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Letters to the Editor

Endothelial Function in Coronary Chronic Total Occlusions

Need for Rigorous Methodology

We read with interest the paper by Galassi et al. (1). We agree with the authors about the fact that immediately after chronic total occlusion (CTO) recanalization, there is an impairment of endothelium-dependent and -independent vasomotion, as also demonstrated in recent studies (2,3). However, some limitations and flaws in the methodology and in the results presentation need to be highlighted and clarified by the authors.

With regard to quantitative coronary angiography (QCA), it is of value to use 3-dimensional QCA (3D-QCA), which is known to overcome the limitations of 2-dimensional QCA (2D-QCA), such as foreshortening, thus making the measurements more reliable (4). However, it is quite unusual and arbitrary that the authors measured only the reference vessel diameter (RVD) or that such measurement was not performed in a coronary segment, but at 3 single points distal to the stent edge. All previous studies classically quantified the vasomotion in a coronary segment, reporting the changes in mean lumen diameter and not in RVD (5,6). The restriction of the analysis to 3 single QCA points limits the observation, multiplying the measurements per patients and not taking into account any data clustering. Moreover, in contrast to what is reported in the Results section, Table 3 shows the intravascular ultrasound (IVUS) data and not the QCA data of the vasomotion substudy.

The coronary segment distal to the CTO was also analyzed by IVUS. The authors again decided to restrict the observation, performing the analysis every 5 mm, instead of the conventionally used 1 mm. Although it is known that the 3D-QCA measurements are closer to the IVUS measurements compared with 2D-QCA, it is noteworthy that in the present study, there was not an increase in lumen diameter by IVUS in contrast to QCA (7). It may have to do with the fact that the QCA points do not match the sampling of IVUS. Nevertheless, this contradictory message (QCA vs. IVUS) makes their observations much less solid: in the best scenario, IVUS is much more reliable to quantify lumen dimensions than QCA and therefore the main conclusion of the

paper should be that there is no increase in lumen dimensions as seen by IVUS.

In addition to this, the IVUS data reported in the table partially differ from those reported in the text and includes the measurement of intimal hyperplasia in the coronary segment distal to the recanalized CTO, where no stent was implanted and no intimal hyperplasia could therefore be measured (8).

Finally, the authors underestimated the role of the drug-eluting stent (DES)–dependent endothelial dysfunction, which is normally present in the coronary segment distal to a first-generation DES, caused by the downstream elution of the antiproliferative drug and that has disappeared with the introduction of second-generation DES (5). As the vasomotion substudy included only patients with first-generation DESs, the persistence or the worsening of the endothelial dysfunction at follow-up distal to the stent previously implanted could be first-generation DES-related and not deriving from a long-acting endothelial dysfunction of the coronary segment distal the CTO after recanalization.

Based on these concerns, most of the findings of the present study should be taken as hypothesis generating and would need further investigation in a well-designed and powered study.

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Reply

We thank Dr. Brugaletta and colleagues for their valuable comments on our paper (1).

First, as they point out, 3-dimensional quantitative coronary angiography (3D-QCA) might overcome several limitations of 2-dimensional (2D-QCA), as previously shown also in our previous experience (2). We concur that it is unusual to select as the primary measurement the reference vessel diameter (RVD) instead of minimal lumen diameter in this kind of investigation. We made this decision because it was unknown at the beginning of the study whether changes in the vessel caliper would be ascribed to coronary vasomotion or to a remodeling phenomenon. Moreover, we disagree that measuring 3 single QCA points might limit the study results. Indeed, with this method, we were able to provide coronary measurements at a certain point and reproduce them at follow-up, further assessing the relationship between vessel diameter measurement and its percentage of variation.

Second, differently from the standards (3), we decided to perform intravascular ultrasound (IVUS) analysis every 5 mm, considering the very long coronary segments assessed. Thus, we were able to limit the bias related to data clustering. Notably, with such analysis, it was easier to reproduce measurements at follow-up. We probably did not observe any changes in IVUS measurements because of the small sample size of the IVUS substudy, which was not sufficiently powered to show any significant difference. In this regard, we would like to emphasize that the primary endpoint of the main analysis was the RVD at angiographic follow-up as assessed by 3D-QCA, and for this evaluation, an appropriate pre-specified sample size was used.

Third, we truly concur with Dr. Brugaletta and colleagues regarding the possibility that because the vasomotion substudy included only patients receiving first-generation drug-eluting stents (DESs), the persistence or worsening of the endothelial dysfunction at follow-up distal to the implanted stent could be first-generation DES related and not caused by a long-acting endothelial dysfunction of the coronary segment distal to the CTO after recanalization. This is a limitation that was discussed in the text.

Fourth, we apologize to the editor and readers for some typing and spelling errors in the Results section, which did not substantially affect the study conclusions.

Finally, we believe that our study clearly shows that recanalization of CTO is followed by a reversible hibernation of the vascular wall at distal coronary segments, which determine an increase in vessel diameter on long-term follow-up due to an increase in shear stress. We hope that using our findings as hypothesis generating, future sufficiently powered investigations will provide a better explanation of this phenomenon.

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