Original Research

Microvascular Dysfunction as Opposed to Conduit Artery Disease Explains Sex-specific Chest Pain in Emergency Department Patients With Low to Moderate Cardiac Risk

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ABSTRACT

Purpose: Chest pain is a common emergency department (ED) presentation that is often unexplained. Recent evidence suggests that disease of the microvessels (arterioles) as opposed to the coronary artery (conduit artery) could explain one third of these cases, particularly in women. Brachial artery reactivity (BAR) is a validated surrogate measure of coronary artery vasomotion.

Objectives: The goal of this study was to compare brachial artery conduit vessel function (BAR) and microvascular function (postischemic peak reactive hyperemia [RH]) in subjects with and without chest pain and grouped according to sex.

Methods: This prospective cohort study was conducted from January through March 2010. Cases were patients admitted to an ED chest pain center with low to moderate risk of acute coronary syndrome; they were eligible for study if their creatinine level was <2.0 mg/dL and systolic blood pressure was >100 mm Hg or <180 mm Hg. Asymptomatic healthy volunteers on no medications were recruited as control subjects. BAR as a change in brachial artery diameter in response to transient forearm ischemia (endothelium-dependent vasodilation) and RH as a change in flow velocities were measured with a high-resolution ultrasound. Telephone follow-up visits were made at 1 month for recurrence of chest pain and recidivism.

Findings: A total of 57 patients and 21 control subjects were enrolled; there was 100% follow-up at 1 month. Most patients (86%) had at least 1 cardiac risk factor. Neither BAR nor RH varied significantly between patients and control subjects ($P > 0.05$). Symptomatic men had lower mean BAR than women (2.67% vs 6.22%; $P < 0.01$), even when normalized for shear stress ($P = 0.01$). Conversely, women with chest pain had lower RH compared with men (2.85 vs 4.61; $P = 0.01$). The sex-specific differences adjusted for age and Framingham risk scores persisted for BAR ($P = 0.003$) and RH ($P = 0.002$). Of 57 patients, 53% had recurrent pain, and 4 returned to the hospital within 1 month.

Implications: Differences in BAR and RH in patients ruled out for myocardial infarction suggest that the pathophysiology of acute chest pain might be sex-specific. Men with chest pain exhibited lower BAR, indicating peripheral conduit artery dysfunction. Conversely, women with chest pain exhibited lower postischemic peak hyperemia, indicative of peripheral microvascular dysfunction. Sex differences in pathophysiology of chest pain and vascular dysfunction could inform development of effective therapeutics for patients with recurrent or persistent chest pain in the

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Key words: brachial artery reactivity, chest pain, emergency department, reactive hyperemia, sex difference.

INTRODUCTION

More than 8 million patients present annually to the emergency department (ED) with chest pain; ~20% are diagnosed with acute coronary syndrome, indicative of focal obstruction of the coronary arteries, known as conduit vessels.[1] The remaining majority are given the diagnosis of "unexplained chest pain" after a comprehensive evaluation (including serial cardiac biomarkers, ECGs, and provocative diagnostic imaging) is conducted. This evaluation primarily focuses on detecting anatomical stenosis of the epicardial coronary vessel (a conduit artery) that causes rate-limiting reduction of blood flow to the myocardium. However, recent research indicates that some patients, particularly women, could have chest pain from alternate causes; that is, either functional limitation of their myocardial blood flow due to depressed endothelial reactivity of conduit vessels or from disease of the smaller microvessels (arterioles). This sex-specific atypical form of angina occurs even in the absence of angiographically evident coronary disease.[2] Recognition and treatment of microvascular angina are important in curtailing poor functional prognosis, with its high rates of persistent symptoms, return visits, and cardiac events associated with this entity.[3–6]

The vascular endothelium is a dynamic structure that plays an integral role in the development of atherosclerosis. In a normal conduit artery, an increase in blood flow causes an increase in shear stress that leads to nitric oxide–dependent increases in vessel diameter. Abnormal coronary artery reactivity is one of the earliest signs of atherosclerosis and precedes anatomical plaque formation.[7] It can therefore be seen in patients with cardiovascular risk factors even before angiographically overt obstruction develops.[8–10] Impaired endothelial reactivity has been linked to increased risk of coronary heart disease and death.[11,12] Brachial artery reactivity (BAR) is a validated measure of conduit artery endothelial function and correlates well with coronary artery reactivity.[13,14] Depressed BAR predicts adverse cardiac events even in the absence of obstructive coronary artery disease (CAD) (>50%).[15,16] It thus correlates with subclinical atherosclerosis, which may offer an alternate cause of angina in symptomatic patients. In addition, the cardiac risk factors that predict obstructive CAD have been shown to reduce BAR in large population-based studies such as the Framingham cohort.[8] Because most of the ED chest pain center patients have ≥1 cardiac risk factor (96%) and are mostly ruled out for myocardial infarction, we hypothesized that they likely would have lower BAR even in the absence of normal results on stress tests. In addition, impaired endothelial function can be reversed quickly by medical therapy (eg, statin therapy) and therefore remains of importance as a therapeutic target.[17–19] This is particularly important in chest pain patients with cardiac risk factors because early recognition could impede progression of atherosclerosis and help curtail their adverse cardiac risk.[20]

Function of small blood vessels (ie, microvascular) function is indirectly calculated by assessing the peak reactive hyperemic flow response to transient limb ischemia. One measure of reactive hyperemia (RH) is ultrasound measurement of hyperemic velocity, which is the ratio of peak velocity of blood flow immediately after cuff deflation compared with peak velocity at rest. Hyperemic velocity corresponds to the increased shear stress that contributes to BAR; thus, the 2 measures are physiologically linked. Impaired microvascular function has been recorded in women undergoing angiography even with normal coronaries.[2] Recognition and treatment of this entity are important because microvascular angina is linked with persistent symptoms and high health care costs.[21,22]

Little is known about microvessel function versus conduit vessel function in patients with acute chest pain in the ED. We designed a study to characterize blood vessel physiology in ED patients presenting with acute chest pain using an inexpensive, validated noninvasive ultrasound technique. Ultrasound is readily available in the ED, making an ED chest pain center a unique venue to study these physiological changes in patients with low to moderate risk in a well-controlled environment.

The goal of the present pilot investigation was to compare the rates of endothelial reactivity as documented by BAR in subjects with and without chest pain after being ruled out for acute myocardial infarction. We also explored the peak RH indicative of microvessel flow as well sex-specific effects between the 2 groups. We hypothesized that BAR would be reduced in ED patients with chest pain compared with healthy control subjects without chest pain, and that