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CORRESPONDENCE

Research Correspondence

Multidetector Computed Tomography Accurately Defines Infarct Size, But Not Microvascular Obstruction After Myocardial Infarction

To the Editor: Early percutaneous coronary intervention (PCI) and reperfusion of obstructed epicardial arteries have improved patient survival after myocardial infarction (MI), but downstream, microvascular obstruction (MVO) remains a significant negative predictor after acute infarct PCI (1). Recently, it has been suggested that dynamic contrast-enhanced multidetector computed tomography (MDCT) may be equally effective as magnetic resonance imaging (MRI) in predicting MVO in the clinical setting (2), but evidence validating this contention is scant. Nitrite ions are microvascular vasodilators, and have been demonstrated to reduce MRI-defined MVO, and to improve endocardial blood flow in a large-animal MI model, verified using the accepted gold standard: thioflavin S exclusion (TSE) to define MVO and microsphere analysis to measure regional blood flow (RBF) (3).

The purpose of this study was: 1) to correlate putative MVO contrast attenuation patterns (hypoenhancement area on MDCT image) with MVO derived from ex vivo TSE and RBF assessment; and 2) to determine whether nitrite-induced dynamic changes in MVO could be equally detected using RBF assessment and MDCT image analysis.

Sixteen female, 25 kg to 30 kg, Landrace pigs (of which 12 survived: 6 in the saline group; 6 in the nitrite group) underwent experimental MI by balloon occlusion of the mid left anterior descending artery for 90 min followed by reperfusion for 2 h (4). After balloon deflation, MDCT and microsphere delivery were performed at the same time point. Areas of hyperenhancement and hypoenhancement were determined using a 5-min delayed enhancement scan. The number of microspheres detected in each region of the heart, corrected for aortic blood flow, provided RBF for that region for each condition (5). Nitrite diluted in saline (0.2 μmol $\cdot$ min^{-1} $\cdot$ kg^{-1}), or an equal volume of saline, was delivered in the mid left anterior descending artery at the onset of reperfusion. Twenty-four hours after MI, animals underwent repeat MDCT and microspheres administration. An injection of 20 ml 4% thioflavin S was made into the left ventricle (LV) 2 min before sacrifice. The heart was then explanted and sliced into short-axis slices 1 cm thick. A 2,3,5-triphenyltetrazolium chloride (TTC)-2% solution was used to delineate the infarct area.

The TTC- and TSE-defined regions for microspheres sampling identified distinct differences in RBF between remote, TTC-defined infarct, and TSE-defined MVO areas 24 h after MI at basal, mid, and apical ventricular levels: infarct and MVO areas had significantly reduced RBF (Fig. 1A and 1B), validating TTC- and TSE-defined areas. Microspheres analysis also showed a significant increase in RBF in remote and MVO ($p < 0.05$) regions in the nitrite-treated group compared with the saline-treated group ($n = 6$ pigs per group) (Figs. 1A and 1C), confirming nitrite beneficial effects on MVO after MI. Combined hypoenhancement and hyperenhancement areas on MDCT (putative infarct zone) correlated well with TTC-defined infarct area ($r^2 = 0.74$, $n = 12$ pigs, $p < 0.004$) (Figs. 1A and 1D). However, MDCT hypoenhancement (putative MVO area) did not correlate well with TSE-defined MVO area ($r^2 = 0.42$, $n = 9$ pigs, $p = 0.21$) (Figs. 1A and 1E). The MDCT imaging analysis after MI did not show any significant difference between saline- and nitrite-treated groups in terms of percent changes in infarct size (combined hypoenhancement and hyperenhancement/LV: $-15.6 \pm 6.9\%$ and $-10.0 \pm 15.7\%$, respectively; $p = 0.76$) or hyperenhancement/LV ratio ($43.1 \pm 36.4\%$ and $27.3 \pm 36\%$, respectively; $p = 0.77$) and hypoenhancement/LV ratio ($-38.7 \pm 15.9\%$ and $-46.0 \pm 18.5\%$, respectively; $p = 0.78$; $n = 6$ pigs per group) (Fig. 1F).

This study demonstrates that MDCT hypoenhancement area after MI does not accurately predict MVO area, suggesting limitations of MDCT for the detection of MVO. Thus, reduced RBF (impairing contrast penetration) may not be the only determinant of hypoenhancement on MDCT. Moreover, in this study, MDCT did not predict dynamic changes in MVO, suggesting that, as well as not being a good imaging modality to detect MVO changes after therapeutic intervention, it may also be suboptimal in detecting dynamic MVO responses to vasodilators. Our data do, however, confirm prior suggestions that combined hypoenhancement and hyperenhancement area on MDCT is a reliable measure of infarct area. In terms of imaging infarction, a significant advantage of MDCT over MRI is that signal density values are unique and determined by the physical properties of individual constituents of the heart resulting from direct attenuation of X-rays by iodine molecules, not an indirect measure resulting from gadolinium-induced alterations of water proton relativity, as on MRI. Therefore, MDCT may be, hypothetically at least, a more accurate modality for measuring infarct size. Our data have clinical implications, suggesting caution when using CT to detect MVO in post-MI patients.

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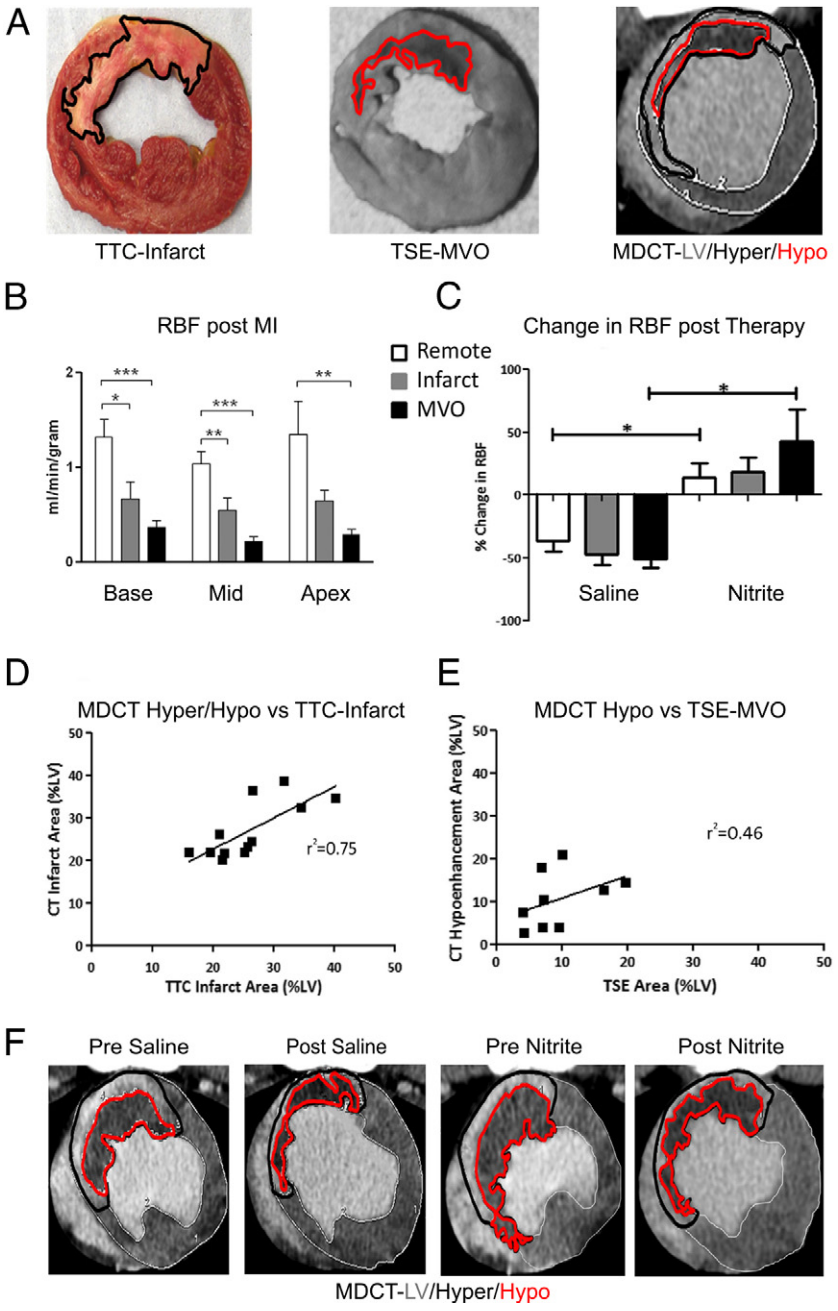

Figure 1 **Multidetector CT and MVO Definition 24 H After MI**

(A) Representative 2,3,5-triphenyltetrazolium chloride (TTC)-stained heart section (infarct delineated in **black**), thioflavin S exclusion (TSE) image under ultraviolet illumination (microvascular obstruction [MVO] delineated in **red**), and multidetector computed tomography (MDCT) image depicting left ventricle (LV) **(gray contour)**, hyperenhancement area **(black contour),** and hypoenhancement area **(red contour)**. **(B)** In base, mid, and apex ventricular sections from remote **(open bars)**, TTC-defined infarct **(shaded bars)**, and TSE-defined MVO areas **(solid bars)**, regional blood flow (RBF) was measured 24 h post-MI using colored microspheres. **(C)** Nitrite beneficial effect on improving RBF in MVO area using microsphere analysis. **(D)** Positive correlation between infarct area assessed by combined hyperenhancement and hypoenhancement area on MDCT and TTC-defined area. **(E)** Poor correlation between MVO area assessed by MDCT hypoenhancement area and TSE-defined area. **(F)** Representative MDCT images depicting LV **(gray contour)**, hyperenhancement area **(black contour)**, and hypoenhancement area **(red contour)** before and 24 h after saline or nitrite treatment. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for all data panels.

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Letters to the Editor

Hypertrophic Cardiomyopathy in Childhood

The Gradient Is Not the Disease. Excessive Use of Experimental Invasive Interventions

We read with much interest the study of Sreeram et al. (1) from Germany and United Kingdom in which the authors used the novel strategy of radiofrequency ablation of the ventricular septum to produce intramuscular scars and reduce outflow tract obstruction in young children with hypertrophic cardiomyopathy (HCM). The study population is unique for HCM: 1) sizable for this age group (mean age: 10 years, with children as young as 2 years [n = 2] and with 25% 6 years of age or younger); 2) symptoms attributed to HCM although seemingly very modest (i.e., tiredness in 28 patients), with some being virtually asymptomatic; and 3) lacking detailed information about preablation pharmacologic therapy and no consideration for surgery.

Subaortic gradients historically have been the most visible component of HCM, almost by reflex triggering concern, which is often disproportionate to hemodynamic significance (2). Notably, the authors aggressively promoted invasive intervention to reduce outflow obstruction in very young patients, using an experimental technique that will undoubtedly prove controversial. Radiofrequency ablation sufficient to reduce septal thickness strikes us as counterintuitive, a concern which is compounded by the authors' failure to report septal thickness before or after ablation.

Experimentation on children with HCM has been an unfortunate part of the disease history (3). Therefore, we take this opportunity to underscore the acknowledged principle that outflow gradients in HCM do not always represent a disease feature that requires immediate action and abolition. Although left ventricular outflow obstruction is a determinant of progressive heart failure in HCM (4), many patients of all ages tolerate gradients for long periods without surgical or other major interventions. Furthermore, gradient-related symptoms can be controlled pharmacologically (5), including disopyramide, which is capable of reducing outflow obstruction (6).

It is rarely (if ever) necessary to invasively remove gradients prophylactically in the absence of severe symptoms, particularly in young patients. This tenet is supported by the American College of Cardiology (4,7), the American Heart Association (7), and the European Society of Cardiology (4) consensus recommendations and guidelines (2003 and 2011). Over the course of almost 10 years, these societies have agreed that invasive intervention to remove outflow obstruction in HCM should be reserved for patients with disabling heart failure symptoms. Tiredness, as reported by Sreeram et al. (1), is difficult to interpret in HCM patients of any age (and particularly in young children), may not be the consequence of outflow obstruction, and is not an indication for invasive intervention.

Indeed, one of the major concerns with prematurely undertaking invasive gradient reduction in young HCM patients is underscored by the outcome data reported in this small cohort (n = 32): 2 deaths (1 procedural death [age: 4 years] and 1 sudden death), 1 patient each with a permanent pacemaker for heart block, implantable defibrillator, or failure to experience symptom improvement; and 2 patients with ventricular fibrillation, one of whom had mitral valve replacement and myectomy at age 5 years. The adverse consequence rate was 22%.

It is important to underscore that HCM is a complex disease, and although outflow obstruction can be an important determinant of clinical course, a subaortic gradient in a young patient should not be regarded as if it were the disease itself, necessitating invasive therapy without regard to the potential consequences.

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