calcification in 34 of 43 (79%). Ossification was seen in 5 of 34 (15%) calcified pericardia. The study was approved by the local ethics committee, and all of the patients gave informed consent.

We isolated pericardial interstitial cells (PICs) and found that they possessed a similar immunophenotype as mesenchymal stem cells. The PICs differentiated into myofibroblasts, chondroblasts, and osteoblasts after stimulation with TGF-β1, indicating that TGF-β1 may promote abnormal differentiation of adult PICs and lead to biological changes.

The effects of TGF-β1 on PICs were consistent with the changes in fibrosis-related genes (compared to control baseline values) in ICP pericardia as mentioned in the preceding text. Incubation of PICs with TGF-β1 (10 to 60 ng/ml) for 48 h or with 10 ng/ml TGF-β1 for 6 to 48 h increased the mRNA expression of collagen I and collagen III in a concentration- and time-dependent manner. After PICs were treated with TGF-β1 (10 ng/ml) for 48 h, MMP-2 and -9 mRNA, critical for elastin degradation, were increased by 5.19-fold and 2.68-fold, respectively. The TIMP-2 mRNA, a natural inhibitor for MMP-2, was also increased by 25.48-fold. However, TGF-β1 decreased the mRNA levels of MMP-1 (~57%) and MMP-13 (~53%) in PICs and increased that of MMP-8 by 6.22-fold. Three days after TGF-β1 (10 ng/ml) stimulation, zymography of conditioned media revealed a band of gelatin degradation at 130 kDa, which represents the heterodimer of MMP-9 and neutrophil gelatinase-associated lipocalin. Heterodimer can prevent MMP-9 degradation, thereby augmenting MMP-9 activity. However, gelatinolytic band of MMP-2 was not detectable until day 28, indicating that TGF-β1–induced robust transcription of TIMP-2 inhibits the activity of MMP-2.

We found TGF-β1 may also contribute to the progression of calcification by inducing apoptosis and osteogenic differentiation of PICs. The TGF-β1 treatment (10 ng/ml, 48 h) resulted in a 1.8-fold increase in apoptosis of confluent PICs compared with untreated cells (Fig. 1A). After treatment with TGF-β1 (10 ng/ml), confluent PICs (Fig. 1B1) spontaneously retracted from neighboring areas (Fig. 1B2) and grouped into aggregates (Fig. 1B3). With the formation of nodules (Fig. 1B4), cells became denser in the central areas of the nodules (Fig. 1B5) and expressed alkaline phosphatase (osteoblast marker) (Fig. 1B6). Propidium iodide counterstaining (Fig. 1B7) showed that a proportion of cells exhibited nuclear shrinkage and chromatin condensation. Terminal deoxynucleotidyl transferase–mediated dUTP nick-end labeling (TUNEL) staining (Fig. 1B8) confirmed the presence of apoptosis. Hoechst 33342 and propidium iodide double staining (Fig. 1B9) revealed a number of cells had already died by apoptosis. Von Kossa staining (Fig. 1B10) detected calcium deposition in the nodules. These nodules displayed increased alkaline phosphatase activity (sevenfold) (Fig. 1C) and contained more calcium (6-fold) (Fig. 1D) than TGF-β1–untreated cells.

In conclusion, our results demonstrate that TGF-β1 exerts pleiotropic effects on PICs by promoting abnormal differentiation, inducing apoptosis, and regulating the expression of fibrosis-related genes in PICs, which indicates that TGF-β1 may act as a regulator of both fibrosis and calcification during the progression of ICP.

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**Letters to the Editor**

Clinical Outcome, Angiographic Outcome, and Coronary Endothelial Function After Drug-Eluting Stent Implantation

I read with interest the paper by Park et al. (1) comparing patients treated with zotarolimus-eluting stents (ZES) with patients treated with paclitaxel-eluting stents (PES) or sirolimus-eluting stents in routine clinical practice. Although the authors demonstrated that ischemia-driven target lesion revascularization and target vessel revascularization at 12 months were significantly more reduced in the ZES group than in the PES group (4.9% vs. 7.5% and 5.2% vs. 7.6%, respectively, see Table 3 of Park et al. [1]), quantitative angiographic analysis (Table 4 of Park et al. [1]) demonstrated no significant differences in binary restenosis between the groups (in stent, 9.6% vs. 10.9%; in segment, 12.1% vs. 12.4%, respectively) as well as in other angiographic variables (minimal luminal diameter and percentage of diameter stenosis).

Previous studies demonstrated that endothelial function of the implanted vessel was preserved in patients treated with ZES (2–4), whereas endothelial dysfunction was observed in vessels treated with PES (3,5–7). Patients with ZES restenosis may present with angina or ischemia less frequently than patients with PES restenosis, even with a similar degree of stenosis. To clarify this point,
it would be of great help if the authors would provide data on how many patients had angina or ischemia (positive functional study) in patients with ZES or PES restenosis.

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Reply

We thank Dr. Kaneda for his comments regarding our paper (1). Although zotarolimus- and paclitaxel-eluting stents showed similar angiographic results, the rate of target lesion and target vessel revascularization was lower in the zotarolimus-eluting stent group. The discrepancy between angiographic parameters and clinical revascularization was also noted in the earlier REALITY (Head-to-Head Comparison Between Cypher and Taxus) trial comparing sirolimus-eluting and paclitaxel-eluting stents, in which the significant differences in several continuous angiographic variables (in-stent minimal luminal diameter, percentage of diameter stenosis, in-stent late loss, and in-stent late loss index) did not translate into significant differences in in-lesion binary restenosis or in target lesion revascularization (2).

Although we do not fully explain this discrepancy between angiographic measures and clinical outcomes, a plausible mechanism is probably multifactorial. First, it might be possible that an angiographically measured critical threshold inducing clinically or ischemia-driven revascularization could differ among the different stent platforms, even with similar angiographic parameters. It raises important questions about the value of angiographic surrogate endpoints as predictors of clinical outcome, as suggested in the literature (3,4). Second, some difference in the incidence of the aggressive form (i.e., proliferative or total type) of in-stent restenosis (1.9% with zotarolimus stents and 0.5% with paclitaxel stents), which make it more difficult for the treating physician to perform repeat intervention, thereby favoring conservative medical treatment, might influence the rate of target-lesion revascularization. Last, as suggested in other studies (5,6), endothelial function of the implanted vessel according to different types of DES could be a possible explanation for this discrepancy.

In the ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PaclTaxel-Eluting Stent for Coronary Lesions) trial, as already defined, all target vessel (or target lesion) revascularization was considered to be ischemia driven and clinically indicated if associated with a positive functional study results, a target vessel (or target lesion) diameter stenosis of ≥50% based on quantitative coronary angiography with ischemic symptoms or a target vessel (or target lesion) diameter stenosis of ≥70% with or without documented ischemia.

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Cardiac Magnetic Resonance for Risk Stratification of Patients With Frequent Premature Ventricular Contractions

The study by Aquaro et al. (1) reported that abnormalities of the right ventricle (RV) detected by cardiac magnetic resonance (CMR)