assessed the components of Ca^{2+} removal through caffeine application, as originally described by Bassani et al. (4). Transient decay rate (K) was significantly greater in contact versus control (3.41 ± 0.15 s^{-1} vs. 2.69 ± 0.07 s^{-1}, n = 26:23 cells; p < 0.001), attributable to 4-fold greater SR Ca^{2+} uptake (2.67 ± 0.12 s^{-1} vs. 0.63 ± 0.67 s^{-1} in control, n = 26:23 cells; p < 0.001). Western blotting demonstrated increased SERCA2a expression (1.02 ± 0.08 vs. 0.55 ± 0.01 in control, n = 4; p < 0.01). Contact culture increased the SR to sodium-calcium exchanger (NCX) ratio from 23:70 in control to 60:32, much closer to the ~70:30 observed in adult cardiomyocytes (4).

Contact culture significantly reduced time to transient peak, a surrogate measure of the rate of SR Ca^{2+} release (**Figure 1**). Caffeine-induced transient amplitude, estimating SR Ca^{2+} content, was significantly greater in contact culture compared with all others, with fractional release, the proportion utilized in voltage-triggered Ca^{2+} transients, greater in contact versus control (16.5 ± 0.40% to 37.4 ± 1.00%, n = 35:32 cells; p < 0.001).

Reverse mode NCX (rNCX) may additionally contribute to the Ca^{2+} transient. Application of ORM-10103, a selective NCX inhibitor (5), resulted in a smaller reduction in transient amplitude in contact versus control (−23.7 ± 1.85% vs. −33.0 ± 1.50%, n = 4; p < 0.001), signifying reduced rNCX contribution.

For cardiomyocytes to maintain homeostasis, SR release must equal SR uptake. Thus, percentage contribution of the SR to all transient Ca^{2+} is equivalent to the percentage uptake calculated previously. Sarcolemmal Ca^{2+}, such as that entering via L-type Ca^{2+} channels, constitutes the remainder after accounting for rNCX. The sarcolemmal to SR flux ratio, a measure of CICR efficiency, was increased from 1:0.5 to 1:3.45 by contact culture.

Overall, our data establish a role for cardiac fibroblasts in regulating SR Ca^{2+} cycling, demonstrating increased SR functionality and engagement in the process of ECC through a mechanism requiring contact or proximity. Future studies will determine whether these effects are brought about through local paracrine signaling or some component of direct cell-cell interaction. Given the significance of diminished SR function and CICR efficiency in cardiac disease, these findings provide valuable insight into the regulation of this fundamental component of cardiomyocyte function.

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In-Scaffold Neoatherosclerosis

An Overestimated Entity?

We read with interest the paper by Moriyama et al. (1) that was published in the *Journal*. The authors investigated the serial neointimal tissue changes in terms of neoatherosclerosis between 1 and 5 years after bioresorbable scaffold implantation as assessed by optical coherence tomography. The reported incidence of neoatherosclerosis was 100% at 5 years.

A therapeutically relevant possibility not taken into account in this study is that the underlying atherosclerotic plaque progression might have as well led to the observed findings (2). If this holds true, the concept that bioresorbable scaffolds seal atherosclerotic plaques would be challenged. Because scaffold struts are no longer visible at 5 years, the authors have arbitrarily assumed a neointimal thickness of 200 μm to distinguish between neoatherosclerosis and underlying native plaque progression.

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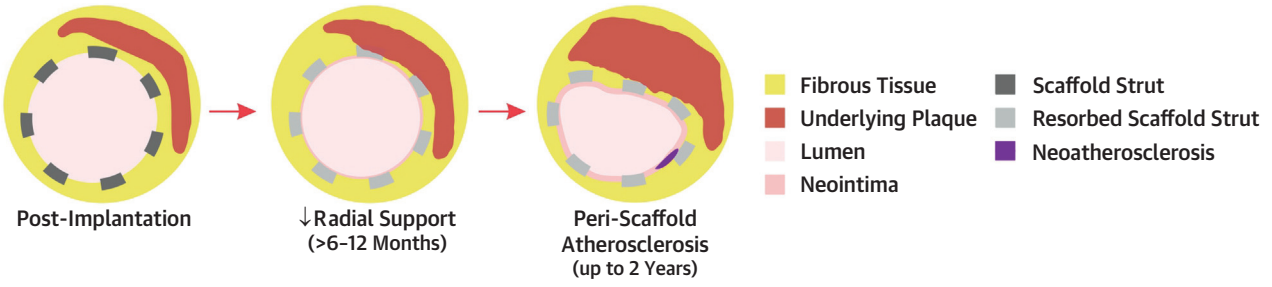
FIGURE 1 Assessment of Atherosclerosis Development Around a Bioresorbable Scaffold



Following loss of the scaffold mechanical support during bioresorption, native atherosclerotic plaque progression might result in inward strut dislocation. In-scaffold neoatherosclerosis development would be seen inside the struts. These changes could be observed during a timeframe when strut remnants are still visible with intravascular imaging.

Bioresorbable scaffolds could serve as an ideal means to provide valuable insights into the mechanisms of periscaffold atherosclerosis development owing to the decreasing radial strength during bioresorption and the black box-like appearance without dorsal shadowing of the optically translucent polymeric struts. That would be interesting if the scaffolded segments could be serially assessed during an earlier timeframe during the bioresorption process when the radial strength of the scaffold has been lost, but the strut remnants are still visible (which could be a period from 6 months up to 2 years post-implantation) and may move freely due to neighboring mechanical forces (e.g., plaque progression or vessel remodeling). As the mechanical integrity of the degrading scaffold diminishes over time, native atherosclerotic plaque ingrowth may lead to dislocation of the strut remnants by pushing them toward the lumen (**Figure 1**). Accordingly, prospective serial optical coherence tomography assessments of bioresorbable scaffolds, combined with intravascular ultrasound to account for potential negative vessel remodeling, with meticulous observation of the strut footprints are warranted.

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REPLY: In-Scaffold Neoatherosclerosis

An Overestimated Entity?

We appreciate Drs. Andreou and Alexopoulos for their valuable comment on the study "Neoatherosclerosis 5 Years After Bioresorbable Vascular Scaffold Implantation" (1). They commented on the possible mechanism that native atherosclerotic plaque ingrowth behind the scaffold may lead to dislocation of the strut remnants by pushing them toward the lumen, which might explain the incidence of in-scaffold atherosclerosis. The term "neoatherosclerosis" has been adopted on the hypothesis that atherosclerosis within the stent/scaffold does not communicate with the underlying native atherosclerosis. Our results cannot make a denial of their theory because our analysis was based on this hypothesis of neoatherosclerosis, and we did not focus on underlying plaque assessment. Therefore, we agree that underlying atherosclerotic plaque may play a role of in-scaffold atherosclerosis growth (2). We also concede that the bioresorbable scaffold is a suitable device to prove their theory by using serial optical coherence tomography (OCT) assessment.