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Review Article

ANGIOTENSIN II IN REFRACTORY SEPTIC SHOCK

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ABSTRACT—Refractory septic shock is defined as persistently low mean arterial blood pressure despite volume resuscitation and titrated vasopressors/inotropes in patients with a proven or suspected infection and concomitant organ dysfunction. Its management typically requires high doses of catecholamines, which can induce significant adverse effects such as ischemia and arrhythmias. Angiotensin II (Ang II), a key product of the renin–angiotensin–aldosterone system, is a vasopressor agent that could be used in conjunction with other vasopressors to stabilize critically ill patients during refractory septic shock, and reduce catecholamine requirements. However, very few clinical data are available to support Ang II administration in this setting. Here, we review the current literature on this topic to better understand the role of Ang II administration during refractory septic shock, differentiating experimental from clinical studies. We also consider the potential role of exogenous Ang II administration in specific organ dysfunction and possible pitfalls with Ang II in sepsis. Various issues remain unresolved and future studies should investigate important topics such as: the optimal dose and timing of Ang II administration, a comparison between Ang II and the other vasopressors (epinephrine; vasopressin), and Ang II effects on microcirculation.

KEYWORDS—Circulatory failure, hemodynamic stabilization, organ dysfunction, sepsis, vasopressors

INTRODUCTION

Sepsis is a common syndrome with increasing incidence over recent years, accounting for up to 30% of all intensive care unit (ICU) admissions worldwide (1). Despite improvements in overall outcomes, the mortality rate remains high (40%–50%), especially when septic shock develops (2). Survival of septic shock is associated with poor longer-term outcomes and persistent disability (3). A particular condition is the ''refractory'' septic shock, which can be defined by the persistence of circulatory failure despite optimized therapy (e.g., adequate fluid resuscitation, high doses of vasopressors, and/or inotropes when necessary) (4). The pathophysiology underlying this clinical presentation is characterized by an imbalance between vasoconstrictor and vasodilator mediators. Indeed, during sepsis, various vasodilating factors (e.g., nitric oxide [NO], tumor necrosis factor [TNF-α], histamine, kinins, and prostaglandins) are released, whereas the vasoconstrictor response to angiotensin II (Ang II) and catecholamines may be decreased (4). Treatment of refractory septic shock often requires high doses of catecholamines for a prolonged period of time. Excessive use of catecholamines is an independent risk-factor for ICU mortality and can induce numerous adverse effects, including peripheral and splanchnic ischemia, acute myocardial infarction, arrhythmias (e.g., atrial fibrillation), increased oxygen consumption and hyperglycemia (5). Adding another vasopressor with a different mechanism of action may contribute to a reduction in such complications. According to international guidelines, the available vasopressor drugs that can be used as an alternative to norepinephrine (NE) are vasopressin and its analogues (6). Some authors have suggested that the exogenous administration of Ang II, a strong vasocostrictive peptide, could also be beneficial in cases of refractory septic shock (7, 8). However, with very few studies having investigated the role of Ang II in critically ill patients, leaving no conclusive evidence for its role in this setting, its use in refractory septic shock is currently limited. Taking into account these limitations, we revised the pathophysiological relevance of Ang II in patients with refractory septic shock and suggested future perspectives in this field.

PHYSIOLOGY

Ang II is a principal product of the renin–angiotensin–aldosterone system (RAAS) which governs essential homeostatic mechanisms that counteract hypotension and hypovolemia (9). The vasoconstrictor and systemic effects of Ang II result from its interaction with different types of receptors and the activation of a number of cell-signalling pathways (10).

The Renin–Aldosterone–Angiotensin System

The RAAS has been evolutionarily conserved over hundreds of millions of years (11). It has pleiotropic effects and operates at three different levels in the body: tissue (autocrine and

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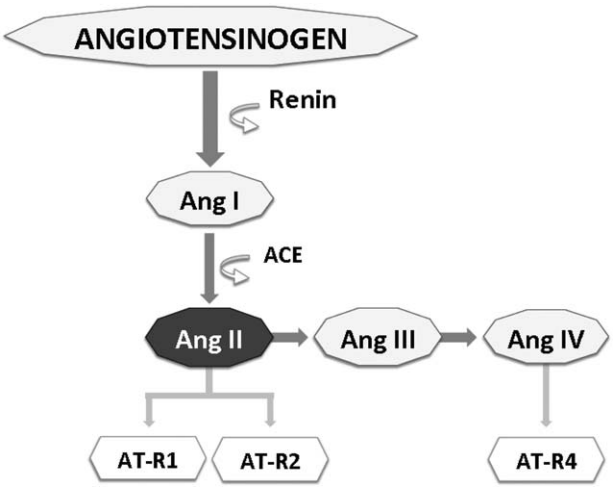

Fig. 1. **RAAS: network of interactions.** Angiotensin-converting enzyme (ACE) cleaves angiotensin I (Ang I) into angiotensin II (Ang II). Ang II exerts its physiologic function by binding to specific receptors (angiotensin-receptor type 1 [AT-R1] and angiotensin-receptor type 2 [AT-R2]). Ang II can be also converted in angiotensin III, Ang III, and angiotensin IV; Ang IV interacts with angiotensin-receptor type 4, AT-R4. RAAS indicates renin–angiotensin–aldosterone system.

paracrine), cellular (intracrine), and systemic (endocrine). At the tissue RAAS level, Ang II synthesis occurs in the interstitial space from components produced in the same tissue (12). The tissue RAAS may utilize enzymes other than renin for the synthesis of Ang II, such as cathepsins and chymase, and acts locally in an autocrine/paracrine manner (12). The cellular RAAS is defined by Ang II synthesis inside the cell either in secretory vescicles (the secretory RAAS) or in other cellular regions or organelles (the non-secretory RAAS) (12). Intracellular Ang II has been localized in the cytoplasm, mitochondria, and nuclei of different tissues (myocytes, vascular smooth muscle cells (VSMCs), fibroblasts, and kidney cells) (12). At the systemic, endocrine level, volume depletion, and decreased mean arterial pressure (MAP) induce the release of renin from the juxtaglomerular cells of the renal afferent arteriole into the systemic circulation (13). Under renin stimulation, angiotensinogen, a circulating α2-globulin produced primarily by the liver, is converted to angiotensin I (Ang I), a decapeptide with weak biological activity. Ang I is converted to Ang II by the angiotensin converting enzyme type 1 (ACE-1), which is predominantly expressed in the pulmonary microcirculation as well as in the plasma and the endothelium of the systemic circulation (14).

Our understanding of the RAAS is constantly evolving. In the last few years, knowledge about the RAAS shifted from the old idea of a linear cascade of biochemical reactions to a hierarchically organized network of interactions (15) (Fig. 1). The converting enzymes ACE-1and ACE type 2 (ACE-2) represent important steps in the system by producing the two main effectors (Ang II and Ang 1-7), which in turn modulate their own activity (15). Specifically, Ang II is cleaved from Ang I by the dipeptidase ACE and then further catalyzed by the monopeptidase ACE-2 into Ang 1-7, which can be further metabolized by ACE into Ang 1-5. On one hand, Ang 1-7 has an established role on a cellular level as an anti-apoptotic, anti-inflammatory, vasodilating agent through its interactions with Mas and Ang 1-7 receptors. In a recent experimental study, the authors found that Ang 1-7 (dose up to 100 nmol/L) can reduce Ang II-induced proliferation and migration in VSMCs (16). However, quantitative data in the literature is lacking and Ang 1-7 has been experimentally tested for the most part in cardiovascular studies. On the other hand, Ang II exerts its physiologic function by binding to specific G protein-coupled receptors: AT-R1 and AT-R2 (17). These receptors are located in the kidneys, heart, brain, adrenal glands, skeletal muscles, and also on cells with important immune function such as peripheral blood mononuclear cells and lymphocytes (17). Key hemodynamic effects mediated by AT-R1 include vasoconstriction, aldosterone secretion by the adrenal zona glomerulosa, vasopressin release, and cardiac remodelling (17). Other—potentially deleterious effects—include increase in vascular permeability (mediated by leukotriene C4, prostaglandin E2, prostacyclin, and vascular endothelial growth factor, promotion of inflammatory cell migration, and the production of other inflammatory mediators (i.e., adhesion molecules—intercellular adhesion molecule-1, and vascular cell adhesion molecule-1; cytokines) (18). Transcriptional regulation, predominantly via nuclear factor-kB, and second mediator systems, such as endothelin-1, the small G protein (Rho), and redox-pathways have been shown to be involved in the molecular mechanism by which Ang II exerts its pro-inflammatory effects through AT-R1 (18). Conversely, AT-R2-mediated mechanisms have not been completely determined although some experimental data suggest that its stimulation might counteract the AT-R1 effects on blood pressure regulation, inflammation, and cell growth (14). Indeed, angiotensin II binding to AT-R2 results in vasodilatation and decreased systemic vascular resistance. Ang II may also interact with AT-R4 inducing different actions such as vasodilation, pro-inflammatory, and procoagulant effects (14).

RAAS in septic shock

Septic shock is a distributive form of circulatory failure, characterized by reduced vascular resistance, relative hypovolemia, increased cardiac output (if septic myocardial depression does not coexist), and microcirculatory dysfunction resulting in high mixed venous blood O2 saturation (4). Furthermore, during septic shock we observe a complex interaction between molecular and hemodynamic alterations. NO induces vasodilatation with resulting changes in preload, afterload, and cardiac perfusion. The main inflammatory mediators (TNF-α; interleukin-1, and interleukin-6) may contribute to myocardial depression in sepsis, both alone and in a synergistic way (4). Under these conditions different physiologic responses try to restore effective circulating volume, vascular resistance, and arterial pressure, including sympathetic nervous system activation; vasopressin release; inhibition of atrial and cerebral natriuretic peptides; increased renin secretion resulting in RAAS activation with elevated Ang II plasma levels (19). During septic shock, activation of RAAS is increased in response to renal hypoperfusion: decreased stretch of the afferent arteriole and decreased delivery of chloride to the distal tubules stimulates renin release from the juxtaglomerular

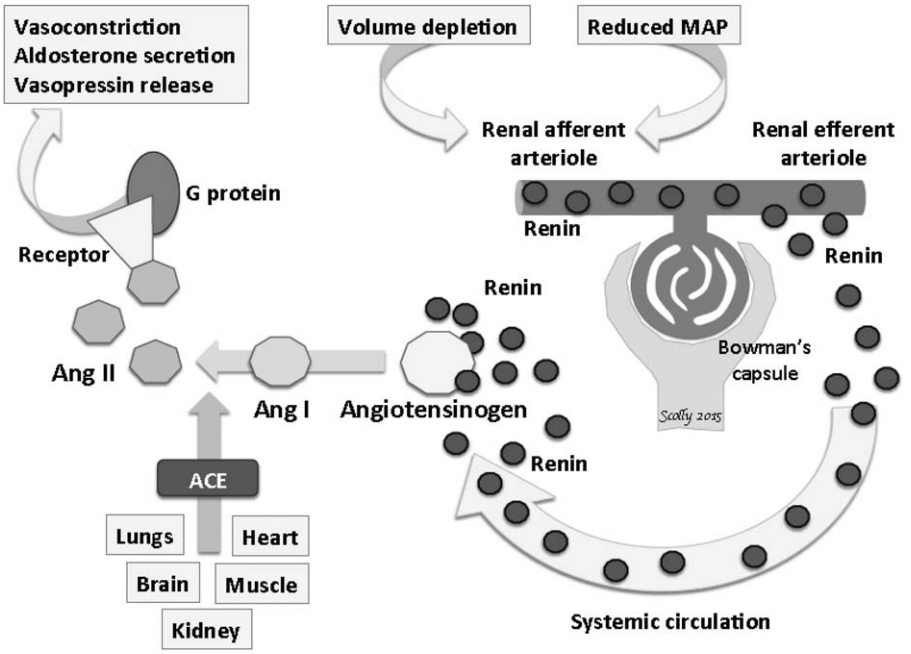

Fig. 2. **Activation of RAAS during volume depletion.** ACE indicates angiotensin-converting enzyme; Ang I, angiotensin 1; Ang II, angiotensin II; MAP, mean arterial pressure.

apparatus (20). Hypovolemia also stimulates different sympatho-adrenal and hypothalamic-pituitary-adrenal axes with resulting renin and Ang II release (20). Ang II acts to preserve glomerular filtration during hypotension due to its preferential vasoconstrictor action on renal efferent arterioles, with consequent increase in intraglomerular pressure (5). In Figure 2, we have summarized the activation of RAAS during volume depletion. Considering high plasma catecholamine levels during refractory septic shock, several authors (14, 21) hypothesized that an exogenous infusion of additional Ang II could have a place in refractory septic shock treatment, facilitating catecholamine de-escalation and minimizing their adverse effects.

WHAT IS THE ROLE OF ANG II IN REFRACTORY SEPTIC SHOCK?

There is a paucity of published studies regarding the administration of Ang II in refractory septic shock; their heterogeneity (animal and human; case reports and observational studies; adult and pediatric), mono-centric design and the small number of patients included precludes any definitive conclusion. During refractory septic shock, we usually observe a vascular hyporesponsiveness to vasopressors. ''Decatecholaminisation'' is a well-defined phenomenon resulting from either α1-adrenergic receptor down-regulation or uncoupling of receptors from their intracellular messengers (22). Moreover, septic states are associated with decreased plasma vasopressin levels and down-regulated V1 receptor expression (22). However, this can usually be overcome by the exogenous administration of vasopressors, particularly catecholamines. In recent years, various studies analyzed the mechanisms responsible for reduced Ang II sensitivity during sepsis. AT-R1 and AT-R2 expression is influenced by cytokines and NO release during the inflammatory phase of sepsis (23, 24). In a murine model of sepsis (intravenous injection of lipopolysaccharide [LPS] to simulate gram-negative sepsis; injection of lipotheicoic acid [LTA] to simulate gram-positive sepsis) the expression of AT-R2 in the adrenal glands was strongly down-regulated by NO when compared with controls (40% decrease in expression for LPS group and 68% for LTA group) (23). Using a similar septic model, Bucher et al. (24) also showed down-regulation of AT-R1 in many organs (i.e., adrenal glands, liver, kidney, heart, and brain) induced by NO and pro-inflammatory cytokines, especially IL-1β, TNF-α, and INF-γ. Further *in vitro* studies on vascular smooth muscle cells confirmed that NO and pro-inflammatory cytokines synergistically down-regulate AT-R1 expression (25, 26). The specific mechanisms of dysfunction of AT-R1 in refractory septic shock had never been clearly investigated until a recent experimental German study (27). The authors showed that Arap1 (AT-R1-associated protein 1) could increase the expression of the AT-R1 on the cell surface; conversely, elevated Ang II levels could induce a marked down-regulation of Arap1, in an autoregulatory fashion, reducing the vasculature's sensitivity to Ang II as observed in sepsis. To confirm this hypothesis *in vivo*, the authors compared Arap1-knockout mice with wild-type mice in an experimental model of sepsis. After LPS injection, they found a significant down-regulation of Arap1 expression in wild-type mice and hemodynamic compromise in Arap1-knockout mice. Arap1 expression is dependent not only on Ang II levels but also on exposure to cytokines, as observed in isolated vascular smooth muscle cells (26, 27). Exogenous administration of Ang II could help overcome decreased vascular reactivity seen as a result of Arap-1-mediated AT-R1 down-regulation in sepsis. However, it could also be expected to further decrease AT-R1 expression through the same mechanism. As such, blocking the downregulation Arap-1 could be an alternative

therapeutic target. Availability of AT-R1 is not the only factor necessary for Ang II to be effective as a vasopressor in refractory septic shock. Once bound to its receptor, Ang II needs to engender improved hemodynamics and tissue perfusion. In an ovine model of sepsis, Ang II infusion (duration: 2–6 h, doses up to 450 ng/kg/min) did not increase cardiac output or renal blood flow (RBF) but the lack of significant macrohemodynamic improvement seen in this model compared with other studies could be explained by the absence of fluid resuscitation (28). Corrêa et al. (29) tested the hypothesis that Ang II can be used as a safe vasopressor without adverse effects on renal perfusion or mitochondrial respiration. Twenty domestic pigs were randomized to either a septic (fecal peritonitis, n = 16) or control group (n = 4). The septic group was further randomized to fluid resuscitation with NE (n = 8) or Ang II (n = 8) infusion. In the control group, the authors tested the effects of Ang II infusion in non-septic animals. In the septic group Ang II reversed sepsis-induced hypotension, while RBF did not differ between Ang II and NE. Exogenous Ang II did not deteriorate mitochondrial respiration, although it has been shown to have negative effects on mitochondrial function elsewhere (30).

Clinical studies

Paediatric—The current available literature regarding clinical use of Ang II is sparse. Recently, two pediatric case reports tested Ang II infusion in refractory septic shock (8). In the first case, a 4-year-old child with meningococcal infection was successfully treated by NE and Ang II (dose up to 0.32 μg/kg/min), after adequate fluid replacement therapy. In the second, the authors treated another patient with *Candida spp.* peritonitis using NE, epinephrine and Ang II. Ang II infusion (dose up to 0.8 μg/kg/min) appeared to permit discontinuation of epinephrine on day 3 and NE on day 7.

Adults—In a case report published in 1991 (31), the authors tested Ang II use in a woman with pneumococcal septicemia and subsequent refractory shock with myocardial dysfunction. Despite treatment with high doses of NE and inotropic support (dobutamine and dopamine) she remained in refractory hypotension. Ang II infusion was started initially at a rate of 5 μg/min and then increased to 20 μg/min with a rapid increase in MAP and a reduction of NE doses. A subsequent case report described the effective use of Ang II in a pregnant African lady with refractory septic shock secondary to Enterobacter cloacae pneumonia which led to ARDS and bacteremia (7). The authors started Ang II with a dose of 8 μg/min and increased the dose to a maximum of 22.5 μg/min. Interestingly, this patient suffered from lupus nephritis (7) and had been initially treated with labetalol for severe hypertension up until the time she developed septic shock. It is then likely that β-blocker therapy had blunted the systemic response to NE or that the hypertensive crisis had driven an over-activation of RAAS, leading to a predominant activity of this system over the catecholamine stimulation; these two conditions might have explained the clinical response to Ang II rather than NE. The most extensive clinical study on Ang II to date, the ATHOS study, is a phase II randomized controlled clinical trial, which analyzed the role of Ang II in the treatment of distributive shock and sought the optimal Ang II doses in this setting (32). Twenty patients with septic shock were randomized to receive either Ang II (n = 10) or placebo (n = 10). Ang II was infused at an initial dose of 20 ng/kg/min plus standard-of-care therapy for distributive shock (NE plus vasopressin or epinephrine). Ang II was administered for 6 h with hourly adjustments of doses (minimum 5 ng/kg/min; maximum 40 ng/kg/min) to achieve an MAP of 65 mm Hg. All but one patient received concurrent vasopressin at fixed doses (0.02–0.08 u/min) during the study. Compared with the placebo group, Ang II led to a significant reduction in NE requirements (mean hour-1 norepinephrine dose for placebo 27.6 ± 29.3 mcg/min versus 7.4 ± 12.4 mcg/min for Ang II, $P = 0.06$). After stopping Ang II, NE requirements rebounded to pre Ang II levels. The 30-day mortality for the two groups was similar for the Ang II cohort and the placebo cohort (50% vs. 60%, $P = 1.00$). Interestingly, two patients were exquisitely sensitive to Ang II causing hypertension on the minimum dose despite withdrawal of NE. This pilot study showed that Ang II was a safe vasopressor in high-output shock in addition to NE; Ang II also decreased NE doses and potential adverse effects of catecholamines infusion. Anyway, the single-center nature of the study and the small number of analyzed patients preclude any definitive conclusions and future large RCTs will be needed to confirm these preliminary results. Table 1 summarizes main studies on Ang II administration.

POTENTIAL ROLE OF EXOGENOUS ANG II IN SPECIFIC ORGAN DYSFUNCTION

Lungs

ACE is principally expressed in pulmonary capillaries (90%) (33). Patients with damaged pulmonary endothelium, such as in ARDS, could be expected to have decreased pulmonary capillary ACE activity, impairing Ang II production. Septic shock and ARDS frequently exist together, and a failure of the lungs to convert Ang I to Ang II could contribute to a state of refractory septic shock that might benefit from exogenous Ang II. However, Ang II may also aggravate lung function in ARDS (34); two animal studies showed that extra-vascular Ang II was increased in bronchoalveolar fluid during ARDS with an imbalance between Ang II (high concentrations) and Ang 1-7 (low concentrations) (35, 36). In one of the two studies, the authors also found that high dose of Ang 1-7 (60 μg/kg/h) reduced inflammatory cell numbers in bronchoalveolar lavage (35). Interestingly, in both studies continuous infusion of Ang 1-7 reduced lung fibrosis (35) and protected against experimental acute lung injury (36), suggesting a potential benefit from Ang 1-7 rather than Ang II infusion in this setting.

Kidneys

Ang II increases efferent renal arteriolar resistance greater than afferent renal arteriolar resistance, serving to increase the intra-glomerular pressure, decrease overall renal blood flow, and augment the filtration fraction (37). Our current understanding of renal blood flow, initially described by Bowman, suggests that all blood going to the renal medulla first passes through the glomerular tufts—and more specifically juxtamedullary glomeruli (38). The renal effects of Ang II could be

Table 1. **Studies on Ang II administration—endpoint of these studies: hemodynamic stabilization (MAP ≥65 mm Hg; decreased doses of NE)**

Authors	Type of study	Population	Models of sepsis	Dose of Ang II	Results
Yunge (8)	Pediatric case report	Two children, 4 y.o.	Meningococcal infection; candida peritonitis	Up to 800 ng/kg/min	Discontinuation of NE and EP
Wan (28)	Animal	Four sheep treated with Ang II	Intravenous injection of live *E coli*	Up to 450 ng/kg/min	No effect on CO and RBF
Correa (29)	Animal	Eight pigs treated with Ang II	Fecal peritonitis	Up to 27 ng/kg/min	↑CO, MAP, RP; no effects on MR
Thomas (31)	Human case report	Woman, 37 y.o.	Pneumococcal septicemia	8–31 ng/kg/min	↑MAP, ↓ NE dose
Chawla (32)	Adult; pilot study	10 patients	Distributive shock	5–40 ng/kg/min	↑MAP, ↓ NE dose

CO indicates cardiac output; EP, epinephrine; MAP, mean arterial pressure; MR, mitochondrial respiration; NE, norepinephrine; RBF, renal blood flow; RCT, randomized control trial; RP, renal perfusion.

expected to increase delivery of filtrate and solutes to the tubules with concurrent decrease in oxygen delivery to the medulla, which could worsen the VO_2/DO_2 ratio at the level of tubular cells in the medulla, favoring ischemia and acute tubular necrosis. However, the juxtamedullary glomeruli (the principal port of entry for blood traveling to the renal medulla) have specially adapted arterioles with a dampened response to Ang II compared with other glomerular arterioles (37) (e.g., an infusion of 5 ng/kg.min of Ang II increases efferent arteriolar blood flow resistance in juxta-medullary glomeruli of 0.025 units and in the cortical glomeruli of 0.128 units)—this mechanism could ultimately prevent undesirable renal ischemia and rather facilitate improved renal function in response to exogenous Ang II during septic shock. The kidneys are the driving organ for the systemic RAAS through renin production. In certain clinical situations, such as bilateral nephrectomy, where a deficit in renin production would be expected, exogenous Ang II could play a crucial role in resuscitating patients. In conclusion, the administration of Ang II should be not deleterious on kidney function.

Liver

Angiotensinogen is principally produced by the liver and its systemic levels are decreased in patients with cirrhosis (39). Although it has been hypothesized that a decreased effective circulating volume in cirrhotic patients leads to activation of RAAS, this has not been corroborated by clinical studies (40). A failure of the cirrhotic liver to produce angiotensinogen during refractory shock could lead to a potential benefit of exogenous Ang II administration in this sub-group of patients.

Brain

In patients with concurrent neurological diseases (i.e., neurodegenerative disorders; traumatic brain injury (TBI); ischemic stroke) and refractory septic shock Ang II administration could be deleterious. RAAS may be implicated in Alzheimer disease (41), neuronal injury, and cognitive disorders (42). In particular, AT-R1 activation could promote the generation of reactive oxygen species and neuroinflammation (43). Moreover, AT-R1 activation leads to glutamate excitotoxicity, apoptosis, cerebral infarction, and astrocyte proliferation (43). In a prospective study, 363 TBI patients were enrolled and genotyped for five tag single nucleotide polymorphisms across the ACE gene. The authors showed a possible influence of genetic variations in a specific region of the ACE gene on the outcome of TBI patients (44). In an experimental model of TBI, Villapol et al. (45) tested candesartan and telmisartan to prove their effects on cognition and motor performance. Both drugs ameliorated cerebral blood flow and reduced cortical impact-induced injury neuronal injury and apoptosis, astrogliosis, microglial activation, and pro-inflammatory signaling. Although these data may suggest a deleterious effect of Ang II administration on brain function, there is a need for additional experimental and clinical data, considering the different pathophysiology of these conditions (e.g., Alzheimer diseases, TBI) when compared with sepsis.

POTENTIAL PITFALLS WITH ANG II IN SEPSIS: A FOCUS ON MICROCIRCULATION

The encouraging findings of improved macro-circulatory hemodynamics and decreased catecholamine requirements after Ang II administration are offset by evidence of microcirculatory dysfunction that could result from high levels of Ang II. Previous data have shown that microcirculatory dysfunction is an independent predictor of mortality despite the normalization of global hemodynamic parameters (46). Refractory septic shock is associated with impaired microvascular flow, reduced capillary density, increased heterogeneity, and impaired oxygen extraction (4). Endothelial hyporesponsiveness to vasoconstriction and vasodilation, altered interactions between the endothelial surface and circulating cells, decreased glycocalyx size, microthrombi formation, and the activation of circulating cells (leukocytes, platelets, red blood cell deformability) are the most frequent causes for these findings (4). Various factors can further influence the development of microcirculatory dysfunction, including low tissular oxygen pressure, production of hypoxia-inducible factors, redox potential alterations, and, potentially, Ang II (4). In a prospective clinical observational study (47), the authors found a positive association between microcirculation dysfunction in sepsis and high Ang II levels. Early measurements of Ang II were also significantly higher in patients who died compared with survivors. On the other hand, Zhang et al. (48) showed in a Chinese cohort of patients that lower activation of RAAS and Ang II was associated with a worse outcome in severe sepsis. Interestingly, downstream metabolites of Ang II (e.g., Ang 1-7, Ang III, and Ang IV; Fig. 1) (48) may also cause vasodilation, inflammation, and endothelial dysfunction (49), although their assessment is technically more challenging and has not been performed in

clinical studies. Considering the potential negative implications of down-stream RAAS mediators on microcirculation, several authors have investigated the effects ACE-i and ARBs on microvascular perfusion in animal models. In experimental models of ischemia/reperfusion, administration of an ACE-i restored liver sinusoid perfusion (50) and reduced leukocyte adhesion in colonic venules, when compared with controls (51). In experimental models of endotoxemia, low dose of Ang II receptor blockers also improved regional mesenteric (52) and renal blood flow (53). Recently, Salgado et al. (54) hypothesized that enalapril could improve the microvascular perfusion in a clinically significant model of sepsis. One hour after injection of feces into the abdominal cavity, 16 adult female sheep were randomized (1:1) in enalapril receiving-group ($n = 8$, dose of 2.5 mg) or placebo group ($n = 8$). NE was administered when persistent hypotension occurs despite fluid resuscitation. The sublingual microcirculation was evaluated using sidestream dark-field videomicroscopy. The authors found a progressive and significant reduction in the proportion of small-perfused vessels and in the microvascular flow index for small vessels at the onset of septic shock; these alterations were prevented by the administration of enalapril. There were no differences between treated and placebo groups in global hemodynamic variables; however, enalapril worsened respiratory gas exchange and renal function in terms of increased creatinine levels, although blood urea or urine output was similar between groups. In a rabbit model of sepsis, perindopril prevented altered endothelium-dependent relaxation to acetylcholine induced but had no effects on histological changes of endothelial cells or on survival (55). In conclusion, Ang II could potentially enhance sepsis-related microcirculation; however, considering that increasing blood pressure is the main determinant of microvascular flow perfusion and the controversial data from experimental studies, this should be evaluated in clinical studies.

UNRESOLVED ISSUES

Various unresolved issues remain concerning Ang II in refractory septic shock. While the available literature heralds hope for the future role of Ang II in refractory septic shock, it is scant, of low quality and has likely been subject to publication bias. There is wide variation in the reported Ang II doses administered (Thomas et al. tested up to 20 μg/min while Chawla et al. administered up to 10 ng/kg/min)—a therapeutic index has yet to be established. Given these pluri-potent effects of Ang II, the optimal timing of initiation (early or late) could be important, but data regarding this is lacking. The pro-inflammatory, procoagulant, and deleterious microcirculation effects of Ang II and its metabolites justify concern about potential harmful effects. On one hand, microcirculatory dysfunction induced by exogenous Ang II infusion during refractory septic shock has never been studied in humans. On the other hand, ACE-i and ARBs have been tested only in experimental models of sepsis. In these studies, although enalapril and/or losartan improved microcirculation, they showed no beneficial effects on survival rate but worsened both renal function and respiratory gas exchange. The RAAS is multidimensional with complicated cascades, autoregulation, and interactions with other hormone systems. The strategy of exogenous Ang II administration may be overly simplistic; improving our understanding of downstream RAAS metabolites (e.g., Ang 1-7) could allow us to manipulate these fundamental homeostatic processes more to our advantage.

CONCLUSIONS

Refractory septic shock remains a serious challenge in critical care medicine. After adequate fluid resuscitation, Ang II has been proposed as an additional vasopressor when high doses of NE are required. The ATHOS study has shown promising results when Ang II is added to NE in the management of distributive shock; however, this is a pilot study performed in a small cohort of patients and the positive findings should be confirmed by large RCTs. Given its potent vasoconstrictor effects through AT-R1, exogenous administration of Ang II is likely going to continue to show improvements in mean systemic arterial blood pressure and reduce individual patient's catecholamine requirements. However, whether this will translate into improved patient outcomes remains unclear, particularly given the complex, and potentially deleterious, effects of Ang II and its metabolites at a tissue, microcirculation, and cellular level. Future large RCTs should aim to identify: the role of Ang II in the management of refractory shock especially when compared with other vasopressors (epinephrine, vasopressin), the optimal doses of Ang II, which patient sub-groups are most likely to benefit from Ang II, optimal timing of Ang II administration, and the adverse effects related to exogenous Ang II infusion, particularly on the microcirculation.

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