JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 2, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.05.043

FOCUS SEMINAR: OXIDATIVE STRESS AND CARDIOVASCULAR DISEASE

STATE-OF-THE-ART REVIEW

Oxidative Stress and Cardiovascular Risk: Obesity, Diabetes, Smoking, and Pollution

Part 3 of a 3-Part Series

Bernd Niemann, MD,[a] Susanne Rohrbach, MD,[b] Mark R. Miller, PhD,[c] David E. Newby, MD,[c] Valentin Fuster, MD, PhD,[d,e,f] Jason C. Kovacic, MD, PhD[d]

ABSTRACT

Oxidative stress occurs whenever the release of reactive oxygen species (ROS) exceeds endogenous antioxidant capacity. In this paper, we review the specific role of several cardiovascular risk factors in promoting oxidative stress: diabetes, obesity, smoking, and excessive pollution. Specifically, the risk of developing heart failure is higher in patients with diabetes or obesity, even with optimal medical treatment, and the increased release of ROS from cardiac mitochondria and other sources likely contributes to the development of cardiac dysfunction in this setting. Here, we explore the role of different ROS sources arising in obesity and diabetes, and the effect of excessive ROS production on the development of cardiac lipotoxicity. In parallel, contaminants in the air that we breathe pose a significant threat to human health. This paper provides an overview of cigarette smoke and urban air pollution, considering how their composition and biological effects have detrimental effects on cardiovascular health. (J Am Coll Cardiol 2017;70:230–51)

Oxidative stress is a pervasive aspect of cardiovascular disease (CVD) and occurs whenever the release of reactive oxygen species (ROS) exceeds endogenous antioxidant capacity. Although physiological levels of ROS are important signaling molecules, prolonged exposure or inappropriate subcellular localization of ROS can have detrimental effects. Previously in this review series, we covered the basic biology of oxidative stress, telomeres, and telomere dysfunction in Part 1 (1), and the role of oxidative stress in both heart failure and vascular disease in Part 2 (2). Here in Part 3, we address the role of several specific and important risk factors, namely, diabetes, obesity, smoking, and excessive pollution, and how they increase cardiovascular risk via increased oxidative stress.

OBESITY, DIABETES, AND OXIDATIVE STRESS

METABOLISM OF THE OBESE AND THE DIABETIC HEART. The metabolic phenotypes of the diabetic and the obese heart have many similarities: fatty acid

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Adult and Pediatric Cardiovascular Surgery, University Hospital Giessen, Giessen, Germany; [b]Institute of Physiology, Justus-Liebig University, Giessen, Germany; [c]BHF/University of Edinburgh Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; [d]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [e]Marie-Josée and Henry R. Kravis Cardiovascular Health Center, Icahn School of Medicine at Mount Sinai, New York, New York; and the [f]Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain. Dr. Rohrbach has received research support from the German Research Foundation (IRTG1566, SFB1213). Drs. Miller and Newby have received funding from grants (PG/10/042/28388, RG/10/9/28286, FS/10/024/28266, SP/15/8/31575, and FS/16/14/32023) and chair (CH/09/002) awards from the British Heart Foundation. Dr. Kovacic has received research support from the National Institutes of Health (R01HL130423), the American Heart Association (14SFRN20490315 and 14SFRN20840000), and The Leducq Foundation (Transatlantic Network of Excellence Award). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Niemann, Rohrbach, Miller, and Newby contributed equally to this work. Kathy Griendling, PhD, served as Guest Editor for this paper.

Manuscript received January 16, 2017; revised manuscript received April 25, 2017, accepted May 10, 2017.

uptake and fatty acid oxidation (FAO) are increased, as are levels of intramyocardial and circulating triacylglycerol and circulating free fatty acids (FFAs), and glucose uptake and glucose oxidation are reduced (3). Despite reduced glucose uptake, there is increased flux through accessory pathways of glucose metabolism, such as the polyol pathway or the hexosamine biosynthetic pathway (4). In the healthy heart, utilization of FFAs and glucose is well-balanced, and enables the heart to switch between energy sources according to their availability and in response to environmental stimuli. This provides the heart with a high degree of flexibility in substrate utilization. The inability of the obese or diabetic heart to appropriately use glucose results in a reliance on FAO and reduced metabolic flexibility. The concurrent cardiac inefficiency is related to increased mitochondrial uncoupling induced by fatty acids, as well as the low oxygen (O_2) utilization efficiency of FAO (5), resulting in decreased adenosine triphosphate (ATP) production despite fuel oxidation. Metabolic alterations observed in the obese or diabetic heart, such as increased FAO, mitochondrial dysfunction, glucose autoxidation, impaired polyol metabolism, or increased hexosamine metabolism, can cause increased ROS release. Accordingly, metabolite-generated ROS play a major role in the development of various diabetes-related cardiovascular complications. The major metabolic changes in the obese and diabetic heart are summarized in **Figure 1**.

ROLE OF MITOCHONDRIAL ROS IN OBESITY AND DIABETES. Across various organs, including the heart (reviewed in Szendroedi et al. [6]), impaired mitochondrial respiration and changes in mitochondrial morphology have been consistently observed in insulin resistance and type 2 diabetes mellitus (DM). Patients with type 2 diabetes have significantly lower cardiac phosphocreatine/ATP ratios (7,8), decreased cardiac oxidative capacity, and increased mitochondrial ROS emission (9). Obesity results in disturbed mitochondrial biogenesis and function (respiratory chain complex I), which occurs prematurely in younger patients with obesity (10). Preclinical studies suggest early ROS up-regulation during diabetes-induced cardiac remodeling, but analogous prospective studies in patients with diabetes are lacking. Mitochondrial dysfunction, increased mitochondrial ROS release, and mitochondria-dependent cell death have been reported in the diabetic human heart (9,11–14). Mitochondrial dysfunction appears to be present mainly in cardiac subsarcolemmal but not in interfibrillar mitochondria of patients with type 2 diabetes (13). Interestingly, impaired mitochondrial function and contractile dysfunction were observed in patients with diabetes, but not in patients with obesity (14). Anderson et al. (9) also demonstrated increased levels of 4-hydroxynonenal- and 3-nitrotyrosine-modified proteins, together with a reduction in the ratio of reduced to oxidized glutathione in diabetic human hearts, indicating persistent oxidative stress in these samples.

Under physiological conditions, electron transport to O_2 is tightly coupled to ATP synthesis. ROS generation by mitochondria occurs through electron leakage from the electron transport chain (ETC) due to a decreased rate of mitochondrial phosphorylation. Normally, <1% of total oxygen consumption leaks from the ETC to generate ROS. Nevertheless, mitochondria are the primary source of cellular ROS production in cardiomyocytes, and increased mitochondrial ROS are a major cause of oxidative stress associated with DM. The hyperglycemia-induced overproduction of superoxide (O_2^-) by the ETC is recognized as a major cause of the clinical complications associated with diabetes and obesity (15). Indeed, attenuation of mitochondrial ROS release results in completely preserved insulin sensitivity despite a high-fat diet (16,17). Accordingly, mice with overexpression of a mitochondrially-targeted catalase show reduced ROS release and do not develop insulin resistance despite a high-fat diet (16). Recently, it was also shown that a mitochondria-targeted antioxidant prevents insulin resistance and diastolic dysfunction, suggesting that mitochondrial oxidative stress may be involved in both conditions (18).

Hyperglycemia increases ETC flux, resulting in mitochondrial hyperpolarization and O_2^- generation (19). Hyperglycemia-induced mitochondrial overproduction of ROS activates 4 major pathways involved in the pathogenesis of cardiovascular complications, including the increased production of advanced glycation end-products (AGEs), the polyol pathway, the hexosamine pathway, and protein kinase C-dependent signal transduction (15). Mitochondrial ROS production can be blocked by certain ETC inhibitors or uncoupling agents (19). Uncoupling proteins (UCPs) such as UCP2 and UCP3, the major human cardiac UCP isoforms (20), can dissipate the electrochemical gradient and thus attenuate ROS production (21) at the expense of decreased cardiac efficiency. Up-regulation of cardiac UCP2 and/or UCP3 has been reported in some, but not in all studies using preclinical models of obesity and DM (22).

ABBREVIATIONS AND ACRONYMS

AGE = advanced glycation end-product

C-DEAP = combustion-derived environmental air pollution

CVD = cardiovascular disease

DE = diesel exhaust

DM = diabetes mellitus

ETC = electron transfer chain

IRS = insulin receptor substrate

NOX = nicotinamide adenine dinucleotide phosphate oxidase

ROS = reactive oxygen species