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).

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 cytokines 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 higher calculated 10-year Framingham CAD risk. Increases in microparticle levels have also been observed in patients with high risk coronary lesions and correlate to the degree of CAD (myocardial infarction>unstable angina>stable angina). The majority of microparticle and CVD research has focused on diseased individuals and those at higher risk of developing CVD. However, other studies have observed increases in specific microparticles in healthy patients after periods of physical exercise, suggesting that elevated microparticles are also a natural response to stress.

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 dobutamine infusion, but not in circulating microparticles. The current study also investigated the kinetics of microparticle (MP) release and clearance after dobutamine infusion. The authors observed a decrease in MP levels immediately after DSE, followed by a gradual increase up to 1 hour after DSE. The data suggest that microparticle release is a dynamic process that is influenced by stress and vascular disease. Further studies are needed to understand the underlying mechanisms and clinical implications of microparticle release and clearance.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Medicine, Division of Cardiology (B.M.W.) and Department of Pathology, Immunology, and Laboratory Medicine (J.C.W.), University of Florida, Gainesville, FL. Correspondence to Julie C. Williams, PhD, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, 2033 Mowry Rd, Room 280 CGRC, Campus Box 103363, Gainesville, FL 32610. E-mail juliewilliams@ufl.edu

Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/CIRCRESAHA.113.302908

Figure. Kinetics of microparticle (MP) release and clearance after dobutamine infusion. Schematic representation of MP levels in circulation before, immediately after, and 1 hour after dobutamine stress echocardiogram (DSE) as documented in Augustine et al. CVD indicates cardiovascular disease.
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. 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 al13 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.17,18 In addition, PS exposure occurs during apoptosis,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 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.2–10

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 al13 evaluated participants who underwent subsequent coronary angiography and found that subjects with a positive angiogram had no microparticle elevation after DSE.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%,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 Haemostasis collective workshop.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.

Sources of Funding
Dr Julie Williams is supported by the Laura McClamma Fellowship at the University of Florida.

Disclosures
None.

References


Key Words: Editorials ■ cell-derived microparticles
Dobutamine Stress–Induced Microparticle Release: A Sign of Health?
Brandon M. Williams and Julie C. Williams

Circ Res. 2014;114:15-17
doi: 10.1161/CIRCRESAHA.113.302908
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/114/1/15

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/