Highlights: 7th International Pulmonary Hypertension Conference & Scientific Sessions

Inflammation in Systemic Vascular Disease: What Can We Learn?

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[Editor's note: The following summary is based on information presented by Paul M. Ridker, MD, at the Scientific Sessions and adapted for publication.]

Abundant research over the past decade has implicated inflammation in several facets of systemic vascular disease. Initially, these data focused on early atherogenesis as well as the conversion of stable to unstable vascular lesions (ie, atherosclerotic plaque rupture). It is now clear that inflammation plays a major role in the risk of myocardial infarction and stroke. It also plays a role in the prognosis of patients with heart failure. The clinical expression of these observations has been the adoption of high sensitivity C-reactive protein (hsCRP) as a clinical marker for the risk of cardiovascular disease.[1,2]

CRP is a circulating pentraxin important in innate immunity and can be measured in the plasma as a marker of inflammation. CRP is made in the liver as an acute phase response protein but is also made in diseased vascular smooth muscle cells, particularly in atherosclerotic vessels. Thus, CRP may not only serve as a marker for cardiovascular disease risk but also suggests the important role of inflammation in vascular disease. This relationship between inflammation and vascular disease also helps to explain why patients with divergent diseases including systemic inflammatory diseases (ie, systemic lupus erythematosus), arthritis, and periodontal disease have higher risk of cardiovascular disease. This also highlights that inflammation from a variety of causes may lead to vascular disease. [1,2]

HsCRP levels < 1, 1 to 3, and > 3 mg/L have repeatedly been shown to add independent prognostic information on the risk of myocardial infarction, stroke, and cardiovascular death. At all levels of low-density lipoprotein cholesterol (LDL-C), increased hsCRP levels are associated with increased risk. Similar results are present in patients with the metabolic syndrome. The addition of hsCRP to global risk prediction algorithms for cardiovascular disease such as the Framingham Risk Score also assists in identifying patients with highest risk. While these levels are grouped into low, moderate, and high risk based on the above levels, indeed the highest levels confer the highest risk.[2,3]

From a population perspective, the proportion of vascular disease attributable to inflammation appears to be as large as that attributable to elevated cholesterol. This observation has had importance for drug development and many novel anti-inflammatory compounds are now being evaluated as potential methods to inhibit atherosclerotic progression.[1-3]

These inflammatory processes, however, extend beyond the coronary and cerebral circulations and appear to have an impact on all portions of the systemic vasculature. With regard to peripheral arterial disease, for example, elevated levels of several cytokines and hsCRP appear to be of similar importance as smoking for disease development and progression. Recent data have also implicated inflammation as a crucial process in vascular hypertension, and certain antihypertensive agents appear to preferentially impact upon this process.[1,2]

To date, the greatest clinical impact of the inflammatory hypothesis of atherosclerosis has been an improved understanding and utilization of statin therapy. Statins lower CRP levels in addition to lowering LDL-C, and data from both primary and secondary prevention trials indicate that the benefit of statin therapy is greater among those with high CRP levels. Further, in the setting of acute ischemia, achieving very low levels of LDL-C (< 70 mg/dL) and low levels of hsCRP (< 2 mg/L) has proven to be important for clinical outcomes. Thus, data now support the concept of "dual targeting," such that monitoring inflammation as well as cholesterol is recognized as an important method to improve long-term patient outcomes. Currently, trials are under way that target persons with LDL less than 130 but CRP greater than 2, subjects who would not ordinarily qualify for statin therapy, in a primary cardiovascular disease prevention strategy.[3,4]

Preliminary reports suggest that CRP is elevated in patients with pulmonary hypertension and a large prospective study is currently under way to define this relationship further. Several lines of evidence suggest the importance of inflammation in the pathogenesis of pulmonary arterial hypertension and improved understanding of inflammation is likely to be of importance in understanding the pathogenesis of pulmonary hypertension, especially since many disorders associated with pulmonary hypertension are associated with several inflammatory pathways.[5-7]

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Magnetic Resonance Imaging in Pulmonary Arterial Hypertension

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During the last few years, magnetic resonance imaging (MRI) has emerged as a modality with enormous potential for the noninvasive evaluation of pulmonary hypertension (PH). It does not involve ionizing radiation or nephrotoxic contrast agents (unlike computed tomography or nuclear techniques) and does not have imaging window limitations (as is the case with echocardiography). These MRI techniques are being applied to assessment of the vascular structure as well as the myocardium.

High resolution MRI and magnetic resonance angiography (MRA) have been used in the imaging of atherothrombotic disease with the advantage of imaging the entire vessel wall, not just the luminal surface as is possible with conventional angiography. The combined use of these imaging modalities has been used to image the aorta and cerebral circulations to characterize plaque size and structure and ultimately regression after interventions such as statin therapy. In the peripheral arteries, MRI techniques have been used to assess response and complications of balloon angioplasty of stenotic lesions. These imaging techniques may also allow for high fidelity imaging of the coronary circulation as well.[1]

The fidelity of MRI techniques to assess the vasculature may also be further enhanced by the use of cell-specific contrast agents that identify a specific cell type in the vessel wall. A wide range of cellular and molecular targets including adhesion molecules, inflammatory cells, apopotic cells, matrix proteins, angiogenic proteins, and thrombosis-related proteins have been suggested to further characterize vascular lesions.[1]

Evolving MRI techniques may also allow for the assessment of flow through a vessel. By tagging the blood cells as they flow through a specific vessel, these techniques would allow for assessment of flow patterns in healthy as well as diseased vessels.[1]

MRI is rapidly evolving as a comprehensive approach to evaluating both the structure and function of the heart. This has obvious implications in the identification of left-sided cardiac disease and congenital heart lesions in the pathogenesis of PH. MRI of the right ventricle (RV) can assess mass, volume, and contractility, yielding accurate measurements that do not depend on geometrical assumptions and that correlate strongly with pulmonary pressures obtained by conventional modalities such as echo and right heart catheterization. Quantification of the anomalous interventricular septal curvature associated with RV pressure overload is highly accurate for the determination of systolic pulmonary pressure and the detection of PH.[2,3]

Contrast-enhanced magnetic resonance angiography (MRA) can be used to visualize the complete pulmonary tree and may be useful in detecting the typical changes of chronic thromboembolic PH.[4,5] Time-resolved MRA additionally provides physiologic information of lung circulatory physiology. Phase-contrast imaging can be employed for accurate flow quantifications and calculations of QP/QS ratios.[6] In addition, the flow profile in the complete cross-section of the pulmonary artery or its branches can be noninvasively evaluated, and various parameters derived from these measurements correlate with the degree of hemodynamic impairment.[6]

MRI techniques have also been used to determine the extent of fibrotic remodeling following myocardial infarction. MRI may also be useful in determining the extent of myocardium that is currently ischemic or at risk of ischemia. This may be important in the identification of exercise-induced PH. Both of these may have important roles in determining the degree of RV impairment in PH as MRI demonstrates the presence of fibrosis in the insertion sites of the RV in the interventricular septum, a finding correlated with the severity of PH.[7,8] Recent advances in interventional MRI, allowing for the simultaneous quantification of pulmonary pressures with the use of MRI-compatible catheters, promise to further increase the utility of this versatile technique.

MRI has much promise in the further structural and functional characterization of the pulmonary circulation and will likely evolve as an additional important diagnostic and prognostic tool.

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