Despite numerous advances in the diagnosis and treatment of cardiovascular disease (CVD), it remains a leading cause of morbidity and mortality in the developed world. CVD is the leading cause of death in the United States with total costs associated with CVD treatment reaching 17% of the national health expenditures. A substantial portion of the cost and time associated with CVD is in the administration of stress tests, including dobutamine stress echocardiogram (DSE), for noninvasive risk assessment of patients presenting with symptoms of obstructive coronary artery disease (CAD).

In addition, microparticle production is vital for removal of kines and miRNA and act as local and systemic messengers. Microparticles (MPs) are subcellular vesicles between 100 nm and 1 μm in diameter which are shed from the plasma membrane of activated or dying cells. Microparticles possess the procoagulant lipid phosphatidyl serine (PS) and cell surface proteins of their parent cells, which allow for efficient identification of cellular source via flow cytometry using fluorescently labeled annexin V, a PS binding protein, and receptor-specific antibodies. Microparticles contain cyto-kines and miRNA and act as local and systemic messengers. In addition, microparticle production is vital for removal of stressed-induced cellular by-products.

Numerous studies have shown that microparticles activate and regulate many physiological and pathological processes. Microparticles likely play a significant role in CVD and CVD risk factors. Studies have shown increased microparticle levels in patients with diabetes mellitus and hypertension. Elevated microparticle levels have been correlated with symptoms of obstructive coronary artery disease (CAD), is available at http://circres.ahajournals.org doi: 10.1161/CIRCRESAHA.113.302908

In the current issue of Circulation Research, the article by Augustine et al13 entitled “Dynamic Release and Clearance of Circulating Microparticles During Cardiac Stress” investigated a wide variety of microparticles before, immediately after, and 1 hour after DSE. Annexin V+ microparticles, platelet-derived (CD31+CD41+) microparticles, erythrocyte-derived (Glycophorin-A+) microparticles, and endothelial cell–derived (CD31+CD41+) microparticles were elevated immediately after DSEs, although levels returned to baseline by 1 hour after dobutamine infusion. By itself, this observation is interesting, although not completely unexpected, given previous studies on exercise-induced microparticle release. However, when the authors separated the subjects based on positive or negative DSE, subjects with a positive DSE were found to have stable microparticle levels across all time points, whereas those with a negative DSE were elevated immediately after dobutamine infusion (Figure). Those with a negative DSE were separated again based on evidence of vascular disease. Subjects with a negative DSE but with evidence of vascular disease had stable microparticle levels before and immediately after DSE. However, individuals with a negative DSE and negative for vascular disease had significantly elevated microparticles after DSE. Importantly, elevations in circulating microparticles also resulted in elevated procoagulant activity, confirming the potential of elevated thrombotic risk with microparticle release. These results suggest that microparticle release from platelets, erythrocytes, and endothelial cells is a normal stress response that is dysregulated in individuals with evidence of vascular disease.

The data presented by Augustine et al13 raise several important questions, including where are microparticles produced after dobutamine infusion? The authors observed elevations in platelet and erythrocyte microparticles...
after the dobutamine stress protocol. Because these are circulating cells, it is unclear whether they are perturbed systemically or locally as they pass through the point of intended stress, the heart. It is also unclear whether the microparticle-releasing endothelium is limited to the endocardium or is released more diffusely from vascular endothelium. As dobutamine is administered intravenously, it is possible that the drug is acting directly on the platelets, erythrocytes, and endothelial cells as these cell types possess dobutamine responsive β-adrenergic receptors.\textsuperscript{14-16} Dobutamine also causes systemic vasodilation, which could affect vascular endothelium resulting in microparticle release. However, if dobutamine is acting directly on the microparticle-releasing cells, then cells in individuals with vascular disease, who do not produce microparticles in response to DSE, would somehow be systemically prevented from microparticle release. Along these lines, it would be interesting to investigate whether dobutamine stimulates release of microparticles from platelets, erythrocytes, and endothelial cells ex vivo, from individuals with CVD compared with healthy controls.

Data presented by Augustine et al\textsuperscript{13} also raise the possibility of an area of cell death and elevated local thrombotic potential resulting from a lack of microparticle release. Augustine et al suggest that release of microparticles in response to dobutamine-induced stress is a normal physiological response, perhaps used to rid cells of unwanted debris and prevent cellular death. Indeed, the proapoptotic molecule caspase 3 is found in platelet and endothelial cell–derived microparticles.\textsuperscript{17,18} In addition, PS exposure occurs during apoptosis,\textsuperscript{19} but it is also conceivable that stressed cells expose PS on their plasma membranes and subsequently release PS via microparticles to relieve stress and avoid cell death. In this scenario, a lack of microparticle release could result in localized PS exposure resulting in a focused area of increased thrombotic potential. However, the question remains as to why individuals with CVD do not make microparticles in response to dobutamine? This question is especially curious given the contrast to previous studies indicating that patients with known CVD have elevated microparticles.\textsuperscript{7-10} Although a positive DSE (presence of left ventricular wall motion abnormalities with dobutamine exposure) is suggestive of obstructive CAD and myocardial ischemia, the gold standard of CAD evaluation is selective coronary angiography. Accordingly, Augustine et al\textsuperscript{13} evaluated participants who underwent subsequent coronary angiography and found that subjects with a positive angiogram had no microparticle elevation after DSE.\textsuperscript{13} Interestingly, 1 subject with a positive DSE but normal elevation in microparticles later received coronary angiography, which showed no significant CAD. A second subject with a negative DSE and no elevation in microparticles was found to have coronary disease by angiography. These discordant subjects underscore the potential of microparticle evaluation in the clinical setting. For example, change in microparticle levels before and immediately after DSEs could be used to assess for false-negative DSE and contribute to the decision-making process when considering coronary angiography.

As the specificity of CAD diagnosis using DSE ranges between 51% and 95%,\textsuperscript{20} attempts at improving identification of false-negative stress tests is warranted. Therefore, evaluation of stress-induced microparticle levels as a biomarker of CVD may allow for improved risk stratification in screening of otherwise asymptomatic individuals, those undergoing noninvasive stress testing, or with evaluating CAD lesions noted on coronary angiography. Manipulation of microparticle release may also provide new treatment strategies for individuals with CVD or in primary prevention of CVD. The use of microparticle evaluation in the clinical setting to provide information contributing to treatment decisions in a time and cost effective manner will require standardized procedures, reagents, and appropriate flow cytometric instruments similar to those outlined for laboratory research by the International Society for Thrombosis and Hemostasis collective workshop.\textsuperscript{21} However, additional studies are required to determine the use of microparticles in the diagnosis and treatment of CVD and to fully understand how microparticles are regulated in both health and disease.

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**References**


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