

Coronary microvascular dysfunction in the setting of chronic ischemia is independent of arginase activity

Neel R. Sodha a, Munir Boodhwani b, Richard T. Clements a, Jun Feng a, Shu Hua Xu a, Frank W. Sellke a,

a Division of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

b Division of Cardiac Surgery, Ottawa Heart Institute, University of Ottawa, Ottawa, ON, Canada

Received 21 May 2007; accepted 21 June 2007

Available online 16 August 2007

Abstract

Background: Chronic myocardial ischemia induces endothelial dysfunction in the coronary microcirculation resulting in impaired nitric oxide signaling. This dysfunction has wide-ranging effects including impaired tissue perfusion and is implicated in impairment of the angiogenic process in settings of endothelial dysfunction. We hypothesized chronic myocardial ischemia results in increased activity of Arginase I, diminishing bioavailability of L-arginine, the substrate for endothelial nitric oxide production.

Methods: Chronic myocardial ischemia was induced for 7-weeks in 6 Yucatan miniswine utilizing an ameroid constrictor placed around the left circumflex coronary artery. Ischemic and non-ischemic tissue was harvested at the 7-week time point. Expression of Arginase I, eNOS, and phospho-eNOS was assessed utilizing Western blotting. Arginase activity was measured. Immunofluorescent staining assessed expression of Arginase I between ischemic and non-ischemic microvessels. Coronary microvascular relaxation studies were performed.

Results: Arginase I expression, activity, and staining was similar between ischemic and non-ischemic territories. Significant impairments in coronary microvascular relaxation were observed in microvessels from the ischemic territory in response to endothelial-dependent agents but remained similar between territories in response to endothelial independent agents. Regression analysis between arginase activity and degree of microvascular vasorelaxation demonstrated no significant correlation.

Conclusions: Coronary microvascular dysfunction in the setting of chronic myocardial ischemia occurs independently of Arginase I activity and expression. Alternative therapeutic strategies focusing away from arginine may be need for the treatment of this dysfunction.

Keywords: Coronary; Endothelial dysfunction; Angiogenesis; Microvascular dysfunction; Arteriolar dysfunction; Arginase; Myocardial ischemia; Coronary artery disease; Arginine

慢性缺血过程中的冠脉微血管功能紊乱不依赖精氨酸酶活性

摘要:

背景: 慢性心肌缺血诱导的冠脉微循环内皮细胞功能紊乱导致 NO 信号途径受损。这种紊乱可引起大范围的后果包括损伤组织灌流并且涉及在内皮功能异常的背景下损伤血管生成过程。我们假定慢性心肌缺血致使精氨酸酶 I 活性增加, 并且逐渐缩小内皮 NO 产生的底物 L-精氨酸的生物利用率。

方法: 选用6只Yucatan小猪, 用Ameroid缩窄器固定在冠状动脉左旋支收缩肌周围7周诱导慢性心肌缺血。第7周收集缺血和非缺血组织。利用免疫印迹法检测精氨酸酶I、eNOS, 和磷酸化-eNOS的表达。测定精氨酸酶活性。免疫荧光染色检测缺血和非缺血微血管精氨酸酶I表达。进行了冠脉微血管舒张研究。

结果: 缺血和非缺血区域精氨酸酶I的表达、活性、染色(定位)相似。内皮依赖的试剂作用于缺血区域时冠脉微血管舒张显著损伤, 但与内皮不依赖的试剂作用时的反应相似。对精氨酸酶活性和微血管舒张程度进行回归分析显示无显著相关。

结论: 在慢性心肌缺血背景下冠脉微血管功能紊乱的发生不依赖精氨酸酶I的活性和表达。处理这种紊乱可能需要选择远离精氨酸的治疗措施。

(曾惠)