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# Metabolic syndrome and endothelin-1 mediated vasoconstrictor tone in overweight/obese adults

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ABSTRACT

*Objective.* To determine whether endothelin (ET)-1 vasoconstrictor tone is greater in overweight and obese adults with the metabolic syndrome (MetS).

*Materials/Methods.* Forty overweight/obese middle-aged and older adults (age: 43–71 years; BMI: 25.1–36.9 kg/m$^2$) were studied: 20 without MetS (13 M/7 F) and 20 with MetS (13 M/7 F). MetS was established according to NCEP ATP III guidelines. Forearm blood flow (FBF; plethysmography) responses to intra-arterial infusion of selective $ET_A$ receptor blockade (BQ-123; 100 nmol/min; for 60 min) and non-selective $ET_{A/B}$ receptor blockade (BQ-123 + BQ-788 [50 nmol/min for 60 min]) were determined.

*Results.* In response to the selective $ET_A$ antagonism, there was a significant increase in forearm blood flow from baseline in both groups. However, the increase in forearm blood flow was significantly higher ($P = 0.03$; ~45%) in the overweight/obese group with MetS than the group without MetS. In contrast, there were no significant group differences in FBF responses to non-selective $ET_{A/B}$ receptor blockade. Peak vasodilator responses to nonselective $ET_{A/B}$ blockade were ~50% higher than baseline blood flow in the overweight/obese groups without and with MetS.

*Conclusion.* MetS is associated with higher ET-1 vasoconstrictor tone in overweight/obese adults. The enhanced ET-1 vasoconstrictor activity with MetS is mediated by the $ET_A$ receptor subtype.

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## 1. Introduction

Overweight and obesity are associated with profound endothelial dysfunction, which is thought to contribute etiologically to the increased risk of cardiovascular disorders and events with excess adiposity. Indeed, we [1,2] and others [3] have shown that overweight and obese adults, independent of other cardiovascular risk factors, demonstrate significant

*Abbreviations:* MetS, metabolic Syndrome; ET-1, endothelin-1; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Plan III; FBF, forearm blood flow.

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impairments in endothelial vasomotor and fibrinolytic function. Metabolic syndrome (MetS) involves a clustering of cardiometabolic disorders, specifically hypertension, dyslipidemia, insulin resistance and hyperglycemia, which often coexist with excess adiposity; further heightening the cardiovascular risk burden in overweight and obese adults [4–6]. With the escalating prevalence of overweight and obesity, it is estimated that ~35% of the US adult population have the MetS [7]. This is alarming considering that the presence of the MetS confers a two- to four-fold increased risk of coronary artery disease [6] and a sharp rise in all-cause mortality [8]. The mechanisms underlying the greater cardiovascular risk with the MetS, especially in overweight and obese adults, are not completely understood.

Endothelin-1 (ET-1) is a powerful endogenous vasoconstrictor peptide that is produced and released by the vascular endothelium. In addition to its role in the regulation of vascular tone, ET-1 has been linked to the pathogenesis of hypertension, heart failure and atherosclerotic vascular disease [9,10]. We have previously reported that ET-1 vasoconstrictor tone is elevated with increases in adiposity, contributing to diminished endothelium-dependent vasodilation and augmented cardiovascular risk in overweight and obese adults [2]. The impact of the MetS on ET-1 system activity in overweight and obese adults is currently unknown. Accordingly, we tested the hypothesis that ET-1 mediated vasoconstrictor tone is higher in overweight/obese adults with MetS compared with overweight/obese adults free of MetS.

## 2. Methods

### 2.1. Subjects

Forty overweight/obese middle-aged and older adults (age: 43–71 years; body mass index [BMI]: 25.1–36.9 kg/m$^2$) were studied: 20 without MetS (13 M/7 F) and 20 with MetS (13 M/7 F). MetS was established according to the National Cholesterol Education Program (NCEP) Adult Treatment Plan (ATP) III criteria [4,11]. NCEP-ATP III criteria for MetS were used rather than other criteria such as the World Health Organization [12] or International Diabetes Federation [13] definition due to its greater strength in predicting CVD [14,15]. Sixteen of the 20 subjects in the MetS group met three of the NCEP-ATP III criteria and four of the 20 met four of the NCEP-ATP III criteria (average number of criteria met: 3.2 + 0.1). In the subjects without MetS, two subjects had two MetS characteristics, 12 subjects had one and six subjects met no MetS criteria. The subjects were sedentary, nonsmokers, nonmedicated (including vitamins), nondiabetic and free of overt cardiovascular disease as assessed by medical history, physical examination, resting and exercise electrocardiograms, and fasting blood chemistries. All of the women in the study were at least 1 year postmenopausal and had never taken or discontinued hormone replacement therapy ≥ 1 year before the start of the study. Before participation, subjects provided written informed consent according to the guidelines of the University of Colorado, Boulder.

### 2.2. Body composition and metabolic measurements

Body mass was measured to the nearest 0.1 kg using a medical beam balance. Percent body fat was determined by dual-energy X-ray absorptiometry (Lunar Radiation, Madison, WI). BMI and minimal waist circumference were measured according to published guidelines [16]. Fasting plasma lipid and lipoprotein, glucose, and insulin concentrations were determined using standard techniques by the clinical laboratory affiliated with the University of Colorado, Clinical Translational Research Center. Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) derived from fasting glucose and insulin concentrations [17].

### 2.3. Intra-arterial infusion protocol

All studies were performed between 7:00 AM and 10:00 AM after a 10-h overnight fast in a temperature-controlled room, as previously described by our laboratory [2]. Briefly, a 5-cm, 20-gauge catheter was inserted into the brachial artery of the non-dominant arm under local anaesthesia. Heart rate and arterial blood pressure were continuously measured throughout the infusion protocol. Forearm blood flow (FBF) at rest and in response to ET-1 receptor blockade was measured in both the experimental (non-dominant) and contralateral (dominant) forearm by strain-gauge venous occlusion plethysmography (D. E. Hokanson, Bellevue, WA).

Following measurement of baseline FBF, BQ-123 (Clinalfa), a selective $ET_A$ receptor antagonist, was infused at a rate of 100 nmol/min for 60 min. FBF was measured every 10 min throughout the infusion period. The selected dose of BQ-123 has been shown to completely inhibit the $ET_A$ mediated vasoconstrictor effect of ET-1 in the human forearm of healthy adults [18]. After 60 min of BQ-123 infusion, the FBF response to nonselective ET-1 receptor blockade was assessed by the co-administration of BQ-123 and BQ-788 (Clinalfa) for an additional 60 min. FBF was measured every 10 min during the combined BQ-123 and BQ-788 infusion. BQ-788, a specific antagonist of $ET_B$ receptors, was infused at a rate of 50 nmol/min, a dose shown to effectively inhibit $ET_B$ receptors [18,19]. Due to limited drug availability, studies involving BQ-788 were performed in a subset of the total study population (10 of the 20 subjects without MetS and 12 of the 20 subjects with MetS).

#### 2.3.1. Statistical analysis

Differences in subject baseline characteristics were determined by between-groups analysis of variance (ANOVA). Group differences in FBF responses to BQ-123 and BQ-123 + BQ-788, expressed as percent change from resting FBF, were determined by repeated-measures ANOVA. Relations between variables of interest were assessed by linear regression analysis. There were no significant gender interactions; therefore, the data were pooled and presented together. All data are expressed as mean ± SEM. Statistical significance was set at $P < 0.05$.

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