

# Evaluation of Vessel Response to Percutaneous Coronary Intervention

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Over the past decades, investigation into vessel response after percutaneous coronary intervention (PCI) has played integral role not only in understanding the treatment mechanisms but in developing effective clues for patients suffering from coronary artery disease. With recent introduction of drug eluting stent (DES) technology, a major breakthrough in the reduction of restenosis was achieved by inhibiting neointimal hyperplasia.<sup>1,2</sup> However, late acquired vessel remodeling and edge effect after DES implantation has emerged as potential causes of stent thrombosis and restenosis.<sup>3,4</sup> As investigated in this issue of *Revista Española de Cardiología* by García-García et al.,<sup>5</sup> the interpretation of vessel response of current DES technology is imperative for effective countermeasure development against such catastrophic phenomena. At the same time, it is also essential to understand accumulated knowledge and established evaluation methodology of vessel response based on our previous experience with detailed intravascular ultrasound (IVUS) analysis.

## Vessel Response After Balloon Angioplasty

Negative arterial remodeling has been shown to be a major determinant of late luminal narrowing after balloon angioplasty.<sup>6,7</sup> As balloon angioplasty began to have wide spread use in the clinical settings, increased neointimal proliferation has been thought to be responsible for late

luminal narrowing after balloon angioplasty.<sup>8,9</sup> However, investigators have clearly demonstrated that change in vessel size rather than the magnitude of neointimal proliferation contributes to the lumen change using serial IVUS.<sup>2,6,10</sup> They showed that: *a*) a decrease in total arterial (EEM) CSA accounted for 70% to 75% of late lumen loss; and *b*) late lumen loss correlated better with a decrease in EEM CSA than with an increase in P+M CSA.<sup>6</sup> Animal studies have suggested that the presence of compensatory arterial dilatation is the greater determinant of restenosis with a universal cellular proliferation after balloon angioplasty.<sup>11-13</sup>

## Vessel Response After Stent Implantation

On the basis of the lessons from the experience with balloon angioplasty, bare metal stents (BMS) was developed, which merely scaffold the vessel lumen to prevent negative remodeling and significantly reduced the incidence of restenosis<sup>14,15</sup> without suppressing proliferative responses. Although over than 30 years have passed since the concept of stenting was first proposed,<sup>16</sup> there is still controversy as to whether persistent remodeling occurs after BMS implantation. In 3 retrospective studies including a total of 121 patients,<sup>17-19</sup> investigators independently reported that remodeling did not occur. On the other hand, the presence of remodeling was reported by 3 groups (Tanabe et al,<sup>20</sup> Hoffmann et al,<sup>21</sup> and Nakamura et al<sup>22</sup>). Interestingly enough, even in these 3 reports, there are disagreements as to whether there is an association between peri-stent remodeling and in-stent neointimal proliferation. Tanabe et al concluded that persistent remodeling occurs without significant correlation with in-stent neointima from the analysis of 152 patients treated with BMS.<sup>20</sup> However Nakamura et al reported inverse correlation,<sup>22</sup> and Hoffmann et al showed positive correlation.<sup>21</sup>

## Vessel Response After DES Implantation

Although BMS helped reduce the incidence of restenosis into about 20%, the benefit was obtained at a cost of an increase in neointimal hyperplasia, which results in BMS restenosis. The bigger is better strategy

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has helped reduce the incidence of BMS restenosis. However, the most striking breakthrough against this phenomenon was achieved by the appearance of DES.<sup>1,2</sup> As several endovascular treatment such as directional atherectomy (DCA) and brachytherapy are associated with distinctive complications due to their direct effect on vessel,<sup>23,24</sup> vessel response after DES implantation have been evaluated with serial IVUS studies, which clearly demonstrated that different DES have different vessel response.

Previous reports have shown that SES are effective in inhibiting neointimal hyperplasia without affecting total vessel volume or plaque volume behind the stent struts at 6 months.<sup>25,26</sup> However, long term vascular responses after SES implantation were not well studied. One small study, evaluating the long-term arterial response after SES implantation, has shown that persistent plaque volume maintained in the first 2 years after SES implantation. However, at 4-year follow-up, a significant negative remodeling of peri-stent plaque was observed accompanied by an increase in hyperechogenicity on IVUS, which has been thought to be associated with a predominance of dense fibrous or elastic tissue.<sup>27</sup> Although this is a small study including 23 event-free patients with simple lesions, it has been suggested that SES might introduce negative vessel remodeling through modification of plaque component behind the struts.

Whereas, as for paclitaxel-eluting stent (PES), positive vessel remodeling in stented segment was consistently reported.<sup>28,29</sup> Interestingly, in the TAXUS-II trial, positive vessel remodeling was observed from post stent to 6-month follow-up with dose dependent manner, and then remodeled vessel regressed completely in the slow-release (SR) group and partially in the moderate-release (MR) group during the following 18 months to 2 years.<sup>30</sup> An integrated analysis, combining the IVUS data from TAXUS-IV, TAXUS-V de novo, and TAXUS-VI trial, have also shown a more pronounced positive remodeling with the MR stent than SR stents.<sup>31</sup> Despite the consistent use of PES throughout those TAXUS trials, the platforms are not identical. NIR stent, which is made of thicker stainless steel, was used in TAXUS-II trial, whereas Express stent, which is made of thinner struts, was used in TAXUS-IV, TAXUS-V de novo, and TAXUS-VI trials. Nevertheless, positive remodeling was consistently observed with dose dependent manner, suggesting that paclitaxel itself may play a key role in vessel remodeling after PES implantation.

### Edge Effect of DES

In the SIRIUS trial, which enrolled patients with more challenging conditions than FIM<sup>32</sup> and RAVEL trial,<sup>25</sup> a higher rate of significant stenosis was observed at the proximal edge of SES (binary restenosis rate; 3.2% for in-stent, 8.9% for in-segment).<sup>32</sup> The contribution of

vessel remodeling to SES edge restenosis was evaluated by several IVUS studies. It has been shown that subsequent negative vessel remodeling, which is correlated with baseline plaque at SES edge, contributes importantly to SES edge restenosis.<sup>33,34</sup> These results suggest that incomplete lesion coverage is an important determinant of SES edge restenosis<sup>4</sup> through negative vessel remodeling after SES implantation.

As indicated by García-García et al in the present study,<sup>5</sup> the edge effect of PES is controversial. In the TAXUS-II trial, significant lumen loss was observed in both MR and SR groups at the proximal edge, which is mainly due to plaque increase without vessel remodeling. On the other hand, despite significant increase in plaque area, lumen area was maintained at the distal edge with complete compensation by positive vessel remodeling. Whereas in TAXUS-II trial, although there was no change in vessel area at the proximal edge, a trend towards negative vessel remodeling was observed at the distal edge. Moreover, García-García et al reported positive vessel remodeling at both edge of PES in the present study.<sup>5</sup> In addition to possible selection bias due to relatively small sample size of these studies, there are several possible explanations for the discrepancy. First of all, basic plaque morphology and character could affect vessel adjacent to stented segment. For second, stent strut thickness and metal can induce different reaction at stent edge. Finally, procedural background may result in different vessel reaction. However there was no information on PCI procedure in these studies.

### The Mechanisms of Vessel Remodeling After PCI

Although the exact mechanisms have not been fully elucidated, multiple factors are apparently involved in the development of vessel remodeling after PCI.

The first category consists of device-related factors, including drug, stent material, design, and the interaction with adjunctive therapy such as directional coronary atherectomy and intracoronary brachytherapy.<sup>23,24</sup> Given DES has become an important option in the treatment strategy for patients with coronary artery diseases, drug choice and release kinetics are probably the most important components as one of the determinants of the type and time-course of vascular response. Paclitaxel is a cytotoxic drug, which suppresses smooth muscle cell and endothelial cell proliferation by disrupting microtubule dynamic cells in the mitosis phase of the cell cycle.<sup>35</sup> Although results of MR Taxus stents demonstrated a moderate inflammatory response without evidence of increased amounts of fibrin deposition with near complete endothelialization, increased dose of paclitaxel resulted in a significant increase in luminal area, which is, in part, due to medial wall necrosis, smooth muscle cell loss.

To our knowledge, no specific stent type has been reported to be associated with increased risk for vessel remodeling. However, some kinds of metal, design, and strut thickness may reduce radial strength, resulting in chronic recoil accompanied by negative vessel remodeling. Additionally, it has been shown that thin-strut BMS were associated with a significant reduction in restenosis compared with thicker strut BMS, probably because of less arterial injury.<sup>36,37</sup> Although it is still controversial whether the extent of neointimal hyperplasia can affect vessel remodeling after stent implantation, however, less arterial injury may end up with less remodeling.

The second category comprises patient or lesion, specific factors, including coronary risk factors, preexistent vessel remodeling, angina status, plaque characteristics, local inflammatory activity, and shear stress. For example, as García-García et al revised in this article,<sup>5</sup> underlying plaque morphology may affect the rate of healing when stent struts penetrate deeply into the necrotic core and are not in contact with cellular areas. Because sirolimus and paclitaxel are highly lipophilic, prolonged tissue retention of these drugs in lipid-rich plaques can theoretically cause longer delays in healing, leading less endothelialization. However, there is no data clearly showing the relation between the presence of necrotic core and vessel remodeling after DES stenting.

The third category includes procedure-related factors. IVUS studies have consistently shown the possible relationship between deep vessel wall cutting and subsequent vessel dilatation after balloon angioplasty, cutting balloon, and DCA.<sup>23,38,39</sup>

### How to Approach the Effect of Intravascular Treatment on Coronary Artery

Since gray-scale IVUS unalterably provide an accurate information on vessel, lumen, and atherosclerotic plaque,<sup>40</sup> it has played substantial role in quantitative monitoring of serial vessel change after PCI. However, despite the several IVUS based approach, none of these methods reproducibly discriminate plaque components.<sup>41-43</sup> Recently, IVUS radiofrequency (IVUS-RF) analysis has gained much attention for its potential ability of plaque characterization. Three different mathematical methods have been applied to RF data analysis including autoregressive modelling (IVUS Virtual Histology<sup>TM</sup> [IVUS-VH], Volcano Corporation, Rancho Cordova, CA, USA), fast Fourier transformation (FFT) (Integrated Backscatter [IB-IVUS]), and wavelet analysis.<sup>44-46</sup> In the present study,<sup>5</sup> García-García et al investigated serial changes of plaque character at both stent edges after Taxus stent implantation using IVUS-VH. It is an IVUS-based technique that analyzes the backscattered ultrasound signal reflected from tissues

and correlates them with a predefined database of frequencybased ultrasound parameters.<sup>44</sup> These parameters were determined by the careful correlation of backscattered data collected from fresh ex vivo human arteries with the corresponding histology sections. Given the lack of accuracy of gray-scale IVUS in plaque characterization mainly derives from the use of ambiguous and subjective parameters, theoretically, analysis of the IVUS-RF data provides a more accurate and reproducible information for measuring tissue properties. However IVUS-VH still has some limitations in clinical use. First, the accuracy of this modality in assessing atherosclerotic plaque composition requires more rigorous assessment. Basically, the results from IVUS-VH analysis are homogeneous; however, human coronary plaques are very complex in histology. For example, each plaque are classified one of these components according to following definitions: *a*) fibrous plaque that consists of densely packed collagen; *b*) fibro-fatty plaque comprised of collagen and interspersed lipid; *c*) calcified necrotic plaque that includes cholesterol clefts, foam cells, and micro-calcifications; and *d*) calcified plaque without adjacent necrosis.<sup>44</sup> This means that IVUS-VH does not detect specific chemical compounds such as lipid or collagen, rather the mixture of compounds that make up 1 of the 4 tissue types. Furthermore, a histological section and an IVUS-RF frame represent different plaque cross-sectional thickness. A histological section may be too thin (several  $\mu\text{m}$ ) to get appropriate correlations with IVUS-RF data which derives from an ultrasound beam whose width may be as great as 300  $\mu\text{m}$  at its interface with the arterial wall. As a consequence, IVUS-RF might have difficulties in figuring out subtle changes in plaque composition that occur over small distances.<sup>47</sup>

For second, VH-IVUS has trouble distinguishing necrotic core from calcification. Necrotic core is often accompanied by calcification on VH-IVUS. However, pathological studies have clearly shown that there are definite areas of necrotic core that lack calcifications. For third, to establish the reproducibility of IVUS-VH of plaque characterization is a critical step in applying it to clinical follow up after PCI. There is only one small study including 15 patients assessing this important validation available so far.<sup>48</sup> Finally, thrombus and stent strut has to be excluded from the analysis due to the lack of proper validation for their IVUS-RF data.

### Clinical Validation of Intravascular Ultrasound-Radiofrequency

Despite some limitations, the concept of in vivo plaque characterization has the potential to add new insight to the interpretation of coronary artery disease. Two clinical studies are underway to elucidate clinical validation of

IVUS-RF analysis. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial is a prospective study, which has enrolled 700 patients with ACS. All 3 coronary arteries will be assessed by quantitative angiography, grey scale IVUS, palpography, and IVUS-VH. Clinical follow-up is scheduled annually for 5 years or is event-driven. The other study is the Virtual Histology Global Registry, an industry sponsored, international, multicenter registry of 2000 patients who have undergone IVUS-VH. This cross-sectional study will provide plaque compositional data across multiple patient subgroups.

## Conclusion

Over the past several years, a numbers of clinical studies have investigated vessel response after PCI using IVUS. Considering recent concern about long-term safety of current DES technology, investigation into the mechanisms of vessel reaction such as the present study by García-García et al<sup>5</sup> are vital. Despite some limitations, the concept of in vivo plaque characterization has the potential to add new insight to the interpretation of coronary artery disease. We may be entering the new age where precise interpretation of plaque composition my allow us to expect future vessel reaction after PCI.

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