Obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are associated with increased levels of aldosterone and activation of cardiovascular mineralocorticoid receptors (MRs) contributing to hypertension and associated cardiovascular disease (CVD) (1). Large randomized controlled trials such as the Randomized Aldactone Evaluation Study (RALES), the Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Epleronone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) have demonstrated the CVD-related mortality and morbidity benefits of MR antagonists, further implicating MR signaling as a key mediator of CVD (2). The actions of kidney MR signaling to increase cardiovascular and renal fibrosis and blood pressure is well known; however, recent research suggests that inappropriate activation of extrarenal MR signaling in vascular endothelial cells (ECs), vascular smooth muscle cells (VSMCs), immune cells, and adipocytes promotes insulin resistance, T2DM, and associated CVD (1,3,4). For example, in association with obesity and insulin resistance, perivascular and visceral adipose tissue (PVAT and VAT) is dysfunctional, in part, because of adipose MR activation (3). Furthermore, PVAT and VAT secrete aldosterone, the ligand for MRs in endothelial and smooth muscle cells, and this is increased in obesity (3,4).

PVAT is a unique depot of adipose tissue that surrounds blood vessels to provide mechanical protection and helps regulate blood vessel tone (5,6). PVAT exerts divergent effects in different vascular beds, perhaps related to differences in fat constitution (5,6). For example, the thoracic aorta is surrounded by brown adipose tissue (BAT) and white adipose tissue (WAT), whereas the abdominal aorta is surrounded only by WAT (6). In rodents, the mesenteric artery is enmeshed in WAT, which is traditionally expanded in conditions of obesity and insulin resistance. Under normal physiological conditions, PVAT releases vasodilator substances such as adiponectin and adipocyte-derived relaxing factors that contribute to the maintenance of normal vascular tone (5,6). In pathological conditions such as obesity, however, enhanced MR signaling in PVAT and VAT activates NADPH oxidase–derived reactive oxygen species and releases proinflammatory adipokines such as visfatin, resistin, tumor necrosis factor-α, and interleukin-6, contributing to impaired vascular insulin metabolic signaling and vascular relaxation (3,7). Indeed, in the Framingham Heart Study (FHS), increased PVAT was an independent risk factor for CVD (8). The effect of PVAT to modulate vasodilation in health and disease is well established; however, much less is known about the impact of MR-dependent adipose signaling on vascular constriction. One recent study demonstrated that coronary PVAT from obese swine augments coronary contractile responsiveness (9).

In this issue of Diabetes, Nguyen Dinh Cat et al. (10) address this issue by evaluating the role of adipocyte-specific MR overexpression, previously shown to promote obesity and insulin resistance, in the regulation of mesenteric microvascular contractility. Increased adipocyte MR activation promoted an increase in adipose-derived hydrogen peroxide (H₂O₂), a vasodilatory reactive oxygen species, and impaired arteriolar vascular smooth muscle contractility involving upregulation of vascular redox–sensitive protein kinase G (PKG)-1, downregulation of redox-sensitive Rho kinase (ROCK) activity, and increased elastin content.
The changes in PKG-1 and ROCK converge to decrease myosin light chain (MLC) kinase phosphorylation/activation, MLC phosphorylation, and calcium sensitivity of smooth muscle contractile machinery (Fig. 1). Thus, overexpression of adipocyte MR leads to production of adipocyte-derived H₂O₂ and an intriguing vascular phenotype providing insight into the complexity of adipose–vascular interactions in conditions of increased MR signaling such as obesity.

Overall, these new and interesting data emphasize the functional importance of adipocyte MR in CVD complications associated with obesity. Indeed, adipose MR overexpression resulted in increased adiposity owing to the known adipogenic actions of MR signaling (7). Therefore, this model presents a unique phenotype of MR-dependent adipose expansion resulting in a unique hypocontractile vascular phenotype that contrasts that typically seen in obesity models such as diet-induced obesity. For example, overnutrition and insulin resistance usually increase vascular contractility, in part, via enhanced ROCK activity, impaired insulin metabolic signaling, reduced nitric oxide bioavailability, and decreased PKG/cyclic guanosine monophosphate in resistance vessels (1,3). These divergent results are consistent with data revealing impaired vasodilation but not adipose inflammation/dysfunction following aldosterone infusion in rodents (11,12). Thus, in the context of available evidence, this study highlights an MR-dependent adipose–vascular axis that may modulate MR-dependent effects in other tissues (i.e., ECs and VSMCs) in states associated with more “global” MR overactivation. Of additional interest is the finding that adipose MR overexpression was associated with increased arteriolar elastin content and reduced vascular stiffness. On the surface this may appear inconsistent with available evidence of profibrotic MR signaling and increased vascular stiffening in models of obesity. The impact of obesity and MR signaling on microvascular versus macrovascular stiffening, however, remains unclear as divergent structural remodeling within and among resistance and conduit vessels has been described in obesity (13–16) consistent with the current study.

In conclusion, data in the current study (10) presents an exciting paradigm of relevant functional cross talk between adipocyte MR and vascular contractility and remodeling in mesenteric resistance vessels. This study highlights the intricacies of tissue-specific MR signaling and the dramatic interactions of MR signaling across tissues as contributors to CVD-associated impairments of vascular function and blood flow control. Further studies are warranted to more definitively define the role of adipocyte-specific MR and PVAT in other adipose and vascular beds, particularly in conditions of obesity and insulin resistance.

Funding. J.R.S. received funding from the National Institutes of Health (R01-HL73101-01A and R01-HL107910-01) and the Veterans Affairs Merit System (0018). S.B.B. received funding from the Department of Veterans Affairs Biomedical Laboratory Research and Development CDA-2 (IK2 BX002030). G.J. received funding from the University of Missouri School of Medicine research grant.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References
1. Sowers JR. Diabetes mellitus and vascular disease. Hypertension 2013;61:943–947
2. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension 2015;65:257–263
3. Bender SB, McGraw AP, Jaffe IZ, Sowers JR. Mineralocorticoid receptor-mediated vascular insulin resistance: an early contributor to diabetes-related vascular disease? Diabetes 2013;62:313–319
4. Marcus Y, Shefer G, Stem N. Adipose tissue renin-angiotensin-aldosterone system (RAAS) and progression of insulin resistance. Mol Cell Endocrinol 2013;378:1–14
5. Omar A, Chatterjee TK, Tang Y, Hui DY, Weintraub NL. Proinflammatory phenotype of perivascular adipocytes. Arterioscler Thromb Vasc Biol 2014;34:1631–1636
6. Gil-Ortega M, Somoza B, Huang Y, Gollasch M, Fernández-Alfonso MS. Regional differences in perivascular adipose tissue impacting vascular homeostasis. Trends Endocrinol Metab 2015;26:367–375
7. Feraco A, Armani A, Mammi C, Fabbri A, Rosano GMC, Caprio M. Role of mineralocorticoid receptor and renin-angiotensin-aldosterone system in adipocyte dysfunction and obesity. J Steroid Biochem Mol Biol 2013;137:99–106
8. Lehman SJ, Massaro JM, Schlett CL, O’Donnell CJ, Hoffmann U, Fox CS. Peri-aortic fat, cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study. Atherosclerosis 2010;210:656–661
9. Owen MK, Witzmann FA, McKenney ML, et al. Perivascular adipose tissue potentiates contraction of coronary vascular smooth muscle: influence of obesity. Circulation 2013;128:9–18
10. Nguyen Dinh Cat A, Antunes TT, Callera GE, et al. Adipocyte-specific mineralocorticoid receptor overexpression in mice is associated with metabolic syndrome and vascular dysfunction: role of redox-sensitive PKG-1 and Rho kinase. Diabetes 2016;65:2392–2403
11. Schäfer N, Lohmann C, Winnik S, et al. Endothelial mineralocorticoid receptor activation mediates endothelial dysfunction in diet-induced obesity. Eur Heart J 2013;34:3515–3524
12. Bender SB, DeMarco VG, Padilla J, et al. Mineralocorticoid receptor antagonism treats obesity-associated cardiac diastolic dysfunction. Hypertension 2015;65:1082–1088
13. Trask AJ, Katz PS, Kelly AP, et al. Dynamic micro- and macrovascular remodeling in coronary circulation of obese Ossabaw pigs with metabolic syndrome. J Appl Physiol (1985) 2012;113:1128–1140
14. Katz PS, Trask AJ, Souza-Smith FM, et al. Coronary arterioles in type 2 diabetic (db/db) mice undergo a distinct pattern of remodeling associated with decreased vessel stiffness. Basic Res Cardiol 2011;106:1123–1134
15. Souza-Smith FM, Katz PS, Trask AJ, et al. Mesenteric resistance arteries in type 2 diabetic db/db mice undergo outward remodeling. PLoS One 2011;6:e23337
16. Bender SB, Castorena-Gonzalez JA, Garro M, et al. Regional variation in arterial stiffening and dysfunction in Western diet-induced obesity. Am J Physiol Heart Circ Physiol 2015;309:H574–H582