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ORIGINAL ARTICLE

Early peripheral endothelial dysfunction predicts myocardial infarct extension and microvascular obstruction in patients with ST-elevation myocardial infarction

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KEYWORDS
Acute myocardial infarction;
Primary PCI;
Endothelial function;
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Reactive hyperemia index

Abstract
Introduction and Objectives: The role of endothelial dysfunction (ED) in patients with ST-elevation myocardial infarction (STEMI) is poorly understood. Peripheral arterial tonometry (PAT) allows non-invasive evaluation of ED, but has never been used for this purpose early after primary percutaneous coronary intervention (P-PCI). Our purpose was to analyze the relation between ED assessed by PAT and both the presence of microvascular obstruction (MVO) and infarct extension in STEMI patients.
Methods: ED was assessed by the reactive hyperemia index (RHI), measured by PAT and defined as RHI <1.67. Infarct extension was assessed by troponin I (TnI) release and contrast-enhanced cardiac magnetic resonance (ceCMR). MVO was assessed by ceCMR and by indirect angiographic and ECG indicators. An echocardiogram was also performed in the first 12 h.
Results: We included 38 patients (mean age 60.0±13.7 years, 29 male). Mean RHI was 1.87±0.60 and 16 patients (42.1%) had ED. Peak TnI (median 118 mg/dl, IQR 186 vs. 67/81, p=0.024) and AUC of TnI (median 2305, IQR 2486 vs. 1076/1042, p=0.012) were significantly higher in patients with ED, who also showed a trend for more transmural infarcts (63.6% vs. 22.2%, p=0.06) and larger infarct mass on ceCMR (median 17.5%, IQR 15.4 vs. 10.1/10.3, p=0.08). Left ventricular ejection fraction (LVEF) was lower and wall motion score index (WMSI) was higher on both echocardiogram and ceCMR in patients with ED. On ceCMR, MVO was more frequent in patients with RHI <1.67 (54.5% vs. 11.1%, p=0.03). ECG and angiographic indicators of MVO all showed a trend toward worse results in these patients.
Conclusions: The presence of ED assessed by PAT 24 h after P-PCI in patients with STEMI is associated with larger infarcts, lower LVEF, higher WMSI and higher prevalence of MVO.

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PALAVRAS-CHAVE
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Função endotelial;
Tonometria arterial periférica;
Índice de hiperemia reativa

A disfunção endotelial precoce prevê a extensão do enfarte e a presença de obstrução microvascular em doentes com enfarte agudo do miocárdio

Resumo
Introdução e objetivos: O papel da disfunção endotelial (DE) em doentes com enfarte agudo do miocárdio com elevação do segmento ST (EAMcST) é mal compreendido. A tonometria arterial periférica (TAP) permite avaliar de forma não invasiva a DE, mas nunca foi usada precocemente após intervenção coronária percutânea primária (ICP-P). O nosso objetivo foi avaliar a relação entre a DE avaliada por TAP, a presença de obstrução microvascular (OMV) e a extensão do enfarte (EE) em doentes com EAMcST.
Métodos: A DE foi avaliada pelo índice de hiperemia reativa (IHR), obtido por TAP, sendo definida como um valor de IHR <1,67. A EE foi avaliada pela troponina I (TnI) e por ressonância magnética cardíaca com contraste (RMCc). A OMV foi avaliada por RMCc e por indicadores indiretos eletrocardiográficos e angiográficos. Foi ainda efetuado um ecocardiograma nas primeiras 12 horas.
Resultados: Foram incluídos 38 doentes (idade média 60,0±13,7 anos, 29 homens). Os valores médios de IHR foram 1,87±0,60 e 16 doentes (42,1%) tinham DE. Os valores máximos (mediana 118/IIQ 186 *versus* 67/81, p=0,024) e a área sob a curva de TnI (mediana 2305/IIQ 2486 *versus* 1076/1042, p=0,012) foram significativamente superiores nos doentes com DE, que também mostraram uma tendência para mais enfartes transmurais (63,6 *versus* 22,2%, p=0,06) e maiores massas de enfarte na RMCc (mediana 17,5/IIQ 15,4 *versus* 10,1/10,3, p=0,08). Os doentes com DE mostraram valores de fração de ejeção do ventrículo esquerdo (FEVE) significativamente menores e valores do índice de motilidade segmentar (IMS) significativamente maiores, por ecocardiografia e por RMCc. A presença de OMV na RMCc foi mais frequente nos doentes com DE (54,5 *versus* 11,1%, p=0,03).
Conclusões: A presença de DE avaliada por TAP 24 horas após ICP-P, em doentes com EAMcST, associa-se a enfartes maiores, menor FEVE, maior IMS e maior prevalência de OMV.

Introduction

Notwithstanding all the improvements seen in primary angioplasty programs, with dramatic reductions in the time between symptom onset and intervention, and although normal epicardial coronary artery flow is almost always achieved in a timely fashion after primary percutaneous coronary intervention (P-PCI) in patients with ST-elevation myocardial infarction (STEMI), a significant proportion of patients (between 20% and 60%) have a poor outcome because of microvascular coronary damage.[1,2]

The negative prognostic implications for the risk of left ventricular (LV) remodeling and of hard endpoints, including death, associated with coronary microvascular damage have been repeatedly confirmed with several invasive and non-invasive indicators.[2–13] However, the precise mechanisms underlying coronary microcirculatory dysfunction before and after the restoration of epicardial blood flow are largely unknown and likely to be multifactorial. Traditionally, coronary microvascular dysfunction in this setting is seen as a consequence of the primary epicardial event and/or of coronary reperfusion, either pharmacological (thrombolysis) or mechanical (P-PCI). Mechanical obstruction (due to distal embolization of atherothrombotic debris[14]), coronary endothelial dysfunction (ED) (mediated by the release of vasoactive factors such as endothelin-1 and tissue factor[15]) and reperfusion injury (through various mechanisms including platelet and leukocyte accumulation leading to thrombosis, vasoconstriction and release of free oxygen radicals, proteases, and pro-inflammatory mediators, and complement activation leading to the release of histamine and to increased cell permeability, resulting in endothelial cell and myocyte swelling, interstitial edema, and further stimulation of leukocyte adherence[16]), have all been suggested as mechanisms involved in coronary microvascular dysfunction in STEMI patients.

An alternative explanation is that pre-existing and/or simultaneous coronary microvascular dysfunction may itself have pathophysiological importance and contribute to myocardial infarct extension, LV remodeling and future events.[16] Whichever theory of microvascular coronary dysfunction in STEMI patients is correct (cause, consequence or both), endothelial function always seems to be at the core of the proposed mechanisms. There is accumulating evidence that ED is not simply a risk factor and precursor of coronary artery disease (CAD), but also plays a central role in processes leading to acute coronary syndrome (ACS) and STEMI.[17] In patients with ACS, endothelial function, measured in the peripheral circulation, has been shown to be an independent predictor of events,[18] and subsequent normalization of endothelial function in these patients predicts a lower risk.[19,20] Similarly, in STEMI