BIOGRAPHICAL SKETCH

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NAME: Joshua A. Beckman

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POSITION TITLE: Professor of Medicine, Vanderbilt University School of Medicine; Director, Section of Vascular Medicine, Co-Director, Vanderbilt Vascular Biology Center

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania	MA	1987	American History
New York University	MD	1991	Medicine
Harvard University	M.S.	03/01	Epidemiology
Columbia-Presbyterian Medical Center	Residency	06/94	Internal Medicine
Brigham and Women's Hospital	Fellowship	06/98	Cardiovascular Medicine

A. Personal Statement

My principal contributions have been in the field of Vascular Medicine and the physiological function of arteries in diabetes and risk factors for atherosclerosis. I have spent the last 15 years studying the impact of diabetes and its constituents on endothelial function. My role in the proposed research application is to oversee all important aspects of this application including, but not limited to, recruitment, endothelial cell acquisition, vascular function testing, data analysis, and participation in preparation of manuscripts. I am fully capable of performing each of the required steps in this application. I have the expertise, leadership, and motivation required to effectively complete this application, performing these measurements for my own research program, starting an ambulatory blood pressure program and Brigham and Women's Hospital, and as the Associate Medical Director of VasCore, the largest ultrasound core laboratory in the United States. I have personally studied the vascular function and phenotype of hundreds of patients, evaluating resistance arteriolar function, carotid intima-media thickness (CIMT) and conduit artery and vein function in a wide variety of pathophysiological states. Moreover, I have studied the vascular dysfunction inherent to diabetes for more than 15 years. This current grant application combines a direct extension of my research interests of vascular dysfunction, collaboration with other investigators, and techniques and medications with which I am facile, enabling successful acquisition of answers to this line of inquiry. As PI or co-Investigator on several previous foundation- and NIH-funded grants, I laid the groundwork for the proposed research by mastering effective measures of vascular function and factors relevant to vascular homeostasis in the intact human. I have established strong ties and collaborated with other researchers and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. The current application builds logically on my prior work, and I am proud to work with Dr. Brown (co-PI) to provide additional expertise in human vascular physiological evaluation. In summary, I have a demonstrated record of successful and productive research projects in an area of high relevance for the study of the effect of androgen deprivation on the progression of atherosclerosis in intact humans, and look forward to working with the team on this proposed project.

B. Positions and Honors

Positions:

1991-1994	Internal Medicine Residency, The Presbyterian Hospital, New York, NY
1994-1995	Chief Medical Resident, The Presbyterian Hospital, New York, NY
1995-1996	Fellow in Cardiovascular Medicine, The Presbyterian Hospital, New York, NY
1996-1998	Fellow in Vascular Medicine, Brigham and Women's Hospital, Boston
1998-2004	Instructor in Medicine, Harvard Medical School
1999-	Society of Vascular Medicine and Biology, Fellow
2000-	American College of Cardiology, Fellow
2004-2010	Assistant Professor in Medicine, Harvard Medical School
2010-2015	Associate Professor in Medicine, Harvard Medical School
2015-	Society for Vascular Medicine, Master
2015-	Professor of Medicine, Vanderbilt University School of Medicine

2006-2012	American College of Cardiology, PVD Committee
2008 -	American Heart Association, Fellow
2008-2010	American Heart Association, Program Chair, PVD Council
2009-2011	Society for Vascular Medicine, President Elect
2010-	Associate Professor of Medicine, Harvard Medical School
2011-2013	Society for Vascular Medicine, President
2013-2015	American Heart Association, PVD Council, Vice Chair
2013-	VasCore, Associate Medical Director
2013-2015	Society for Vascular Medicine, Past President
2015-	American Heart Association, PVD Council, Chair

Honors:

1989	William Osler Medal, American Association of the History of Medicine
1998	American College of Cardiology/Merck Fellowship Award
2000	Daniel D. Federman Outstanding Clinical Educator, Harvard Medical School
2007	W. Procter Harvey Young Teacher Award, American College of Cardiology

C. Contributions to Science

1. Diabetes, Oxidative Stress, and Vascular Function.

I have had a longstanding interest on the mechanisms by which diabetes mellitus affects conduit arteries and arterioles using both high-resolution B mode ultrasonography and brachial artery administration of endothelium-dependent and independent vasodilators. I was the first to establish that type 2 diabetes mellitus impairs both the bioavailability of endothelium-derived nitric oxide endothelial function and vascular smooth muscle function in intact humans. I subsequently led several investigations to determine the mechanisms by which this occurs in humans. We demonstrated that acute hyperglycemia impairs endothelial but not vascular smooth muscle function in arterioles and that this impairment could be rescued through infusion of ascorbate. This study showed the importance of increases in oxidative stress. We next demonstrated that activation of protein kinase C beta was an obligate step in this process by again using this hyperglycemic model and pre-treating subjects with placebo or ruboxistaurin, and protein kinase C beta inhibitor. Ruboxistaurin prevented the attenuation of endothelial function in healthy humans exposed to acute hyperglycemia. Finally, we tested the proposition that reductions of oxidative stress, through the administration of oral antioxidants or protein kinase C beta inhibition may restore the bioavailabilty of endothelium-derived nitric oxide in humans with diabetes. In neither case did the treatment improve vascular function, providing a mechanistic base for the lack of effectiveness of these therapies in large clinical trials.

a. **Beckman JA,** Goldfine AB, Gordon MB, Creager MA. Ascorbate restores endothelium-dependent vasodilation impaired by acute hyperglycemia in humans. Circulation. 2001 Mar 27;103(12):1618-23.
b. **Beckman JA**, Goldfine AB, Gordon MB, Garrett LA, Creager MA. Inhibition of protein kinase Cbeta prevents impaired endothelium-dependent vasodilation caused by hyperglycemia in humans. Circulation research. 2002 Jan 11;90(1):107-11.

c. **Beckman JA**, Goldfine AB, Gordon MB, Garrett LA, Keaney JF, Jr., Creager MA. Oral antioxidant therapy improves endothelial function in Type 1 but not Type 2 diabetes mellitus. American journal of physiology. 2003 Dec;285(6):H2392-8.
d. **Beckman JA**, Goldfine AB, Goldin A, Prsic A, Kim S, Creager MA. Inhibition of Protein Kinase C{beta} Does Not Improve Endothelial Function in Type 2 Diabetes. The Journal of Clinical Endocrinology and Metabolism. 2010 August; 95(8): 3783 - 3787. PMCID:PMC2913029

2. **The Impact of Insulin Resistance on Endothelial Function.**

We next began to pursue a mechanistic understanding of the impact of insulin resistance on vascular function using high resolution B mode ultrasonography. These studies began with an examination of endothelial and vascular smooth muscle function in women with insulin resistance of varying origins including type 2 diabetes mellitus, nonobese polycystic ovarian syndrome, lipodystrophy, and healthy controls. In this study we established that only type 2 diabetes mellitus, despite significant insulin resistance, was associated with impaired endothelium-dependent vasodilation. These studies made clear that insulin resistance states associated with increases in cardiovascular disease may not have endothelial function as a necessary intermediate. We went on to study androgen deprivation therapy in men treated for prostate cancer because of its association with increases in cardiovascular morbidity and mortality, finding that the induced insulin resistance increased the bioavailability of endothelium-derived nitric oxide. We then tested the hypothesis that direct suppression of inhibitor of kappa B kinase (IKK) activity through the administration of salsalate to limit upregulation of NF-kappa B activity in a subjects with the metabolic syndrome and subjects with atherosclerosis would improve inflammation and vascular function. In contrast, we demonstrated that high-dose administration of salsalate, a therapy being tested for its use in diabetes, impaired endothelial function when compared to placebo. This series of papers made clear that vascular function in insulin resistance is specific to the disease of origin, opened the possibility that insulin resistance may augment the risk of cardiovascular disease independent of endothelium-derived nitric oxide, and showed that the impact of therapy for insulin resistance is pathway specific.

a. **Beckman JA,** Goldfine AB, Dunaif A, Gerhard-Herman M, Creager MA. Endothelial function varies according to insulin resistance disease type. *Diabetes Care*. 2007;30:1226-1232
b. Nguyen PL, Je Y, Schutz FA, Hoffman KE, Hu JC, Parekh A, **Beckman JA,** Choueiri TK. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: A meta-analysis of randomized trials. *JAMA*. 2011;306:2359-2366
c. Nguyen PL, Jarolim P, Basaria S, Zuflacht JP, Milian J, Kadivar S, Graham PL, Hyatt A, Kantoff PW, **Beckman JA.** Androgen deprivation therapy reversibly increases endothelium-dependent vasodilation in men with prostate cancer. *Journal of the American Heart Association*. 2015;4
d. Nohria A, Kinlay S, Buck JS, Redline W, Copeland-Halperin R, Kim S, **Beckman JA.** The effect of salsalate therapy on endothelial function in a broad range of subjects. *Journal of the American Heart Association*. 2014;3:e000609

3. Characteristics Associated With Arterial Occlusive Disease

We performed a series of investigations to understand common factors in arterial disease and their impact on clinical outcome. The role of vascular calcification was controversial with conflicting data showing higher coronary calcium scores associated with increased cardiovascular risk yet more basic studies suggested that calcification may stabilize local disease. We studied patients brought to the cardiac catheterization laboratory for stable angina, unstable angina, and acute myocardial infarction using intravascular ultrasound to interrogate the region of interest. Clinical and lesion stability associated directly with increases in coronary calcification. We were the first to show this relationship directly. We next investigated the role of inflammation on vascular function and cardiovascular outcomes. First, we studied the impact of statin therapy on vascular function, showing it improved endothelium-dependent vasodilation independent of changes in cholesterol. Next we studied the dual roles of atherosclerotic plaque burden and systemic inflammation. We showed that an additive relationship between these two parameters suggesting that burden of disease was as important as an activated atherogenic system. Finally, we established a new methodology to study surgically-placed lower extremity bypass grafts. We were the first to show that mature vein bypass grafts demonstrate flow-mediated, endothelium-derived nitric oxide-dependent vasodilation. These studies showed the impact of commonly present factors on atherosclerotic vascular disease and created a new methodology to study vein graft function.

a. **Beckman JA,** Ganz J, Creager MA, Ganz P, Kinlay S. Relationship of clinical presentation and calcification of culprit coronary artery stenoses. *Arterioscler Thromb Vasc Biol*. 2001;21:1618-1622
b. **Beckman JA,** Liao JK, Hurley S, Garrett LA, Chui D, Mitra D, Creager MA. Atorvastatin restores endothelial function in normocholesterolemic smokers independent of changes in low-density lipoprotein. *Circ Res*. 2004;95:217-223
c. **Beckman JA,** Preis O, Ridker PM, Gerhard-Herman M. Comparison of usefulness of inflammatory markers in patients with versus without peripheral arterial disease in predicting adverse cardiovascular outcomes (myocardial infarction, stroke, and death). *Am J Cardiol*. 2005;96:1374-1378
d. Owens CD, Wake N, Conte MS, Gerhard-Herman M, **Beckman JA.** In vivo human lower extremity saphenous vein bypass grafts manifest flow mediated vasodilation. *J Vasc Surg*. 2009;50:1063-1070

4. Cancer Therapeutics and Vascular Function.
A particular interest of mine has been the intersection of treatments for cancer and cardiovascular outcomes. Many of the therapies now in common use have been associated with a heightened cardiovascular risk in the long-term. We began this series of investigations by evaluating the effect of radiation therapy on vascular function. Radiation therapy is associated with arterial occlusive disease in the locations it is employed years to decades after its administration. We evaluated the vascular function of women who received unilateral radiation therapy (40 Gy) for breast cancer more than three years previously. We demonstrated that subclavian artery endothelium-dependent but not vascular smooth muscle-mediated vasodilation was impaired only in the regions of radiation therapy. Moreover, vascular function in the contralateral subclavian artery was the same as in age-matched control subjects. This study was the first to establish a chronic vascular impairment mediated by radiation therapy. More recently, inhibitors of vascular endothelial growth factor receptor 2 tyrosine kinases have been shown to increase blood pressure, cause proteinuria, and increase cardiovascular events. We investigate the impact of vandetanib on conduit artery function in women with breast cancer. We found that Vandetanib treatment for 6 weeks significantly increased blood pressure, decreased resting brachial artery diameter, and decreased plasma systemic nitrate/nitrite levels compared with baseline. However, flow-mediated vasodilation was preserved, and no change was noted in nitroglycerin-mediated vasodilation. We then went on to study the mechanism in vitro. We showed that endothelial cell nitrite levels and akt(473) phosphorylation were reduced, vascular endothelial growth receptor 2 levels did not change, but endothelial NO synthase membrane concentration doubled. We studied a second, more potent tyrosine kinase inhibitor, tivozanib, finding impairment in endothelium-dependent vasodilation. These studies have demonstrated a cardiovascular impact of cancer therapeutics on cardiovascular function. The tyrosine kinase studies make clear that the description of an agent as a tyrosine kinase inhibitor is a general one, as the impact of these agents on vascular function will be dependent on the tyrosine moieties impacted by treatment. Moreover, it suggests that therapy may eventually be targeted to specific moieties as their function becomes clear.

a. Beckman JA, Thakore A, Kalinowski BH, Harris JR, Creager MA. Radiation therapy impairs endothelium-dependent vasodilation in humans. *J Am Coll Cardiol*. 2001;37:761-765
b. Mayer EL, Dallabrida SM, Rupnick MA, Redline WM, Hannagan K, Ismail NS, Burstein HJ**, Beckman JA.** Contrary effects of the receptor tyrosine kinase inhibitor vandetanib on constitutive and flow-stimulated nitric oxide elaboration in humans. *Hypertension*. 2011;58:85-92
c. Mayer EL, Scheulen ME, **Beckman JA**, Richly H, Duarte A, Cotreau MM, Strahs AL, Agarwal S, Steelman L, Winer EP, Dickler MN. A phase i dose-escalation study of the vegfr inhibitor tivozanib hydrochloride with weekly paclitaxel in metastatic breast cancer. *Breast Cancer Res Treat*. 2013;140:331-339

Complete List of Published Work on MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/10oM-VsiK9Akz/bibliography/48067789/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

Investigator Initiated Grant

Bristol Myers Squibb

Atazanavir and Endothelial Function in Older HIV Patients Beckman (PI)
This projects is designed to test two hypotheses: 1) To determine whether switching to atazanavir will improve vascular endothelial function in older subjects (>45 years) compared to continuing non-atazanavir based therapy. 2) The second objective of this study is to determine whether switching to atazanavir reduces oxidative stress, inflammation, and insulin resistance compared with non-atazanavir ART.
Role: Primary Investigator Budget 375,000

Investigator Initiated Grant
Merck, Sharp, Dohme
A double-blind, randomized, parallel design two-center study to compare the effect of vorapaxar vs. placebo on lower extremity vein graft maturation, remodeling, and function in patients undergling lower extremity revascularization.
This project is designed to test the following two hypotheses: 1) Protease-activated receptor (PAR) 1 activation participates in bypass vein graft maturation after surgical implantation and 2) PAR 1 activation impairs vascular endothelial function in patients with atherosclerosis.
Role: Primary Investigator Budget 477,000.

Completed Research Support

1R03DK094510 Beckman (PI) 09/15/2011 – 8/31/12

A pilot study of moderate hyperbilirubinemia in type 1 diabetes
These projects are designed to test the hypothesis that pharmacological increases of the antioxidant bilirubin will improve vascular endothelial function in subjects with type 1 diabetes mellitus. Systemic levels of oxidative stress and inflammation will be assessed in addition to conduit artery vascular function in the prospective single arm trial.
Role: Primary Investigator Budget: 89,000.

1-06-CD-01 Beckman (PI) 1/01/06-12/31/10
American Diabetes Association

Mechanisms of endothelial dysfunction in insulin resistance
This series of projects is designed to determine whether abnormal endothelial insulin signaling in insulin resistance causes endothelial dysfunction. The proposal tests three hypotheses: 1) Whether inhibition of IKK- beta, 2(inhibition of protein kinase C beta, and 3) attenuation of adipose cell free fatty release restores whole- body insulin sensitivity and endothelial function in insulin resistant subjects.
Role: Primary Investigator Budget 525,000.

Watkins Discovery Award Beckman (PI) 8/15/2013 – 8/15/2015

Ex Vivo Endothelial Cell Analysis in Diabetes and Insulin Resistance
This project is designed to test the hypothesis that human endothelial cell signaling demonstrates and inflammatory and oxidative phenotype in subjects with type 2 diabetes compared with control subjects. Cell-specific signaling analysis will be investigated in the context of a physiological characterization of dysmetabolism and vascular function
Role: Primary Investigator Budget: 150,000