LETTER TO THE EDITOR

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Renin, a prognostic marker to watch out for in cardiac surgery!

The renin-angiotensin-aldosterone system (RAAS) has drawn considerable limelight over the past years, being ardently researched across diverse pathophysiological scenarios. The recent literature on its' role in vasoplegic syndrome (VS), acute kidney injury (AKI) and sepsis is particularly captivating.[1] This opens newer avenues in refining our management of the cardiac surgical cohort who can be particularly predisposed to VS, AI and sepsis, owing to the baseline high-risk profile, the complex surgical procedures, and the extracorporeal circulation (cardiopulmonary bypass, or CPB): a "physiological-trespass".[2]

In the most fundamental sense of the matter, activation of RAAS results in the formation of angiotensin-I from angiotensinogen, promoted by renin. Subsequently, angiotensin-I is acted upon by angiotensin-converting-enzyme (ACE) present in the pulmonary and the renal endothelium to be converted to angiotensin-II. Angiotensin-II herein binds to receptors on smooth muscle cells, resulting in vasoconstriction. Derangements such as acute respiratory distress syndrome or pneumonia, which could impair the conversion process, results in the accumulation of angiotensin-I, which when subsequently degraded into angiotensin 1-7 and angiotensin 1-9, act as potent vasodilators. These vasodilators in turn affect renal perfusion, triggering the release of renin via a biofeedback mechanism. Hence, the renin levels tend to follow an increasing trend in face of a refractory hypotension in pathophysiological conditions impairing RAAS.[1,3-5]

The aforementioned explains why renin is increasingly being employed to predict prognosis and mortality in vasodilatory shock patients of varied aetiology.[1,3-5] As an extension of the same, in a trial on Angiotensin-II for Treatment of High Output Shock (ATHOS 3) by Khanna et al, the research group proposes angiotensin-II as an effective modality for the management of refractory vasodilatory shock.[4] Similarly, Bellomo et al in a post-hoc study of the ATHOS 3 cohort, discovered markedly elevated renin in catecholamine-resistant vasodilatory shock and a significant reduction in 28-day mortality following administration of angiotensin-II over standard-of-care therapy (hazard ratio: 0.56; 95% CI: 0.35-0.88; p=0.012).5 The ATHOS 3 and its' post-hoc analysis portrays a promising therapeutic role of the RAAS pathway in vasodilatory shock.

In the specific context of renin in cardiac surgery, Montgomery et al found that the plasma renin levels in patients who developed post-CPB VS reached levels 3 times higher than in the rest of the cohort.[6] At the same time, Küllmar et al studied the association of plasma renin with hypotension and AKI in cardiac surgical patients. They outline that the patients with an elevated difference in the pre-operative and postoperative renin levels had a higher incidence of AKI (43% versus 12.2%, p<0.001) and interestingly, this

subset manifested lower systemic pressures with a prolonged need for inotropic support and increased length of intensive care unit-hospital stay.[7] Meersch et al also retrospectively found that post-cardiac surgery hyperreninemia is intricately related to hemodynamic instability wherein the renin elevation responded to angiotensin-II alongside reduction of the concurrent norepinephrine usage.[8]

There are various mechanisms implicated in disruption of the RAAS pathway following CPB which include: endothelial dysfunction or polymorphism of the ACE gene, bypassing the pulmonary vasculature and, direct inflammatory insult of pulmonary endothelial damage owing to extracorporeal circulation.[1-8] These mechanisms are possibly at the heart of an association between the raised renin levels and VS-AKI following CPB. Simultaneously, the Gleeson et al depiction of insignificant influence of diurnal variation, continuous renal replacement therapy or RAAS-related drugs, on the plasma renin in a heterogeneous population, is equally encouraging.[9] Moreover, Jeyaraju et al propose the prognostic superiority of the renin-kinetics in comparison to the lactate-kinetics in a setting of critically-ill patients on vasopressors.[10] They discovered a positive rate of change in renin concentration levels greater than 40 pg/mL to be linked with the resultant mortality. They additionally concluded that, with every unit rise in the slope of log-renin, the odds of in-hospital mortality increase considerably by 10 times.10

It is indeed the time to attempt applying our growing knowledge of the RAAS into prognostically and therapeutically relevant decisions. On one hand where it can aid in identifying the at-risk patient population, on the other hand it may also assist "timely-interventions" aimed at improving cardiac surgical outcomes. Nonetheless, future well-designed randomized controlled trials are warranted to truly characterize the benefits of targeted therapies in cardiac surgical subset manifesting a high plasma renin activity.

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