JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 2, 2021

EDITORIAL COMMENT

Modeling Acute Pericarditis

An Inflammatory Step Toward Tailored Therapeutic Strategies*

Jean-Sébastien Silvestre, PhD

Pericarditis refers to the inflammation of the pericardial layers and can be categorized as acute, incessant, recurrent, or chronic. Among the different types of pericarditis, acute pericarditis is diagnosed in ~0.2% of all cardiovascular in-hospital admissions and accounts for 5% of intensive care unit admittances for chest pain in Western Europe and North America (1). Acute pericarditis is characterized by an intense immune-inflammatory reaction involving the pericardium, mostly ensuing in healthy persons as a unique symptom or as a sign of a systemic disease. Its clinical diagnosis is based on 4 major criteria, including chest pain, pericardial friction rub, electrocardiogram changes, and new or worsening pericardial effusion. Activation of inflammatory entities and imaging-based evidence of pericardial inflammation also guide the diagnosis and the monitoring of the disease evolution (2). Despite various efforts for identifying an exact origin, most clinical events are referred to as "idiopathic," likely revealing, however, an incapacity to ascertain a specific etiology. The mainstay of treatment of pericarditis is represented by a regimen of anti-inflammatory drugs. Anti-inflammatory treatments vary, however, in both effectiveness and side-effect profile (1). It is likely that the nature of the anti-inflammatory therapies should be tailored to the nature of the pericarditis. Of note, among patients with recurrent pericarditis, rilonacept, a fusion protein that prevents soluble interleukin-1α and -1β from binding to their receptor, directs resolution of pericarditis episodes and reduces the risk of recurrence (3). Nevertheless, the lack of suitable animal models of pericarditis, and notably in its acute form, likely explains our limited understanding of this syndrome and the absence of specific anti-inflammatory therapies, which are urgently needed to reduce the disease morbidity in its different forms.

In this issue of *JACC: Basic to Translational Science*, Mauro et al. (4) have elegantly attempted to take up this challenge and have designed a new experimental model of acute pericarditis in mice. Acute pericarditis is induced through the intrapericardial injection of zymosan A, a known activator of the nucleotide-binding domain leucine-rich repeat and pyrin-containing protein 3 (NLRP3) inflammasome. The NLRP3 inflammasome is critical for host immune defenses against bacterial, fungal, and viral infections; nonetheless, inflammasome activation is also associated with the pathogenesis of a number of inflammatory disorders. NLRP3 deleterious effects are mediated at least in part through the release of proinflammatory cytokines, such as interleukin (IL)-1α, IL-1β, and IL-18. Intrapericardial injection of zymosan A leads to the classical features of the inflamed pericardium including pericardial effusion, pericardial thickening, IL-1α and IL-1β upregulation, as well as increased expression apoptosis-associated speck-like protein as an unambiguous marker of NLRP3 inflammasome activation (4). The pathophysiological relevance of this experimental model is supported by the demonstration of the efficiency of distinct anti-inflammatory strategies such as ibuprofen, a cyclooxygenase-2 inhibitor; NRLP3 inhibition by means of colchicine or specific inhibitor; IL-1 blockade via 2 different drugs: anakinra, an IL-1 receptor antagonist; and a fusion protein mouse homologue of rilonacept (4).

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Université de Paris, Paris Cardiovascular Research Center, Institut National de la Santé et de la Recherche Médicale, Paris, France.
The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.12.005

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 2, 2021
FEBRUARY 2021:151–3

Of note, ibuprofen reduced pericardial effusion but not pericardial thickness and apoptosis-associated speck-like protein accumulation, suggesting that not all anti-inflammatory strategies display similar therapeutic potential. Hence, this experimental model of acute pericarditis could be particularly interesting for profiling the nature and type of inflammatory cells at work locally in the cardiac tissue but also in the blood as well as in the medullary and extramedullary reservoirs containing inflammatory entities. This is of paramount interest because the pericardium and its fluid have been shown to contain cytokines, growth factors, and micro-ribonucleic acids associated with proinflammatory and reparative responses under different pathological conditions. More interestingly, immune myeloid cells, including distinct pericardial macrophage subpopulation, have been localized within the cavity under physiological conditions and respond to injury in mice. The maintenance and phenotype of this macrophage population is mainly reliant on the expression of the transcription factor GATA-binding factor 6 (GATA6), which is driven by local cues. $GATA6^+$ pericardial macrophages are not circumscribed to rodents and are also detected in pig and human pericardial fluids, where the macrophages are even more abundant than in mice. This population of $GATA6^+$ macrophages migrates from the pericardial cavity to the epicardium after acute myocardial infarction and promotes tissue healing and limits fibrosis (5). Such $GATA6^+$ macrophages have also been identified in another type of cavity, the peritoneal cavity, and can rapidly invade visceral organs such as the liver to promote tissue repair (6). Although fate mapping approaches aimed to identify the origin of these cavity macrophages would be very informative, this supports the concept that a specific subpopulation of pericardial-resident inflammatory cells can adjust cardiac homeostasis. Similarly, pericardial adipose tissue contains lymphoid cell populations that can influence the cardiac immune response. Larger B-cell clusters are identified in pericardial adipose tissue of human patients with coronary artery disease and infarcted mice. Removal of pericardial adipose tissue reduces cardiac neutrophil infiltration as well as fibrosis and preserves left ventricular ejection fraction after acute myocardial infarction (7). On the same note, IL-10-producing $CD5^+$ B cells are expanded in pericardial adipose tissues during the resolution of acute myocardial infarction-induced inflammation. In this setting, however, B-cell-specific deletion of IL-10 worsens cardiac function, exacerbates myocardial injury, and delays resolution of inflammation (8). Altogether, these results reveal the existence of a highly conserved subpopulations of resident pericardial cavity immune cells across mammalian species. These studies also suggest that intrapericardial injection of zymosan A can specifically shape local recruitment, activation, and/or proliferation of resident inflammatory cells in the pericardial cavity, as in the neighboring adipose tissue, guiding the cardiac outcomes in this setting.

One can also speculate that the deleterious cardiac phenotype observed in this acute pericarditis model depends on the balance among the pericardial, myocardial, systemic, and remote organ inflammatory responses. It is, therefore, likely that the nature of the initial inflammatory stimulus plays a preponderant role. Zymosan is a yeast-derived particle composed principally of polysaccharides, of which β-glucan, the active component, mediates the cellular effects. A better understanding of the mechanisms of zymosan and/or β-glucan recognition will inform our attempts to utilize a specific compound to modulate innate and adaptive immune responses. Hence, employing the same approach of intrapericardial administration, the use of distinct pathogen-associated molecular patterns, and/or damage-associated molecular patterns in combination with suitable transgenic mice could be very informative to establish a specific etiology of signals that stimulate acute pericarditis onset. This could also prevent the all too famous reviewer number 3 from whispering distinctly in the editor's ear that such mouse model does not completely mimic the clinical situation in humans and could allow him to acknowledge that this new tool permits the field to move forward with its inherent limitations.

In any case, this work by Mauro et al. (4) is an important first step in the experimental modeling of the acute pericarditis, paving the way for in-depth mechanistic studies supporting a causal relationship between the different molecular and cellular actors of innate and adaptive immunity and for the elaboration of tailored therapeutic strategies in this pathological setting.

FUNDING SUPPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Jean-Sébastien Silvestre, Paris Cardiovascular Research Center, INSERM U970, Université de Paris, F-75015 Paris, France. E-mail: jean-sebastien.silvestre@inserm.fr.

REFERENCES

1. Chiabrando JG, Bonaventura A, Vecchie A, et al. Management of acute and recurrent pericarditis: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:76–92.

2. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36:2921–64.

3. Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. N Engl J Med 2021;384:31–41.

4. Mauro AG, Bonaventura A, Vecchié A, et al. The role of NLRP3 inflammasome in pericarditis: potential for therapeutic approaches. J Am Coll Cardiol Basic Trans Science 2021;6:137–50.

5. Deniset JF, Belke D, Lee WY, et al. Gata6(+) pericardial cavity macrophages relocate to the injured heart and prevent cardiac fibrosis. Immunity 2019;51:131–40.e5.

6. Wang J, Kubes P. A reservoir of mature cavity macrophages that can rapidly invade visceral organs to affect tissue repair. Cell 2016;165:668–78.

7. Horckmans M, Bianchini M, Santovito D, et al. Pericardial adipose tissue regulates granulopoiesis, fibrosis, and cardiac function after myocardial infarction. Circulation 2018;137:948–60.

8. Wu L, Dalal R, Cao CD, et al. IL-10-producing B cells are enriched in murine pericardial adipose tissues and ameliorate the outcome of acute myocardial infarction. Proc Natl Acad Sci U S A 2019;116:21673–84.

KEY WORDS experimental model, inflammasome, inflammation, pericarditis