therapeutic strategies focus on heart rate control to reduce adrenergic stress, e.g., by titrating beta blockers (15) or $alpha_2$-receptor agonists (16). In this regard it should be mentioned, that an infusion of vasopressin is commonly associated with reduction in heart rate. On the way to a more individualized therapy, this could be a distinctive feature for the therapy of different groups of patients. However, this assumption needs confirmation in future studies.

In the present study there were no differences in cardiac adverse events between groups, but overall rates of cardiac adverse events were low (1). However, this study—mentioned by the authors themselves—was, due to a small sample size, not able to provide definitive information about the possibility of clinically important side effects following an infusion of angiotensin II. Additionally, the study was underpowered to detect effects on mortality (1). Thus, it is crucial to investigate the safety and efficacy of angiotensin II in a cohort of patients that is large enough to answer these questions. Additionally, it could be assumed that at least in part the elevated heart rate contributed to the increase in MAP, and as a result, relativize the vasopressor effect of

angiotensin II.

Third, angiotensin II was not able to raise the blood pressure in all patients. Overall, approximately 30% of the patients were "non-responders" to the first main endpoint. In a multivariate analysis, positive predictors of a response with respect to MAP were an albumine concentration at baseline ≥2.5 g/dL and a norepinephrine-equivalent dose of less than 0.5 µg/kg/min (corresponding to an earlier therapy start in contrast to patients receiving ≥0.5 µg/kg/min). In contrast, significant negative predictors were hypoalbuminemia, an elevated vasopressor dose ≥0.5 µg/kg/min, and no chest X-ray findings of acute respiratory disease syndrome (ARDS). Latter most likely attributable to an endogenous deficiency of angiotensin II in patients with ARDS, because the majority of angiotensin is converted in the lung (17). In this context, it would have been most desirable if plasma levels of angiotensin II would have been available at baseline and during the course of the study. Thus, further studies should focus on this subject und elicit which patients might benefit most from angiotensin II infusion.

Fourth, a pragmatic approach was chosen to evaluate the effects of angiotensin II as a supplement to standard of care vasopressor therapy (as "background infusion"), and the vasopressor dose was summarized as norepinephrine or equivalent. In fact, more than two thirds of all patients received AVP, which was converted into norepinephrine equivalent (0.04 U/min vasopressin were equated 0.1 µg/kg/min) (1). Additionally, in the period between 3 to 48 h, attending physicians could choose between standard of care vasopressors and the dosing regimen to achieve MAP. This approach is in outright accordance with basic principles of phase III studies for the "Proof of Concept of Clinical Efficacy and Safety" for the official approval of a drug. As a consequence, however, the results of the study should not be overestimated. Due to the design of the study, it is not possible to deduce the value of an angiotensin II therapy against norepinephrine and/or vasopressin. Synergic effects between vasopressors were described, but this requires further investigation (18).

Finally, it should not be let out of sight that vasopressor treatment is only one of several measures to eventually improve tissue perfusion. The kind of vasopressor and its individual dose nothing, if tissue perfusion is not preserved by its usage. Since bedside measurement of microcirculation and tissue perfusion are nowadays available quite comfortably, a future study should evaluate the effects of add-on angiotensin II on these variables. Notably, being close-minded on macrohemodynamics may spell doom for angiotensin II when it comes to multicentre randomized controlled trials.

In conclusion, Khanna and colleagues' well performed study is an important contribution to the search for the holy grail of vasopressors for vasodilatory shock. They showed that angiotensin II has the ability to increase blood pressure in vasodilatory shock states in patients receiving high-dose vasopressors, and allows dose reductions of catecholamines. Hopefully, the above-mentioned issues are investigated in near future; afterwards angiotensin II would be able to broaden the spectrum of vasopressors for vasodilatory shock. At present, angiotensin II should not be used outside clinical studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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