Crosstalk Between the Heart and Blood in Heart Failure

Naoki Sato, MD, PhD

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In 1628, William Harvey published “*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*”, in which he described systemic blood circulation being pumped to the organs by the heart.¹ Based on his discovery, the relationship between the heart and blood was found to be important for understanding the pathophysiology of heart failure (HF). The heart beats approximately 100,000 beats per day and pumps blood to organs. An abnormality in any component of the blood results in a blood circulation disorder. Bone marrow dysfunction also affects the blood circulation and the heart. Bone marrow generates hundreds of billions of new blood cells every day. It contains hematopoietic stem cells and mesenchymal stem cells. Hematopoietic stem cells produce myeloid stem cells, which develop into red blood cells, platelets, and white blood cells, and lymphoid stem cells, which develop into lymphocytes. In contrast, mesenchymal stem cells are multipotent² and can differentiate into cardiomyocytes.³ Therefore, bone marrow has important roles in terms of cell generation, as well as circulation, hemodynamics, and immunological

status in HF.

In this issue of the Journal, Yamaguchi et al⁴ demonstrate that a low platelet count was associated with a poor outcome in patients with acute HF. Their study was single-center, retrospective and observational, with several limitations. However, it sheds important light on the pathophysiology of HF from the viewpoint of the relationship between the heart and blood. However, the relationship between platelet count and outcome has not been shown in previous studies that have clarified the relationship between platelet volume, but not platelet count, and outcome in acute HF.^{5,6} These differences might be related to etiological factors of HF (i.e., ischemic or non-ischemic, medications, and comorbidities, such as diabetes mellitus, dyslipidemia, and hypertension). Fundamentally, activated platelets could be related to a poor outcome. One of the markers of activation of platelet function is platelet

Figure. Crosstalk between the heart and blood.

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Cardiology and Intensive Care Unit, Nippon Medical School, Musashi-Kosugi Hospital, Kawasaki, Japan
Mailing address: Naoki Sato, MD, PhD, Cardiology and Intensive Care Unit, Nippon Medical School, Musashi-Kosugi Hospital, 1-396 Kosugi-cho, Nakahara-ku, Kawasaki 211-8533, Japan. E-mail: nms-ns@nms.ac.jp
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count, and platelet volume could be another marker of activated platelets because an increased volume of platelets correlates with rapid aggregation and increased production of thromboxane B₂, serotonin, β -thromboglobulin, glycoproteins, and P-selectin.⁵⁻⁹ These activated platelet-related changes occur in acute HF, but not in chronic HF.⁸

Activation of the sympathetic nervous system increases plasma norepinephrine concentrations, which causes activation of platelets and the coagulation system, and is related to outcome in acute HF. The increase in plasma epinephrine levels by an activated sympathetic nervous system also induces platelet aggregation and damage to the vessel wall. Furthermore, the renin-angiotensin-aldosterone system (RAAS) is activated and angiotensin II levels are elevated in severe HF.¹⁰ Angiotensin II increases platelet aggregation. This could be caused in part by a thrombin-induced, dose-dependent elevation of intraplatelet free calcium levels and it could enhance hemostatic abnormalities.¹⁰ Therefore, enhanced neurohumoral systems in HF are related to activation of platelets and hemostatic abnormalities, as well as to poor outcome.

In HF with reduced left ventricular ejection fraction (HFrEF), inhibition of the RAAS and sympathetic nervous system is recommended for improvement of symptoms.¹¹ Guideline-directed medical therapy (GDMT) improves outcome in HFrEF because it improves cardiac and vascular function, and consequently improves outcomes.¹⁰ However, GDMT cannot prevent worsening of HFrEF or improve the outcome for all patients with HFrEF. There are several reasons why GDMT does not work well for some patients with HFrEF. The most important reason is inappropriate modification of the activated sympathetic nervous system and RAAS. Another reason is that hematological abnormalities, including activated platelets, have not been well reported. This hematological mechanism should be considered, especially in patients with HFrEF who cannot tolerate GDMT. This is because some β -blockers¹² or renin-angiotensin inhibitors^{13,14} can reduce platelet aggregation. Non-selective lipophilic β -blockers stabilize the platelet cell membrane and block β_2 -receptors of platelets, resulting in a decrease in intraplatelet calcium availability. Subsequently, these effects reduce platelet aggregation.¹² Angiotensin-converting enzyme inhibitors¹³ or angiotensin II receptor blockers¹³ also decrease platelet activation. Possible mechanisms for inhibiting activated platelets by angiotensin II receptor blockers are inhibition of cyclooxygenase 2 and platelet adhesion/agglutination stimulated by nitric oxide.¹⁴ Furthermore, both of these drugs can reduce plasma catecholamine levels by improving inappropriate activation

of the sympathetic nervous system and RAAS, and can consequently decrease platelet activation.

Therefore, crosstalk between the heart and blood in HF, especially in acute HF, should be considered to understand the pathophysiology of HF (Figure). This viewpoint might shed light on the development of novel approaches to improving the outcome of HF.

Disclosures

None.

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