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Editorial

Open arteries and pandemic viruses: Tackling today's clinical conundrums for the future of cardiology

Merriam Webster defines a conundrum as "an intricate or difficult problem" or "a question…having only a conjectural answer" [1]. With the growth in our knowledge over the last 50 years, Cardiologists confront far fewer clinical conundrums than our predecessors did. When a patient presents with symptoms of an acute MI, for example, in the majority of cases, we understand the cause and know the optimal treatment pathway based on the results of numerous large phase III clinical trials. Likewise, for heart failure, whether the ejection fraction is reduced or preserved, we have a wealth of clinical data to guide therapeutic decisions to help our patients get better and live longer. But, despite everything we have learned, there are still times when even Cardiologists are left with clinical uncertainty. Identifying and understanding our knowledge of two clinical uncertainties in Cardiology was the impetus for this special issue, "Conundrums in Cardiology".

The first topic relates to a condition we know well: coronary ischemia. And while we understand the mechanism and optimal treatment strategies for patients with chest pain due to obstructive atherosclerotic coronary disease, we often struggle with patients who present with symptoms of angina or myocardial infarction, but whose coronaries are free of apparent flow-limiting obstructive disease. Whether manifest as angina with open coronary arteries (ANOCA), ischemia with open coronary arteries (INOCA), or myocardial infarction without obstructive coronary artery disease (MINOCA), these patients are a conundrum to most Cardiologists. As Dr. Carl Pepine describes in his review of these conditions, the traditional opinion that they are "benign" is incorrect. With our lack of understanding and dearth of treatment options these patients suffer in terms of recurrent episodes that lead to an impaired quality of life, repeat hospitalizations, and in the case of MINOCA, increased mortality, with adverse event rates approaching those of patients with traditional MI [2]. While these patients are often told their arteries are "normal" or "clean" on cardiac catheterization, the review by Bakhshi and Gibson explains that coronary angiography is not sufficient to make a diagnosis in these patients [3]. Instead diagnosis requires a systematic approach, with careful review of the angiographic images to detect subtle findings, and a low threshold for additional imaging using intravascular ultrasound (IVUS) or optical coherence tomography (OCT). In some cases, additional testing for microvascular dysfunction and coronary vasospasm is indicated, as is cardiac MRI to assess the myocardium. It is only through such a methodical approach that one can hope to identify the underlying etiology to allow for a targeted treatment strategy. Unfortunately, our ability to diagnose the cause of a patient's open artery ischemia is more advanced than our ability to manage it. The mainstay of therapy for most causes of open artery ischemia are traditional medications, such as vasodilators and antiplatelet agents. The final article in this section a review by Henry et al., however, suggests new therapies, particularly CD34+ cells to promote angiogenesis, are on the horizon [4]. Finally, perhaps the biggest conundrum related to open artery ischemia is why these conditions predominantly affect women. It suggests a fundamental difference in vascular biology between the sexes that deserves further study.

The other focus of this special issue is the challenge of treating patients with COVID-19. While our understanding of the pathophysiology of this novel virus has exponentially increased since it first appeared in 2019, the negative effects it has on the heart and vasculature remain incompletely understood. Thankfully, evolution of the virus and development of vaccines have blunted cardiovascular morbidity and mortality, yet it seems inevitable that we will face future pandemics where lessons learned from COVID-19 might be employed. In the first article in this section Pareek et al. show the prognostic value of elevated high sensitivity troponin levels in patients hospitalized with COVID-19 in Denmark. The incidence of myocardial injury was high: 56 % of patients had elevated cardiac enzymes, which was associated with a greater than two-fold increase in mortality compared to patients without cardiac enzyme elevation [5]. Not surprisingly, patients with elevated cardiac enzymes were more likely to be older and have a history of cardiovascular disease, but in an adjusted analysis, the risk of mortality remained significantly higher in those with elevated cardiac enzymes compared to those who did not. The conundrum to this study comes in the fact that despite elevated cardiac enzymes, very few of these patients were thought to have a true MI, as evidenced by <4 % of patients undergoing invasive angiography or percutaneous coronary intervention. The etiology of the cardiac injury induced by COVID-19 in some patients and how this in turn leads to an increase in mortality remains poorly understood, but one can imagine that future pandemic viruses could have similar effects. In the second article, Lazzeri et al. show how the use of echocardiography to assess right ventricular function can help predict which patients with acute respiratory distress syndrome (ARDS) due to COVID-19 infection will fail non-invasive ventilation and require intubation [6]. While this study was specific to patients with COVID-19, the "lessons learned" almost certainly can be applied to patients with non-COVID ARDS. With increasing use of extracorporeal membrane oxygenation (ECMO) and right ventricular hemodynamic support, it is critical to have criteria we can use to help determine who will benefit most from mechanical circulatory support, which can save lives, but also carries significant risk of device-related complications.

In summary, many young physicians in training choose Cardiology because the pathophysiology of the conditions we commonly treat are now well understood, allowing us to address the cause and have the

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satisfaction of seeing patients with life-threatening illnesses get better quickly. Yet it is important to remember that for our predecessors, the conditions we now treat routinely were once clinical conundrums with few options for therapy. Only by taking a methodical approach to understand the underlying cause and develop targeted therapies did we reach the current state of clinical cardiology. Only by taking the same approach to the clinical conundrums we face can we ensure our successors have time to focus on their own challenges.

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Peter V. Johnston
Johns Hopkins University School of Medicine, Department of Medicine, Division of Cardiology, Baltimore, MD, USA
E-mail address: pjohnst1@jh.edu.