REVIEW | *The Pathophysiology of COVID-19 and SARS-CoV-2 Infection*

Role of the renin-angiotensin system in the development of severe COVID-19 in hypertensive patients

Rodrigo Pacheco Silva-Aguiar,[1]* Diogo Barros Peruchetti,[1]* Patricia Rieken Macedo Rocco,[1,2,3] Alvin H. Schmaier,[4,5] Patrícia Machado Rodrigues e Silva,[3,6] Marco Aurélio Martins,[3,6] Vinícius Frias Carvalho,[3,6] Ana Acacia Sá Pinheiro,[1,3] and Celso Caruso-Neves[1,2,3]

[1]*Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil;* [2]*National Institute of Science and Technology for Regenerative Medicine, Rio de Janeiro, Brazil;* [3]*Rio de Janeiro Innovation Network in Nanosystems for Health-NanoSAÚDE/Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Rio de Janeiro, Brazil;* [4]*Case Western Reserve University, Cleveland, Ohio;* [5]*University Hospitals Cleveland Medical Center, Cleveland, Ohio; and* [6]*Laboratory of Inflammation, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil*

Silva-Aguiar RP, Peruchetti DB, Rocco PRM, Schmaier AH, e Silva PMR, Martins MA, Carvalho VF, Pinheiro AAS, Caruso-Neves C. Role of the renin-angiotensin system in the development of severe COVID-19 in hypertensive patients. *Am J Physiol Lung Cell Mol Physiol* 319: L596–L602, 2020. First published August 12, 2020; doi:10.1152/ajplung.00286.2020.—A new form of severe acute respiratory syndrome (SARS) caused by SARS-coronavirus 2 (CoV-2), called COVID-19, has become a global threat in 2020. The mortality rate from COVID-19 is high in hypertensive patients, making this association especially dangerous. There appears to be a consensus, despite the lack of experimental data, that angiotensin II (ANG II) is linked to the pathogenesis of COVID-19. This process may occur due to acquired deficiency of angiotensin-converting enzyme 2 (ACE2), resulting in reduced degradation of ANG II. Furthermore, ANG II has a critical role in the genesis and worsening of hypertension. In this context, the idea that there is a surge in the level of ANG II with COVID-19 infection, causing multiple organ injuries in hypertensive patients becomes attractive. However, the role of other components of the renin angiotensin system (RAS) in this scenario requires elucidation. The identification of other RAS components in COVID-19 hypertension may provide both diagnostic and therapeutic benefits. Here, we summarize the pathophysiologic contributions of different components of RAS in hypertension and their possible correlation with poor outcome observed in hypertensive patients with COVID-19.

angiotensin II; COVID-19; hypertension; renin-angiotensin system; SARS-CoV-2

INTRODUCTION

In early December 2019, a new form of severe acute respiratory syndrome (SARS) caused by a new virus, SARS-coronavirus-2 (CoV-2), was characterized in Wuhan and called COVID-19 (82). In addition to previously identified SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is the third coronavirus identified to replicate in the human lower respiratory tract (44). SARS-CoV-2 has higher transmissibility rate and greater adaptability to different environments, making the spread of this virus more difficult to contain and a greater threat to humanity.

The role of the renin angiotensin system (RAS) in the pathogenesis of COVID-19 begins with the observation that angiotensin-converting enzyme 2 (ACE2) is the respiratory membrane receptor of SARS-CoV-2 (20). Further, ACE2 is considered to be the major enzyme degrading ANG II into angiotensin (1–7) (ANG-(1–7) (63, 64, 68). It is proposed that in patients infected with SARS-CoV-2, an acquired deficiency (i.e., inhibition) of ACE2 occurs, resulting in an increase in ANG II (5). However, these events probably do not occur in isolation and may be associated with additional modifications in renin-angiotensin system (RAS) components, contributing to the overall pathophysiology of COVID-19 infection. In the present review, we highlight the possible participation of different components of RAS as an integrating system connecting undesirable worsening of COVID-19 with hypertension.

HYPERTENSION IS A RISK FACTOR FOR THE DEVELOPMENT OF SEVERE COVID-19

Epidemiologic data have demonstrated that hypertension is a pivotal comorbidity related to increased susceptibility to the

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* R. P. Silva-Aguiar and D. B. Peruchetti share first authorship.
Correspondence: C. Caruso-Neves (caruso@biof.ufrj.br).

severe form of COVID-19. In a follow-up study of 168 patients in China, Xie et al. (74) showed that hypertension was the most common comorbidity associated with COVID-19 mortality. In a meta-analysis, Zhao et al. (81) compiled data on ~56,000 patients affected by COVID-19. Hypertension was present in ~19% of all patients hospitalized and was correlated with a higher risk of COVID-19-related mortality. A meta-analysis of several scientific databases report showed that hypertensive patients have up to 2.5-fold higher risk of developing severe or fatal COVID-19 (30). Since RAS is the central biochemical pathway involved in hypertension (41, 54), it remains unclear to what extent this system contributes to the undesirable worsening of COVID-19 in hypertensive patients.

ANGIOTENSIN II AND CORONAVIRUS INFECTION: IS THERE A CAUSAL RELATIONSHIP?

There are two different types of RAS, systemic and tissue, that are activated by distinct signals and have different roles under physiologic and pathophysiologic conditions (41, 54). The production of ANG II in pulmonary vessels accounts for most of the circulating peptide. On the other hand, the synthesis of ANG II in extra-pulmonary tissues works to amplify its systemic level (4). Liu et al. (33) showed the level of ANG II in plasma was increased in patients with COVID-19 and was associated with lung injury. Based on the current knowledge obtained from other respiratory viruses, it is possible to propose a causative relationship among RAS, hypertension, and COVID-19.

Role of Plasma Renin Activity

Plasma renin activity (PRA) is used to predict the prognosis of hypertensive patients and determining the therapeutic approach. Essential hypertension can be stratified into two categories based on PRA: those with low PRA and those with normal-to-high PRA. Genest et al. (15) analyzed PRA and its correlation with cardiovascular complications in different types of hypertension, including essential and secondary hypertension. They observed that patients with higher PRA are at higher risk for developing severe cardiovascular complications. In line with this idea, Verma et al. (67), in the Heart Outcomes Prevention Evaluation (HOPE) study, observed that high PRA is an independent predictor for vascular damage and mortality in patients with atherosclerosis and diabetes. Based on these observations, we believe that determination of PRA in both hypertensive and nonhypertensive patients with COVID-19 would be a useful marker to indicate those with a worse prognosis to guide treatment decisions for the best therapeutic approach.

Role of ACE and ACE2

An interrelationship between ANG II level and ACE2 activity in SARS-CoV infection was initially proposed by Kuba et al. (28) using a murine model. They showed that the level of ANG II in the lung was increased after intravenous infusion of S spike protein from SARS-CoV, which correlated with inhibition of ACE2 activity and induction of lung injury. Sriram and Insel (60) proposed that inhibition of ACE2 by SARS-CoV-2 binding leads to imbalance in the action of ACE- and ACE2-derived peptides, ANG II and ANG-(1–7), respectively, and could be involved in the pathogenesis of COVID-19. In

addition, the possible specific positive modulation of ACE activity mainly in hypertensive patients stricken by COVID-19 should be taken as an attractive possibility.

Deletion of ACE2 worsened lung injury in a murine model of H7N9 infection (79). Treatment with recombinant human ACE2 (rhACE2) improved acute lung injury in mice induced by acid aspiration or sepsis (23). Furthermore, a human soluble ACE2 binds to SARS-CoV-2 and inhibits the infection rate to 1,000–5,000 times in engineered organoids of human blood vessels and human kidney (39). Plasma ANG II level is increased in patients infected with H7N9 and H5N1, followed by a decrease in ACE2 activity, with no change in ACE activity (21, 84). Further, ACE activity increased and ACE2 decreased in the bronchoalveolar lavage fluid of animals and patients with acute respiratory distress syndrome (ARDS) (52, 70, 71). Thus, it can be hypothesized that, with a decrease in ACE2 followed by SARS-CoV-2 infection, ANG II would increase.

This idea is reinforced by the observation that influenza A H5N1 decreases ACE2 lung expression and enhances plasma ANG II levels in mice (84). Although, it is worth mentioning that unlike the SARS-CoV-2 virus, H5N1 infection is not mediated by ACE2, but RAS is involved in the pathogenesis of the ARDS as well. In addition, plasma ANG II levels is associated with disease severity in H7N9-infected patients (21). These observations indicate that RAS dysregulation could be a general mechanism associated with ARDS caused by different etiologies, including COVID-19, even with important differences among pathogenesis of distinct viral infections.

The interrelationship of ACE and ACE2 in the pathogenesis of essential hypertension has been proposed previously (22, 49). ACE2 has a protective role against the development of hypertension because it breaks down ANG II (54, 63), producing ANG-(1–7), which has cardioprotective effects (26). Thus, not only an increase in ANG II but also the loss of ANG-(1–7) could be involved in the development of hypertension. Although ACE expression is unaltered or increased in hypertensive animals, hypertension progression is associated with decreased ACE2 expression in the kidney and heart in hypertensive patients and animal models (11, 27, 45, 62).

Pharmacologic approaches aimed to increase the ACE2/ANG-(1–7) axis reduce blood pressure in spontaneously hypertensive rats (SHR) (11, 34) and attenuate cardiac dysfunction in ANG II-induced hypertension (83). An autopsy study of 20 patients diagnosed with hypertensive nephropathy or cardiomyopathy revealed a decrease in ACE2 expression in kidney, whereas ACE expression was increased in the kidney and heart (27). Little is known regarding the expression of ACE and ACE2 in the lung of hypertensive patients or animals.

The expression of ACE2 in specific tissues is also modulated by its shedding mediated by TNF-α converting enzyme (TACE)/ADAM-17, which is increased by ANG II (25, 43). TACE/ADAM-17 is involved in cardiovascular hypertrophy and perivascular fibrosis in a model of hypertension induced by ANG II in C57BL/6 mice (61). These findings indicate positive feedback between ACE2 inhibition and increased cardiac ANG II levels. Further, plasma ACE2 activity is an independent predictor of major adverse events in cardiac obstructive coronary disease and correlates positively with systolic blood pressure in patients with diabetes (47, 59).

TACE/ADAM-17 knockdown decreased SARS-CoV infection in human embryonic kidney 293T (HEK293T) cells (19). Based on the similarities between SARS-CoV and SARS-CoV-2 infection, we may speculate that ANG II increases entry of the virus into the target cell despite the lower expression of ACE2 at the cell membrane. This assessment is supported by the clinical observation that the severity of COVID-19 is not necessarily correlated to a high viral load (32), suggesting a pivotal role of the host response to the initial viral replication and the environment. In agreement, Xie et al. (75) showed age-related loss of ACE2 in the lungs. Despite this, increased mortality and worsened phenotype has been observed in elderly patients with COVID-19 (30).

Together, the findings suggest that ACE2 expression in the lung might contribute to increased infection rate of SARS-CoV-2. This process is followed by a decrease in ACE2 expression, leading to an increase in ANG II levels. On the other hand, the decreased ACE2 expression in the kidney and heart in hypertensive patients, could contribute to a further increase in plasma and/or tissue ANG II, a response possibly associated with an undesirable outcome in patients stricken by COVID-19. In addition, activation of TACE/ADAM-17 could be involved in the exacerbation of inflammation noted in COVID-19, due to increased shedding of pro-TNF-α and consequently increased concentrations of soluble TNF-α in the plasma.

Beyond ACE and ACE2: Role of Prolylcarboxypeptidase and Prolyl Oligopeptidase

Other proteases such as prolylcarboxypeptidase (PRCP) and prolyl oligopeptidase (POP), also called prolyl endopeptidase, may contribute to the surge in the level of ANG II in COVID-19 because they also cleave after Pro-X COOH-terminal peptide bonds like those in ANG II (52, 57). These serine carboxypeptidases have broad expression among the primary target tissues affected by COVID-19 and hypertension (12, 40). It is well established that these peptidases are present in cell membranes and lysosomes (58). PRCP has been called lysosomal carboxypeptidase because it was first discovered in the lysosomal fraction of kidney. It has been shown to be widely distributed by cell membranes (1, 55). It is also prominent in kidney and the hypothalamus in the brain (1, 69). POP function is better understood in the brain, where it correlates with inflammation in neurodegenerative diseases, but its role in the development of hypertension is still poorly defined (3). This enzyme is also highly expressed in lung, kidney, liver, and spleen, all of which are strongly associated with the pathogenesis of COVID-19 (12, 40). Recently, Serfozo et al. (53) proposed that POP is the main enzyme responsible for the conversion of ANG II into Ang-(1–7) in the systemic circulation, whereas ACE2 is more prominent in the lung and kidney, suggesting the potential involvement of POP as a determinant of the ANG II level in tissues infected by SARS-CoV-2. Nevertheless, its role in hypertension and its correlation with the severe form of COVID-19 have not yet been determined.

PRCP polymorphism (E112D) is associated with hypertension, and its expression is reduced in renovascular hypertensive rats (80). Recently, a novel polymorphism (rs12290550) was found to be associated with essential hypertension in a discrete Chinese ethnic group (72). PRCP gene trap mice (PRCP$^{gt/gt}$)

constitutively have a small, but significant, increase in blood pressure. Their vessels express increased reactive oxygen species (ROS), and cardiac hypertrophy and renal glomerular tubulization are observed. These animals also have a constitutive higher risk of induced arterial thrombosis (1, 36). Furthermore, Marangoni et al. (37) proposed that reduction in PRCP expression is associated with the SHR phenotype, a response not reversed by treatment of SHRs with the angiotensin type 1 receptor blocker (ARB) losartan. This finding is an indication that modification in PRCP expression seems to be a cause rather than a consequence of an increase in the tissue level of ANG II.

In kidney, ACE2 is the dominant ANG II-cleaving peptidase. However, in $ace2^{-/-}$ kidney, ANG-(1–7) is still produced by PRCP (18). At low pH in the kidney, however, PRCP is the dominant ANG II-degrading enzyme (18, 53). Because PRCP is expressed in the luminal membrane of renal proximal tubule, and this segment has a great capability to secrete H^+, it is plausible to postulate that acidic microdomains, such as the space between microvilli of the brush border, can strongly favor the activity of this enzyme. Furthermore, PRCP cleaves ANG II in the distal nephron segments, where the luminal pH is acidic (36). However, the significance of these observations in the development of hypertension and susceptibility to severe COVID-19 is still an open matter.

One crucial clue comes from the observation that PRCP has an important effect on thrombosis and endothelial function (1). A reduction in PRCP levels ($prcp^{gt/gt}$ mice) is associated with a prothrombotic state and increase in ROS, which, in turn, leads to endothelial dysfunction and loss of anticoagulant properties. Curiously, these phenomena are similar to that observed in patients with severe COVID-19 (16). It is possible that hypertensive patients may have a decrease in the expression of PRCP in endothelial and renal cells, which make them more susceptible to severe COVID-19. In addition to this pathway, PRCP could contribute to COVID-19 pneumonia because it is a plasma prekallikrein (PK) activator to form plasma kallikrein (PKa) (51, 55, 73). The PKa formed cleaves high molecular weight kininogen to liberate bradykinin, which alone or when degraded by other carboxypeptidases to form des-Arg-BK, binds to bradykinin B2 and B1 receptors to stimulate the local edema seen in COVID-19 pneumonia. This topic is discussed further in other studies (65, 66).

Finally, there is a third possible mechanism whereby PRCP can contribute to hypertension. PRCP in the hypothalamus degrades α-melanocyte-stimulating hormone (α-MSH) so that it cannot stimulate the melanocortin 4 receptor to induce satiety and increase blood pressure (17, 69). In PRCP deficiency states, there is less degraded α-MSH binding to the melanocortin 4 receptor, leading to thin, hypertensive individuals (1, 69).

AT$_1$R Mediating ANG II Effects During COVID-19 Progression

ANG II exerts its main effects through the angiotensin II type 1 receptor (AT$_1$R), which belongs to the G protein-coupled receptor family and is a target for specific blockers (angiotensin type 1 receptor blockers, ARBs) in several diseases (14). The AT$_1$R-mediated effects of ANG II include vasoconstriction, inflammation, and fibrosis (42). Several stud-

ies indicate a potential role of the ANG II/AT_1R pathway in tissue damage caused by infections such as H7N9 and H5N1, as well as SARS-CoV and SARS-CoV-2 (21, 78, 84). Consistent with this interpretation, Kuba et al. (28), also showed that lung injury caused by SARS-CoV S protein infection in a murine model is attenuated by the ARB losartan.

There is consensus that an enhanced circulating level of IL-6 is a major hallmark of the profound inflammatory state seen in patients with COVID-19 associated with undesirable outcome (31). In addition, the use of cytokine-modulatory therapies, especially anti-IL-6 agents, for critically ill patients with CO-VID-19 offer a perspective to its treatment (2). In agreement, a phase 3 clinical trial is currently being performed (35). Nevertheless, the cost of and access to anti-IL-6 is a concern, especially as the numbers of cases worldwide continue to climb. On the other hand, Meng et al. (38) demonstrated that in hypertensive patients with COVID-19 treated with an ACE inhibitor/ARB, the levels of IL-6 decreased in peripheral plasma and was associated with a better outcome. Therefore, these drugs have potential to be a successful strategy for the treatment of COVID-19 provided the cost is not prohibitive. Furthermore, the use of an ARB could be beneficial for COVID-19 not only for inhibiting the proinflammatory actions of the ACE/ANG II/AT_1R axis but also for inducing the anti-inflammatory actions of the ACE2/ANG (1–7)/MASR axis, which increases IL-10 levels (24). In addition, the use of an ACE inhibitor could be useful to the increase the level of ANG-(1–7) because it is well known that ACE cleaves ANG-(1–7) into ANG-(1–5) (48). In agreement, two trials on patients with COVID-19 are ongoing, one evaluating the therapeutic effect of rhACE2 (NCT04335136) and the other verifying the effect of intravenous ANG-(1–7) (NCT04332666).

The ANG II/AT_1R pathway appears to be involved in the proinflammatory response in hypertensive patients and animal models (9, 29, 50). In essential hypertensive patients, AT_1R gene expression is increased in leukocytes, including T cells (7, 8). Increased AT_1R mRNA expression was detected in isolated adipocytes obtained from obese hypertensive patients compared with obese patients who were not hypertensive (13). Finally, AT_1R (A1166C) gene polymorphism correlates with essential hypertension (6). Based on these findings, it is possible that a change in the expression or sensitivity of AT_1R to the ANG II response in hypertensive patients may correlate with worse outcome in patients with COVID-19. How does ANG II increase COVID-19 susceptibility to a severe outcome?

Preexposure of ANG II is known to sensitize different tissues to a hyperresponsiveness to further ANG II exposure. In mice, preexposure to a low pressor dose of ANG II leads to an exacerbated hypertensive response to additional exposition to ANG II (77). This effect was correlated to the increase in mRNA expression of ANG II receptors, renin, angiotensinogen, and the increase in ACE/ACE2 ratio in the brain. RAS hyperresponsiveness is similarly sensitized by a high-fat diet (76). The authors showed that a high-fat diet upregulated RAS components in the brain. Furthermore, it has been shown that ANG II, through AT_1R, induces a proinflammatory, hyperresponsive phenotype, including in infectious diseases such as malaria (56, 57, 85).

These observations are in accordance with data showing that patients with COVID-19 display lung T-cell infiltrate, with positive markers of exhaustion, likely caused by a hyperinflammatory stimulus (10). In addition, heterodimers between AT_1R with bradykinin receptors, AT_2R, or Mas may also alter
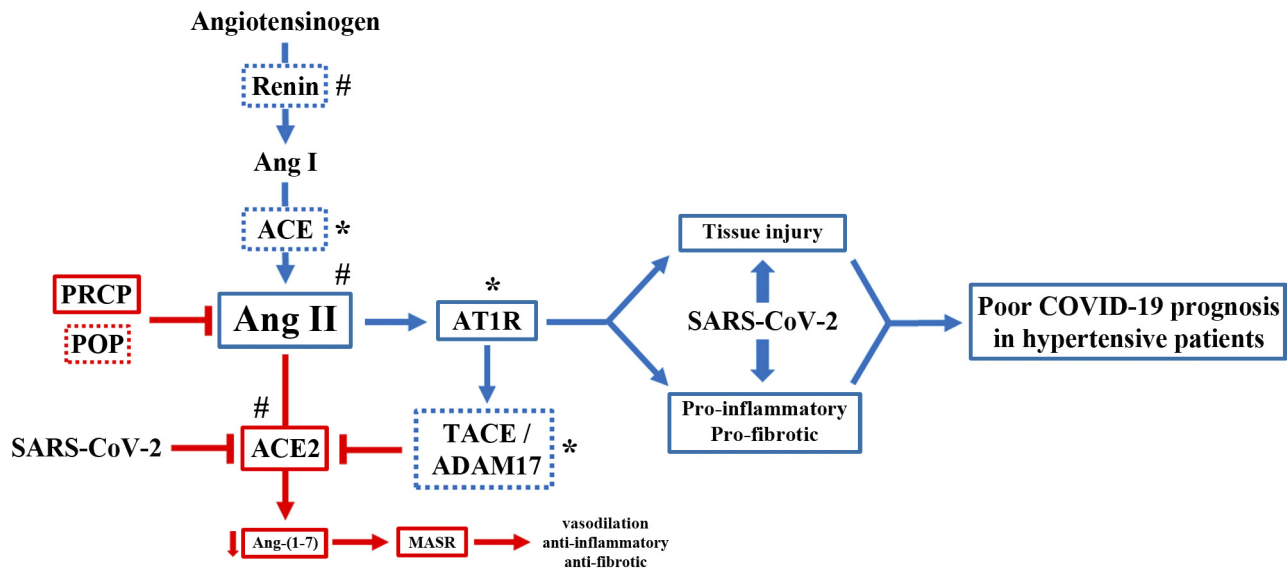

Fig. 1. Proposed model to explain why hypertensive patients with coronavirus disease 2019 (COVID-19) progress to an undesirable outcome. In hypertensive patients with COVID-19, we propose that there is a further increase in the level of ANG II as well as higher responsivity of angiotensin II type 1 receptor (AT_1R) to ANG II. The increase in the level of ANG II could be due to 1) a decrease in ANG II degradation by angiotensin-converting enzyme 2 (ACE2), prolylcarboxypeptidase (PRCP), and prolyl oligopeptidase (POP). ANG II could also decrease tissue ACE2 expression by increasing TNF-α converting enzyme (TACE)/ADAM17-mediated shedding, creating a positive feedback; 2) an increase in ANG II synthesis caused by an increase in renin and ACE activities. In addition to the increase in the level of ANG II, we also propose that the increase in expression and/or hyperresponsiveness of AT_1R in hypertensive patients could potentiate the effect of ANG II on different tissues affected by COVID-19. In this context, the inhibition of AT_1R could be a primary or coadjutant therapy for the treatment of patients with COVID-19. In agreement, a clinical trial of treatment with losartan is under way (NCT04328012). Red outline denotes reduced hypertension; blue outline denotes increased hypertension; dashed red outline denotes possible reduction in hypertension; dashed blue square denotes possibly increase in hypertension. *Possible therapeutic target; #possible biomarker.

ANG II binding to AT_1R and subsequent signaling, as has been reported in preeclampsia (46). In this way, tissue ANG II could be an additional link between hypertension and severe COVID-19, functioning as an initial sensitizer, shifting the system toward a harmful phenotype, and thus contributing to the worsening of the disease noted in patients with COVID-19.

SUMMARY AND PERSPECTIVES

In conclusion, we postulate that there are several possible interaction points between hypertension and COVID-19, forming a dangerous cascade of events that could be responsible for the poor outcome of hypertensive patients with COVID-19 (Fig. 1). In this review, we have described at least three possible points of interaction between hypertension and CO-VID-19: *1*) degradation of ANG II by different carboxypeptidases; *2*) synthesis of ANG II; and *3*) hypersensitization and/or increase in the expression of AT_1R. All of them are associated with the ACE2/ANG-(1–7)/MASR pathway. The interaction of these pathways may form an amplifying loop able to upregulate ANG II levels to explain why hypertensive patients are more susceptible to the severe form of COVID-19. In addition, when hypertensive patients are stricken by COVID-19, there could be stimulation of the cellular pathways triggered by a presensitized AT_1R, leading to a more intense proinflammatory response and tissue injury.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.P.S.-A., D.B.P., and C.C.-N. prepared figure; R.P.S.-A, D.B.P. and C.C.-N. drafted manuscript; R.P.S.-A., D.B.P., P.R.M.R., A.H.S., P.M.R.S., M.A.M., V.F.C., A.A.S.P., and C.C.-N. edited and revised manuscript; and R.P.S.-A., D.B.P., P.R.M.R., A.H.S., P.M.R.S., M.A.M., V.F.C., A.A.S.P., and C.C.-N. approved final version of manuscript.

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