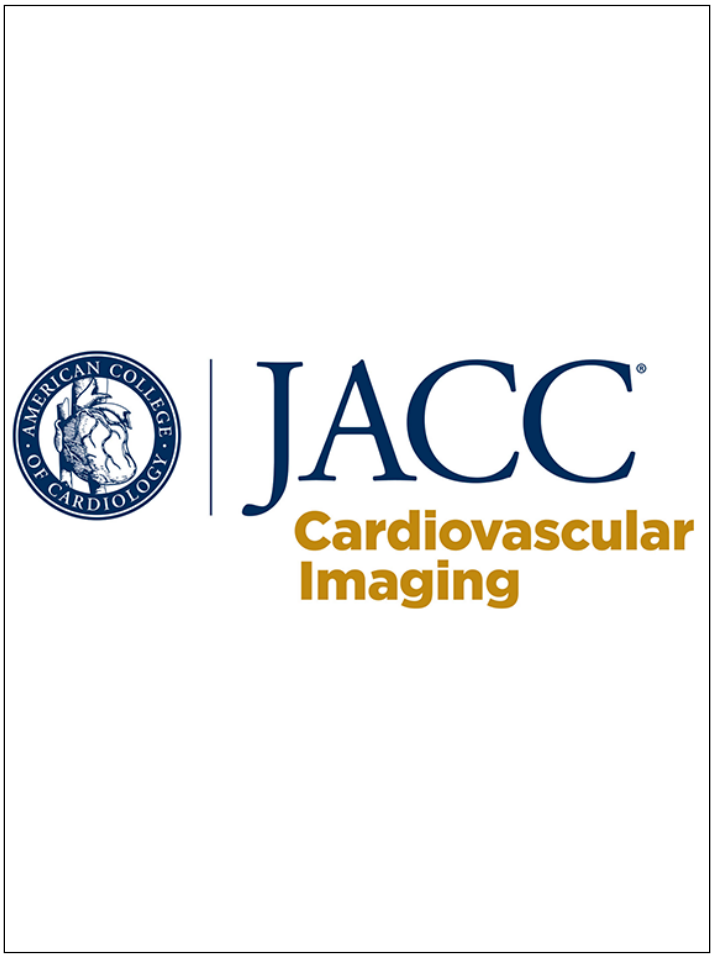

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LETTERS TO THE EDITOR

Micro-Optical Coherence Tomography for Endothelial Cell Visualization in the Coronary Arteries

Coronary arteries are covered by a layer of endothelial cells (ECs) that have a thickness of approximately 1 μm. Impairment of ECs is at the origin of coronary atherosclerosis and its clinical manifestations. The current gold standard, scanning electron microscopy (SEM), has demonstrated that ECs form an endoluminal feature referred to as "endothelial pavementing" (1). However, the assessment of ECs in humans remains elusive because a clinical imaging modality with sufficient resolution does not exist. This study investigated the use of a new form of optical coherence tomography (OCT), termed micro-OCT (μOCT) (2), which offers an axial resolution of 1 μm and a lateral resolution of 2 μm, for evaluating EC morphology.

First, we stripped the endothelium from fresh swine coronary segments with cyanoacrylate adhesive. Coronary segments were imaged 3 dimensionally (3D) with μOCT. μOCT images were then 3D-volume rendered using ImageJ (3). 3D μOCT allowed clear visualization of endothelial pavementing (**Figure 1A**, left top and middle panels) with cells oriented parallel to the coronary flow direction (**Figure 1A**, left top and middle panels), not seen at the sites where ECs were stripped off (**Figure 1A**, top right panel). The surface roughness, measured as root mean squared (RMS), diminished significantly at sites of EC stripping compared with intact sites (3.4 ± 0.1 μm vs. 1.5 ± 0.1 μm, $p < 0.01$). Subsequently, swine coronary segments were processed for SEM and were co-registered to the same area imaged by μOCT. The morphology of ECs visualized by 3D μOCT was similar to that seen by SEM (**Figure 1A**, middle panels). 3D SEM data were computed from 2-dimensional SEM images using intensity thresholding and MountainsMap software (Digital Surf, Besançon, France). For both intact and stripped sites, strong positive correlations were noted between the RMS calculated for μOCT and SEM ($R^2 = 0.95$, $p < 0.01$; $R^2 = 0.97$, $p < 0.01$, respectively) (**Figure 1B**, left top and bottom graphs). We also used μOCT to explore EC morphology in human cadaver coronary plaques. Conventional OCT cross sections were obtained before μOCT to characterize human coronary lesion tissue type. After standard OCT pullback, 1-cm-long coronary segments (n = 45) from 8 fresh cadaver hearts were opened and imaged in 3D with μOCT and co-registered with SEM. As per the corresponding standard OCT images, the tissue type of each coronary segment was classified as intimal hyperplasia, fibrous plaque, fibroatheroma, or fibrocalcific plaque. **Figure 1A**, bottom panels, show typical endothelial morphology of a fibrous plaque seen by 3D μOCT and co-registered SEM. μOCT RMS was significantly lower over fibroatheroma and fibrocalcific plaques compared with intimal hyperplasia and fibrous segments ($p < 0.01$) (**Figure 1B**, right).

The major findings of the present study were that: 1) 3D μOCT was capable of clearly visualizing EC morphology that manifested endothelial pavementing in intact swine coronary arteries, as confirmed by surface morphology seen by SEM; and 2) 3D μOCT imaging was able to identify and quantify EC morphology overlying various human cadaver coronary lesions. These results suggest that μOCT could be useful for improving our understanding of the role of ECs in the pathogenesis of the diverse manifestations of coronary artery disease.

Importantly, μOCT is a noncontact, 3D imaging technology that can ultimately be implemented in catheters to study ECs in living patients (4). 3D μOCT visualization of ECs may allow a more precise capability to predict plaque progression. Although the extent to which μOCT can visualize ECs beneath thrombus remains an open question, μOCT could also be helpful for making a more precise diagnosis of coronary "endothelial" erosion that has emerged as the second most prevalent histopathological finding in acute coronary syndrome. The use of μOCT technology to assess coronary stent strut endothelial coverage may also help resolve current questions and controversies regarding stent healing and optimal antiplatelet therapy durations.

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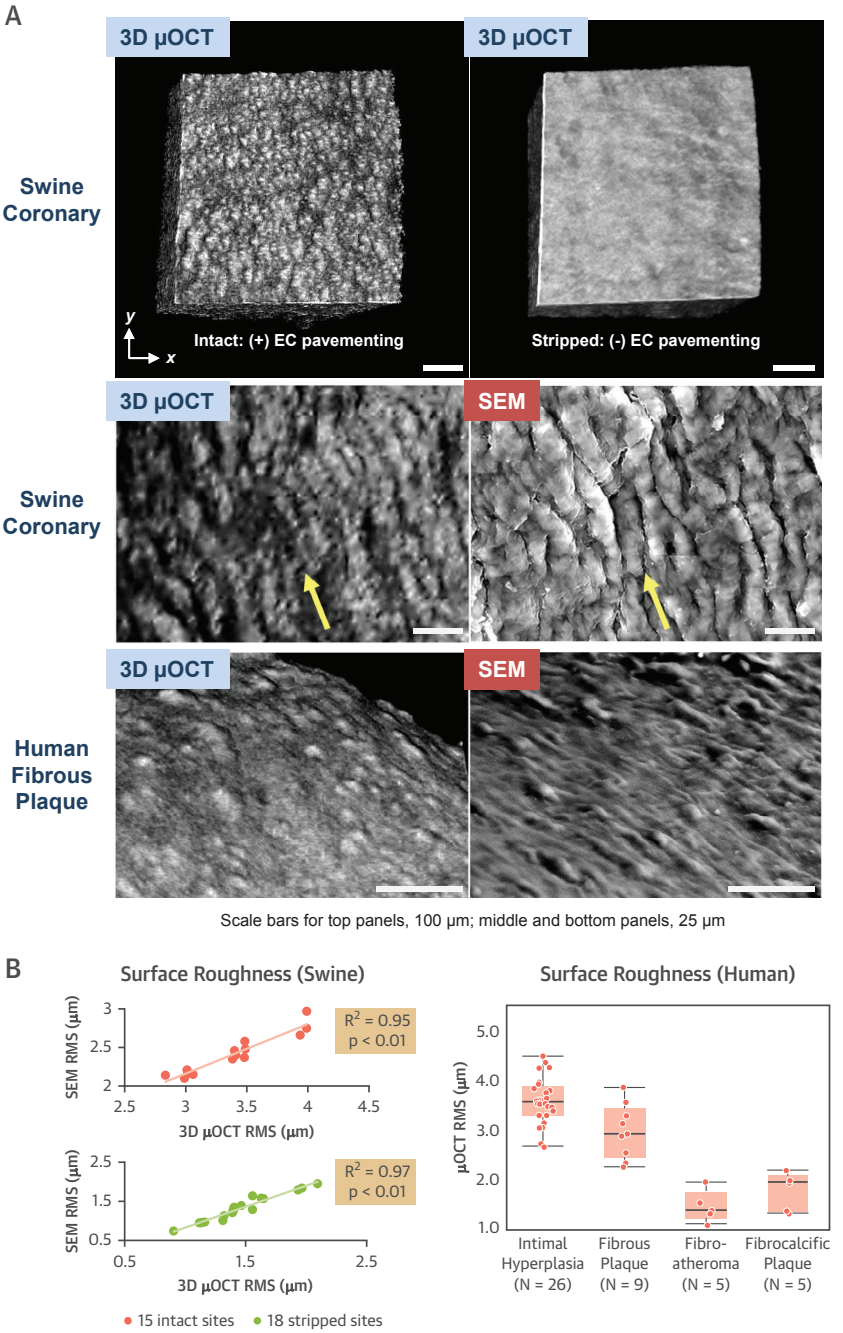
FIGURE 1 3D μOCT and SEM Images of Coronary Endothelial Cell Morphology



(A) Three-dimensional (3D) micro-optical coherence tomography (μOCT) of an intact swine coronary artery showing endothelial cell (EC) pavementing **(top left panel)**. In contrast, a comparatively smooth surface is seen at the site of endothelial stripping **(top right panel)**. Endothelial pavementing of a swine coronary segment and human fibrous plaque visualized by 3D μOCT is similar to that seen by scanning electron microscopy (SEM) **(middle and bottom panels)**. Blood flow direction in the images of the swine coronary artery is depicted using **yellow arrows (middle panels)**, demonstrating an alignment of endothelial cells with flow. Scale bars, 100 μm **(upper panels)**; 25 μm **(middle and bottom panels)**. **(B)** Scatter plots showing significant correlations between 3D μOCT and SEM root mean squared (RMS) measurements in both 15 intact **(left top graph)** and 18 stripped sites **(left bottom graph)**. Box plot of μOCT root mean squared for different OCT-delineated coronary lesions **(right)**. Statistical differences were examined using Wilcoxon signed rank test. Intimal hyperplasia root mean squared (3.6 ± 0.1 μm) was higher than that of fibrous plaque (3.0 ± 0.2 μm) ($p < 0.01$), and both intimal hyperplasia and fibrous plaque root mean squared were higher than those of fibrocalcific plaque (1.8 ±0 .2 μm) and fibroatheroma (1.5 ± 0.1 μm) ($p < 0.01$).

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Please note: Dr. Tearney has reported receiving catheter materials from Terumo Corporation, with which Massachusetts General Hospital has a licensing arrangement and from which he has the rights to receive royalties; has received sponsored research funding from Vivolight and Canon Inc.; has reported a financial or fiduciary interest in SpectraWave, a company developing an OCT-Near Infrared Reflectance Spectroscopy intracoronary imaging system and catheter; and has reported consulting for SpectraWave; his financial or fiduciary interest was reviewed and is managed by the Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. Drs. Tearney and Gardecki are named inventors on OCT and μOCT patents. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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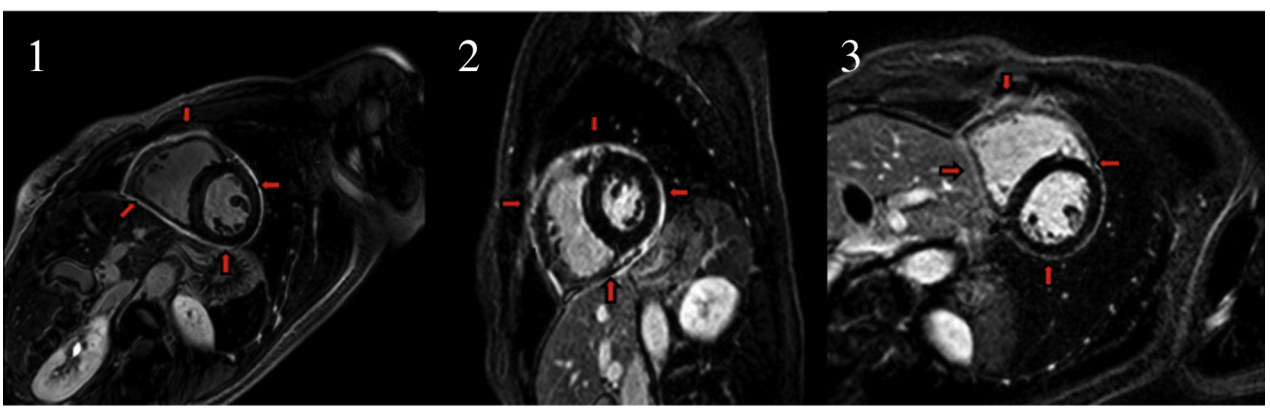
Exercise Is Good for the Heart But Not for the Inflamed Pericardium?

Pericarditis is a condition that has the potential to be associated with significant morbidity and mortality (1). Unfortunately, little is known about the nonpharmacological therapies of pericarditis that go along with traditional anti-inflammatory treatment, particularly the role of exercise restriction. Current U.S. and European guidelines are geared more toward athletic populations and recommend exercise restriction until there is resolution of inflammation on the basis of clinical, laboratory, and echocardiographic data (2,3). However, these guidelines are largely based on expert consensus without strong trial evidence to back them up, and limiting exercise in active individuals may not be desirable. Most explanations of the pathophysiology of exercise-induced harm are just postulated theories, the adverse effects of exercise-induced tachycardia and shear stress on the pericardium leading to worsening inflammation, or increased blood flow to the pericardium secondary to inflammation and resulting oxidative stress from free radicals. Studies have also reported a relationship between pericarditis and genetic variations of the immune system that can predispose people to worsening inflammation from environmental triggers such as exercise (4).

Although we do not yet have a large, robustly analyzed patient series, in our substantial experience, some patients receiving medical therapy who continue to exercise seem to show worsening late gadolinium enhancement on cardiac magnetic resonance (**Figure 1**), and they have higher inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. The late gadolinium enhancement and elevated inflammatory markers tend to improve with exercise restriction, a finding that may support the theory of a proinflammatory role for

FIGURE 1 Worsening LGE on CMR With Exercise



(1) Initial cardiac magnetic resonance with late gadolinium enhancement (LGE) of the pericardium in a case of active pericarditis during anti-inflammatory therapy **(red arrows)**; **(2)** cardiac magnetic resonance after ongoing exercise during medical therapy with worsening late gadolinium enhancement; **(3)** cardiac magnetic resonance after restriction of exercise without changes in medical therapy and improved late gadolinium enhancement.