Annexin A5 and the failing heart; lost or found in translation?

Leonard Hofstra and Stephane Heymans*

Cardiovascular Research Institute Maastricht, Department of Cardiology, P Debyeelaan 25, 6202 AZ, Maastricht, The Netherlands

Online publish-ahead-of-print 17 October 2007

This editorial refers to ‘Upregulation of myocardial Annexin A5 in hypertensive heart disease: association with systolic dysfunction’ by S. Ravassa et al., on page 2785.

Heart failure is the number one reason for hospital admission in patients above 65 years of age. It is predicted that the number of heart failure patients will almost double in the next 20 years. Ischaemic and hypertensive heart disease are the major causes of this disabling disease. Approximately 22% of women and 46% of men who have had a myocardial infarction will develop heart failure within 6 years. Still, hypertension is a chief cause of cardiac failure: diastolic dysfunction accounts for >50% of all heart failure patients. In the world we live in, an increasing number of people become at risk of developing hypertension due to the epidemic proportions of obesity and the concomitant development of diabetes. The obesity epidemic is not restricted to countries in the developed world, but is also starting to conquer some developing countries such as India and China.

Efficient and rapid identification of patients who are susceptible to develop chronic heart failure (CHF) is going to be of imminent importance. In clinical practice, a combination of clinical exam, serum biomarkers, and imaging technology will provide the tools to establish the diagnosis of heart failure. Advances in serum biomarker diagnostics include the use of N-terminal pro-B type natriuretic peptide (NT-proBNP) as a marker of the failing left ventricle. The release of NT-proBNP is triggered by stretch of myocardial cells and, therefore, is a direct reflection of myocardial cell stress. Novel studies on serum biomarkers in CHF comprise the detection of galectin-3, which reflects the activation of macrophages in the failing heart.

This marker for heart failure, since it is an indicator of a different mechanism for the development of CHF.

The study presented by Ravassa and co-workers provides data obtained from a unique set of myocardial biopsies, ranging from healthy individuals, hypertensive patients without left ventricular hypertrophy (type A), hypertensive patients with left ventricular hypertrophy (type B), to patients with hypertension-related overt heart failure (type C). The authors used these samples to look for the presence of Annexin A5 in the myocardium in relation to cardiomyocyte apoptosis, left ventricular systolic function, and serum levels of Annexin A5. The main findings of their study are the increased cardiac and plasma levels of Annexin A5 in hypertensive patients with left ventricular hypertrophy or heart failure compared with controls. They observed an inverse relationship between the myocardial presence of Annexin A5 and systolic function of the left ventricle in all hypertensive individuals. Moreover, they showed that the myocardial presence of Annexin A5 was not related to any of the markers tested for apoptosis, including DNA laddering or the presence of activated caspase-3.

What can we learn from the data retrieved from this one-of-a-kind collection of myocardial biopsies? Does Annexin A5 have any diagnostic or prognostic significance in hypertensive heart disease or heart failure in general? Annexin A5 is a 35 kDa plasma protein, with a high affinity for phosphatidylserine (PS) in the nanomolar range. PS, a plasma cell membrane phospholipid, is only present on the inner leaflet of the plasma cell membrane in viable cells, but is rapidly exposed during the activation of the apoptotic machinery. In addition, PS externalization has been observed in non-apoptotic circumstances, such as the activation of macrophages and ageing of red blood cells. PS exposure serves as an ‘eat-me-flag’, and is required for the phagocytosis of apoptotic cells by professional phagocytes. Due to its strong PS-binding properties, Annexin A5 is used in thousands of laboratories worldwide to detect apoptotic cells. In addition, labelling of Annexin A5 with contrast agents has provided researchers with a non-invasive imaging tool to detect apoptosis in vivo, including in patients.

One of the intriguing questions arising from the work of Ravassa et al. is the origin of the cardiac Annexin A5. The
authors argue, based on a higher concentration of Annexin A5 in the failing heart. Although the authors speculate that Annexin A5 may be involved in calcium handling by cardiomyocytes, this function is still highly speculative. Previous studies indicate that substantial uptake of Annexin A5 binding. Therefore, Annexin A5 could be to shield and internalize PS exposure by the cardiomyocytes, thereby preventing exposure of cardiomyocytes to phagocytes. More definitive conclusions on the role of Annexin A5 in heart failure require detailed studies in Annexin A5 knockout and transgenic mice. Annexin A5 knockout mice are available, but do not show a spontaneous cardiovascular phenotype. Therefore, their response to cardiac stress, such as myocardial infarction or pressure overload, requires further investigation. The outcome of these studies might also be that Annexin A5 is not an innocent bystander, rather than a cause of diseases. Finally, since the elevated plasma concentration of Annexin A5 is significantly related to systolic dysfunction, it might be tempting to try and use plasma Annexin A5 levels as serum biomarkers for the detection of CHF in high risk cohort patients. However, as stated by the authors, they presented a cross-sectional study, and did not provide data with respect to the predictive value of this potential biomarker. In addition, it remains uncertain to what extent plasma Annexin A5 will give incremental value over the clinically used NT-proBNP. In order to provide incremental value over existing markers, novel markers need either to detect the disease in an earlier stadium or to be better indicators of the disease in specific patient subsets. Before reaching conclusions on the predictive value of Annexin A5 as a serum biomarker, robust clinical trials need to be conducted. Both the scientific and the clinical community would eagerly await the outcome of such trials.

In conclusion, Ravassa et al. provide us with an intriguing new aspect of heart failure development in hypertensive patients, which is the increased presence of myocardial Annexin A5 in cardiac biopsies of patients with hypertensive heart disease. These data may open novel avenues for diagnosis, and provide new insights into the development of CHF. However, rigorous studies on the exact function of Annexin A5 and its use as a novel biomarker for CHF are required.

References