Endothelial-dependent vasomotion in a coronary segment treated by ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioresorption of the polymer: indirect finding of vascular reparative therapy?

Salvatore Brugaletta¹,²†, Jung Ho Heo¹†, Hector M. Garcia-Garcia¹,³, Vasim Farooq¹, Robert Jan van Geuns¹, Bernard de Bruyne⁴, Dariusz Dudek⁵, Pieter C. Smits⁶, Jacques Koolen⁷, Dougal McClean⁸, Cecile Dorange⁹, Susan Veldhof⁹, Richard Rapoza¹⁰, Yoshinobu Onuma¹, Nico Bruining¹, John A. Ormiston¹¹, and Patrick W. Serruys¹*  

¹Interventional Cardiology Department, ThoraxCenter, Erasmus MC, ’s Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands; ²Department of Cardiology, Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain; ³Cardialysis B.V., Rotterdam, The Netherlands; ⁴Cardiovascular Center Aalst, Aalst, Belgium; ⁵Jagiellonian University, Krakow, Poland; ⁶Maasstad Hospital, Rotterdam, The Netherlands; ⁷Catharina Hospital, Eindhoven, The Netherlands; ⁸Christchurch Hospital, Christchurch, New Zealand; ⁹Abbott Vascular, Diegem, Belgium; ¹⁰Abbott Vascular, Santa Clara, CA, USA; and ¹¹Auckland City Hospital, Auckland, New Zealand  

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Aims  
To analyse the vasoreactivity of a coronary segment, previously scaffolded by the ABSORB bioresorbable vascular scaffold (BVS) device, in relationship to its intravascular ultrasound—virtual histology (IVUS—VH) composition and reduction in greyscale echogenicity of the struts. Coronary segments, transiently scaffolded by a polymeric device, may in the long-term recover a normal vasomotor tone. Recovery of a normal endothelial-dependent vasomotion may be enabled by scaffold bioresorption, composition of the underlying tissue, or a combination of both mechanisms.  

Methods and results  
All patients from the ABSORB Cohort A and B trials, who underwent a vasomotion test and IVUS—VH investigation at 12 and 24 months, were included. Acetylcholine (Ach) and nitroglycerin were used to test either the endothelial-dependent or -independent vasomotion of the treated segment. Changes in polymeric strut echogenicity—a surrogate for bioresorption—IVUS—VH composition of the tissue underneath the scaffold and their relationship with the pharmacologically induced vasomotion were all evaluated. Overall, 26 patients underwent the vasomotion test (18 at 12 and 8 at 24 months). Vasodilatory response to Ach was quantitatively associated with larger reductions over time in polymeric strut echogenicity (y = −0.159x − 6.85; r = −0.781, P < 0.001). Scaffolded segments with vasoconstriction to Ach had larger vessel areas (14.37 ± 2.50 vs. 11.85 ± 2.54 mm², P = 0.030), larger plaque burden (57.31 ± 5.96 vs. 49.09 ± 9.10%, P = 0.018), and larger necrotic core (NC) areas [1.39 (±1.14, ±1.74) vs. 0.78 mm² (±0.20, ±0.98), P = 0.006] compared with those with vasodilation.  

Conclusion  
Vasodilatory response to Ach, in coronary segments scaffolded by the ABSORB BVS device, is associated with a reduction in echogenicity of the scaffold over time, and a low amount of NC. In particular, the latter finding resembles the behaviour of a native coronary artery not caged by an intracoronary device.  

Keywords  
VH • ABSORB BVS • Echogenicity • Vasomotion

† These authors equally contributed to this work.  
* Corresponding author. Tel: +31 10 4635260, Fax: +31 10 4369154, Email: p.w.j.c.serruys@erasmusmc.nl  

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Introduction

The ABSORB biodegradable vascular scaffold (BVS; Abbott Vascular, Santa Clara, CA, USA) has been introduced in clinical trials with the aim to provide temporary vessel scaffolding and to be subsequently bioabsorbed, thereby allowing the artery to respond to the shear stress and to have pharmacologically induced vasomotion, akin to a non-treated coronary segment.\(^1\)\(^2\)

This entire process, making the coronary segment transiently scaffolded fully amenable to biological, pharmacological, and physiological stimuli, has recently been termed ‘vascular reparative therapy’.\(^3\)

Vasomotor testing, using nitroglycerin (NTG) and acetylcholine (Ach) as endothelial-independent or -dependent vasoactive drugs, were performed in the ABSORB trials at various time points. Clear signs of vasomotion in the scaffolded segment were demonstrated at 12 and 24 months in ABSORB Cohort B and ABSORB Cohort A trials, respectively, suggesting that the mechanical integrity and radial forces of the scaffold had substantially subsided at these time points.\(^3\)\(^4\) In addition, changes in the echogenicity of the polymeric struts appeared to be correlated to the recovery of vasomotion over time points.\(^2\)\(^4\) In addition, changes in the echogenicity of the polymeric struts appeared to be correlated to the recovery of vasomotion over time points.\(^2\)\(^4\)

We sought to analyse: (i) the changes in the echogenicity of polymeric struts, a surrogate of bioresorption, and its relationship with the vasoreactivity in the scaffolded segment, and (ii) the IVUS–VH composition of the coronary segment scaffolded by an ABSORB BVS device at the time of the vasomotion test.

Methods

Study population

The ABSORB trial includes the ABSORB Cohort A and Cohort B trials. Briefly, in the ABSORB Cohort A trial (NCT00300131), 30 patients with a diagnosis of stable or unstable angina or silent ischaemia, were enrolled. All treated lesions were single and de novo in a native coronary artery of 3.0 mm diameter, shorter than 8 mm for the 12 mm scaffold and shorter than 14 mm for the 18 mm scaffold, with a diameter stenosis >50 and <100%, and with a thrombolyis in myocardial infarction (TIMI) flow grade more than 1. Major exclusion criteria were patients presenting with an acute myocardial infarction, unstable arrhythmias, or patients who had a left ventricular ejection fraction <30%, restenotic lesions, lesions located in the left main coronary artery, lesions involving an epicardial side branch ≥2 mm in diameter by visual assessment, and the presence of thrombus or another clinically significant stenosis in the target vessel. All lesions were treated by implantation of an ABSORB first-generation scaffold (revision 1.0) (3.0 × 12 mm and two lesions by 3.0 × 18 mm) and invasively imaged at 6- and 24-month follow-up. The ABSORB Cohort B trial (NCT00856856) enrolled 101 patients with the same clinical profile and lesion type, divided into two groups according to the timeline of invasive follow-up: Cohort B1 with invasive imaging at 6 and 24 months; Cohort B2 with the same invasive imaging at 12 and 36 months. The 12-month follow-up has so far been performed. All lesions were treated by implantation of an ABSORB second-generation scaffold (revision 1.1) (3.0 × 18 mm).\(^7\)

The Ethics Committee at each participating institution approved the protocol and each patient gave written informed consent before inclusion.

As an optional investigation, vasomotion testing with Ach and NTG—according to local practice—was performed at 24-month follow-up in the ABSORB Cohort A trial and at 6- or 12-month follow-up in ABSORB Cohort B trial. As the integrity of the scaffold has been shown to be still present at 6-month follow-up, the present analysis only included patients with a 12- and 24-month follow-up.\(^4\)\(^7\)

Study device

The ABSORB BVS device consists of a polymer backbone of poly-L-lactide coated with a thin layer of a 1:1 mixture of poly-D,L-lactide polymer, and the anti-proliferative drug everolimus to form an amorphous drug-eluting coating matrix containing 100 μg of everolimus/cm\(^2\) of scaffold. The details of the device have been described previously.\(^8\)\(^–\)\(^10\) In brief, the ABSORB BVS revision 1.1 has a smaller maximum circular unsupported surface area compared with revision 1.0, with the struts arranged as in-phase zigzag hoops linked together by three longitudinal links, similar to the XIENCE V design.\(^9\)

Study procedure and intravascular ultrasound acquisition/analysis

Target lesions were treated using standard interventional techniques, with mandatory pre-dilatation. Post-dilatation with a balloon shorter than the implanted scaffold was allowed at the operator’s discretion, up to the prescribed maximal post-dilatation diameter.

The IVUS was performed using the Eagle Eye 20 MHz catheter (Volcano Corp., Rancho Cordova, CA, USA) with an automatic continuous pullback at a rate of 0.5 mm/s (30 frames/s) at the level of the scaffolded segment after ABSORB BVS implantation and at follow-up. Grey-scale images and radiofrequency data, required for VH analysis, were acquired during the same pullback and raw radiofrequency data capture gated to the R-wave (In-Vision Gold, Volcano).

Quantitative IVUS measurements were performed within the scaffolded segment and 5 mm distal to the device, including vessel area, lumen area, plaque area (vessel area – minus lumen area), and plaque burden ([plaque area/vessel area] × 100). For the radiofrequency IVUS analyses, four tissue components [NC—red; dense calcium (DC)—white; fibrous (FT)—dark green; and fibrofatty (FF)—light green] were identified with autoregressive classification systems. All individual tissue components were quantified as area and percentage (per cross-section, NC + DC + FF + FF = 100%).\(^2\)\(^11\)

Echogenicity analysis

It has been previously shown that during in vivo ABSORB BVS degradation, a diminishing grey-level intensity of the struts over time can be detected by IVUS.\(^2\)\(^12\)\(^13\) A dedicated computer-aided greyscale value analysis program was used to assess the echogenicity of the polymeric struts after implantation and at the various follow-up time points.\(^12\)\(^14\) The applied algorithms of this software have been previously published
Quantitative coronary angiography and vasomotion test

β-Blockers, calcium channel blockers, and nitrates were withheld at least 48 h before the coronary angiogram. Quantitative coronary angiography (QCA) was performed with the CASS II analysis system (Pie Medical BV, Maastricht, The Netherlands) by an independent CoreLab (Cardialysis, Rotterdam BV, The Netherlands). The accuracy of this method has previously been reported in detail.13 The scaffolded segment was defined as the segment between the two radio-opaque platinum markers at both ends of the ABSORB BVS. The 5 mm edges distal to the device were also analysed.

The mean lumen diameter in the scaffolded and distal segments was measured by QCA after a baseline infusion of saline and subselective intracoronary administration of Ach, infused through a microcatheter at increasing doses up to a maximum of 10−6 M. In particular, a 2 min selective infusion of Ach (10−8, 10−7, and 10−6 mol/L) was administered with a washout period of at least 5 min between each dose.2 Nitrate (200 µg) was administered following Ach. Vasorelaxation to Ach was defined as a 3% change of the mean lumen diameter to nitrates compared with the 12-month group [+5.79 (+1.41, +12.0) vs. −0.60% (−5.46, +3.91); P = 0.032]. The response to nitrates tended to be greater in patients with a normal response to Ach compared with those without [+4.37 (−1.77, +9.15) vs. −0.39% (−5.58, +3.45); P = 0.093].

Reduction in hyper-echogenicity in the scaffolded segment was larger at 24 than at 12 months [−66.76 (−91.15, −50.45) vs. −18.73% (−30.56, −0.74); P < 0.001]. Scaffolded segments with a vasodilatory response to Ach demonstrated a greater reduction in hyper-echogenicity, compared with those with a vasoconstrictive response to Ach [(−54.75 (−78.95, −41.51) vs. −16.34% (−30.56, −0.74); P = 0.009]. A significant negative relationship between changes in the mean lumen diameter after Ach administration and in hyper-echogenicity was demonstrated (r = −0.781; P < 0.001) (Figure 1). A significant negative relationship was also found between changes in the mean lumen diameter after nitrates administration and hyper-echogenicity (r = −0.511; P = 0.030).

By greyscale IVUS and VH, scaffolded segments with a vasoconstrictive response to Ach had larger mean vessel area, plaque burden, and NC content compared with those with a vasodilatory response to Ach (Table 3). A significant negative relationship was found between NC area and changes in mean lumen diameter after Ach administration (r = −0.676, P = 0.001) (Figure 2).

Response to acetylcholine and nitroglycerin at the distal edge of the scaffold

In 22 patients (14 at 12 and 8 at 24 months), both IVUS–VH analysis and an Ach test were available at the distal edge of the scaffold (Table 2). Overall, no significant changes in the mean lumen diameter after Ach (−2.60% (−9.02, +4.38); P = 0.201) were demonstrated. Patients at 24 months (n = 8) exhibited, on average, a significant increase in the mean lumen diameter after Ach administration compared with patients at 12 months [+6.16 (−1.07, +13.14) vs. −6.41% (−11.74, −1.17); P = 0.006]. Taken individually, 5 patients (22.7%) had a vasodilatory response to Ach (1/14 at 12 and 4/8 at 24 months; P = 0.017), whereas 14 (63.3%) exhibited a vasoconstrictive response to Ach; the remaining 3 patients did not show changes in the mean lumen diameter.

After nitrate administration, a significant increase in the mean lumen diameter was found [+1.43% (+1.01, +19.49); P = 0.006], especially at 24-month follow-up when compared with 12 months [+21.57 (+12.50, +27.26) vs. +7.91% (−4.26, +10.50);
The response to nitrates was greater in the presence of a normal response to Ach than in its absence \([ + 12.99 ( + 12.85, + 13.29) \text{ vs.} - 7.78\% (- 13.43, - 3.90); P < 0.001]\).

By greyscale IVUS and VH, edge segments with a vasoconstrictive response to Ach had larger plaque burden, DC, FT, and NC area compared with those with a vasodilatory response to Ach.
(Table 4). A significant negative relationship was found between NC area and changes in the mean lumen diameter after Ach administration ($r = -0.552$, $P = 0.011$).

**Discussion**

The major findings of the present study are: (i) the ability of a coronary segment scaffolded by an ABSORB BVS device to react to vasoactive drugs is related to the bioresorption of the polymeric struts, as indirectly evaluated by changes in their echogenicity; (ii) the presence of endothelial dysfunction in this segment is correlated to plaque burden and VH-NC, resembling the behaviour of a native diseased coronary vessel; moreover, recovery of a normal endothelial function was associated with a low plaque burden and VH-NC. (iii) The vasoreactivity behaviour of the distal edge of the scaffold does not differ substantially from the physiological reaction observed in the scaffolded segment. These findings suggest the return of a normal physiological reactivity to vasoactive drugs in the treated coronary segments—with a relative absence of NC—once the mechanical integrity of the device has disappeared.

**Progressive return of vasoreactivity as a function of polymeric bioresorption**

Over the past 15 years, much attention has been focused on endothelial dysfunction in the segment distal to the implanted metallic drug-eluting stent (DES). Subsequently with the introduction of bioresorbable scaffolds, the interest about reactivity to vasoactive drugs has moved to the segment where the device was implanted. As the mechanical integrity of the ABSORB BVS is aimed a priori to disappear within 2 years, the scaffold’s resistance to vasomotion induced by vasoactive drugs decreases over time, thereby allowing for the potential recovery of normal vasomotor tone. This is in contrast to a vascular structure permanently caged by a metallic prosthesis.2

The ABSORB Cohort A trial was the first study demonstrating some degree of return of vasoreactivity in a coronary segment scaffolded by a polylactide device, after administration of Ach, methylergonovine, and nitrates at 2-year follow-up.2 Recently, the ABSORB Cohort B trial demonstrated that the scaffolded segments react by vasomotion to Ach and methylergonovine as early at 12 months, due to the partial subsidence of the radial force of to vasoactive drugs is related to the bioresorption of the polymeric struts, as indirectly evaluated by changes in their echogenicity; (ii) the presence of endothelial dysfunction in this segment is correlated to plaque burden and VH-NC, resembling the behaviour of a native diseased coronary vessel; moreover, recovery of a normal endothelial function was associated with a low plaque burden and VH-NC. (iii) The vasoreactivity behaviour of the distal edge of the scaffold does not differ substantially from the physiological reaction observed in the scaffolded segment. These findings suggest the return of a normal physiological reactivity to vasoactive drugs in the treated coronary segments—with a relative absence of NC—once the mechanical integrity of the device has disappeared.

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![Figure 1](https://academic.oup.com/eurheartj/article-abstract/33/11/1325/547776/Downloaded_fromhttps://academic.oup.com/eurheartj/article-abstract/33/11/1325/547776)

**Figure 1** Correlation at the scaffolded segment between changes in hyper-echogenicity between post-implantation and follow-up and changes in the mean lumen diameter after administration of Ach.

| Table 3 Intravascular ultrasound and virtual histology findings at follow-up in the scaffolded segment, according to the presence of vasoconstriction or vasodilation response to Ach. (12 and 24 months pooled) |
|---|---|---|
| **Scaffold vasoconstriction (n = 14)** | **Scaffold vasodilation (n = 11)** | **P-value** |
| Mean vessel area (mm²) | 14.37 ± 2.50 | 11.85 ± 2.54 | 0.030 |
| Mean lumen area (mm²) | 6.04 ± 0.71 | 5.89 ± 1.08 | 0.766 |
| Mean plaque area (mm²) | 8.33 ± 2.07 | 5.96 ± 1.99 | 0.006 |
| Mean plaque burden (%) | 57.31 ± 5.96 | 49.09 ± 9.10 | 0.018 |
| Dense calcium area (mm²) | 1.26 (0.98–1.48) | 0.65 (0.20–1.31) | 0.055 |
| Dense calcium (%) | 25.35 (17.47–34.88) | 23.19 (16.46–27.85) | 0.820 |
| Fibrous tissue area (mm²) | 1.91 (1.02–2.99) | 1.17 (0.43–1.90) | 0.119 |
| Fibrous tissue (%) | 36.79 (32.78–46.92) | 46.86 (36.31–52.22) | 0.207 |
| Fibrofatty tissue area (mm²) | 0.19 (0.09–0.29) | 0.08 (0.03–0.15) | 0.134 |
| Fibrofatty tissue (%) | 4.16 (2.97–6.02) | 3.99 (2.70–5.05) | 0.865 |
| Necrotic core area (mm²) | 1.39 (1.14–1.74) | 0.78 (0.20–0.98) | 0.006 |
| Necrotic core (%) | 28.00 (24.32–31.63) | 24.31 (23.18–26.61) | 0.047 |

Data are expressed as mean ± SD or median (IQR), as appropriate. SD, standard deviation; IQR, interquartile range. One patient did not exhibit any changes in the mean lumen diameter after Ach administration and was excluded from the table.
the scaffolded vessel. Conversely, at 6 months, the scaffold is still able to counteract the pharmacologically induced vasoconstrictive effect of methylergonovine (Figure 3). The differences in the degradation behaviour between the two revisions of the ABSORB device may be an explanation for the differing degree of vaso-motion recovery.

Previous reports have described that degradation of the scaffold can be monitored in vivo by a reduction in hyper-echogenicity of tissue over time. It is also known from animal data that the scaffold polymer has a mass loss of 70 and 90% at 12 and 18 months, respectively, and becomes undetectable at 24 months. In the present analysis, a greater reduction in hyper-echogenicity of the scaffolded segment was associated with a normal vasodilatory response to Ach. These findings may support a link between the grade of scaffold degradation and the restoration of a normal vascular reactivity in the treated segment.

Influence of virtual histology composition of the underlying tissue on the vasoreactivity of the scaffolded coronary segment

In an untreated coronary artery segment, vasoconstriction to Ach has previously shown to be correlated to specific features of vulnerable plaque, in particular high content of DC and NC. These findings were in part confirmed in the present analysis at the level of the distal edge, where the presence of a vasoconstrictive response to Ach was related to high plaque burden, DC, and NC area. However, whereas the relative content (%) of DC was not different between the two groups, the relative content of NC tended to be higher in the edges with vasoconstriction to Ach (P = 0.095): the small number of patients or the short length of the segments analysed could explain the lack of statistical significance.

It was of note that in the scaffolded segment, the ability to recover a vasodilatory response to Ach appeared to be dependent on the plaque burden and NC content (Figure 4). The present study further supports the fact that NC, a proven site of active inflammation and oxidative stress, may constitute a pathophysiological link between plaque composition and endothelial dysfunction. Acetylcholine normally lowers the capillary resistance, thereby increasing flow and shear stress with stimulation of

Figure 2 Correlation at the scaffold segment between necrotic core area and changes in the mean lumen diameter after administration of acetylcholine.

Table 4 Intravascular ultrasound and virtual histology findings at follow-up at the distal edge of the scaffold, according to the presence of vasoconstriction or vasodilation response to Ach (12 and 24 months pooled)

<table>
<thead>
<tr>
<th></th>
<th>Vasoconstriction of the distal edge (n = 14)</th>
<th>Vasodilation of the distal edge (n = 5)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean vessel area (mm²)</td>
<td>12.58 ± 3.28</td>
<td>9.59 ± 1.76</td>
<td>0.173</td>
</tr>
<tr>
<td>Mean lumen area (mm²)</td>
<td>6.81 ± 1.35</td>
<td>6.68 ± 1.34</td>
<td>0.924</td>
</tr>
<tr>
<td>Mean plaque area (mm²)</td>
<td>5.76 ± 2.46</td>
<td>2.91 ± 0.51</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean plaque burden (%)</td>
<td>44.51 ± 9.17</td>
<td>30.50 ± 2.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Dense calcium area (mm²)</td>
<td>0.23 (0.12–0.36)</td>
<td>0.01 (0.00–0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dense calcium (%)</td>
<td>10.61 (6.88–27.51)</td>
<td>4.55 (0.00–22.71)</td>
<td>0.208</td>
</tr>
<tr>
<td>Fibrous tissue area (mm²)</td>
<td>1.03 (0.43–2.62)</td>
<td>0.00 (0.00–0.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fibrous tissue (%)</td>
<td>57.82 (44.36–61.51)</td>
<td>0.00 (0.00–56.38)</td>
<td>0.026</td>
</tr>
<tr>
<td>Fibrofatty tissue area (mm²)</td>
<td>0.21 (0.03–0.43)</td>
<td>0.00 (0.00–0.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fibrofatty tissue (%)</td>
<td>7.98 (4.15–14.65)</td>
<td>0.00 (0.00–8.35)</td>
<td>0.019</td>
</tr>
<tr>
<td>Necrotic core area (mm²)</td>
<td>0.30 (0.18–0.64)</td>
<td>0.01 (0.00–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Necrotic core (%)</td>
<td>18.81 (13.60–24.32)</td>
<td>6.28 (0.00–13.10)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median (IQR), as appropriate. SD, standard deviation; IQR, interquartile range. Three patients did not exhibit any changes in the mean lumen diameter after Ach administration and were excluded from the table.
endothelial receptors and eventual release of nitric oxide through endothelial nitric oxide synthesis activation. For this reason, the anatomical and functional integrity of coalescent endothelial cells is a \textit{conditio sine qua non} for a vasodilatory reaction to Ach.

It is also important to highlight the analogy in response to Ach in relation to VH plaque composition between a coronary segment scaffolded by a bioresorbable device and previous findings in a native diseased coronary segment. It is the fact that they both exhibited the same dependence of the Ach response, to the presence of NC, may support the concept of recuperation of a normal reaction to shear stress and vasoactive drugs, in a coronary vessel, initially treated with a bioresorbable scaffold, once the scaffold is bioresorbed.

Previously, in a small series of patients investigated pre, post, 6, and 24 months after scaffold implantation (ABSORB Cohort A), it was demonstrated that the scaffold bioresorption process did not globally affect the VH-NC content of the vessel wall. Everolimus has been shown to have some anti-inflammatory effects that can lead, in the long-term, to the VH-NC reduction in the plaque behind the polymeric scaffold.

The vasoconstrictive reaction to Ach has to be therefore related to the pre-existing level of NC prior to the treatment with the scaffold. Further and novel strategies to halt or regress the NC need to be considered, in conjunction with the focal treatment with this transient scaffold. In particular, darapladib and lipid-lowering therapy, such as statins, have previously been shown to be promising drugs to reduce the NC content.

Eventually, it should be mentioned that two different versions of the ABSORB device have been therein analysed. Although both are made with the same polylactide material, a potentially different impact on coronary endothelium cannot be excluded.
Vasoreactivity of the coronary segments adjacent to a polymeric device

The coronary segment distal to a first-generation DES classically exhibits a paradoxical response to Ach, especially when compared with bare metal stent.16,24,25 The introduction of the second-generation DES has been shown to reduce this endothelial dysfunction. The present analysis investigating a new generation of the BVS device, made of poly lactide that completely bioresorbed in ~2 years, demonstrated that on average, the segment distal to the implanted scaffold did not have a significant vasoconstriction response to Ach administration. Four out of the eight cases tested at 24 months exhibited an intense endothelium-dependent vasodilatory response to Ach, while the majority of the cases tested at 12 months (12/14) had vasoconstriction.

It is widely known that the drug eluted during the first months after device implantation tends to reach the vessel wall distal to the device by elution, diffusion through the tissue, and the vessel vasorum.16 Clinical data support the hypothesis of drug impregnation distally but not proximally to the device, contributing to a lower restenosis rate at the distal compared with the proximal edge.26 The present results may therefore be in favour of a more ‘endothelium friendly impact’ of the drug-eluting bioresorbable scaffold in minimizing the local device- and drug-specific response, affecting the endothelium-dependent vasomotion of the coronary segment distal to the device.27 In particular, not only the presence of a non-metallic cage, but also the elution of everolimus should be considered as hypotheses to explain the present data. While sirolimus was suggested to have a direct determinant effect on the endothelium and/or signalling pathway,16,28 everolimus was shown to cause a marked clearance of macrophages, by autophagy induced by mTOR inhibition, but without altering the endothelial or smooth muscle cell viability.29,30

Limitations

The major limitation of the present analysis is the small number of patients. Nevertheless, this cohort of patients represents the largest series of patients receiving an ABSORB device studied by IVUS–VH and vasoreactivity testing. The second limitation is that the VH composition of the scaffolded plaque may be influenced by the presence of the scaffold; however, analysis of the plaque underlying the scaffold requires acquisition by a specific VH console, further limiting the number of the patients.21 Our analysis lacks of a control group, although the relationship between vasomotor response to Ach and VH composition of plaque in segments without scaffold has been reported previously.6

Conclusions

The present study demonstrated that endothelial dysfunction in a coronary segment scaffolded by an ABSORB BVS device is correlated to plaque burden and NC, resembling the behaviour of a native non-stented coronary segment. Reduction in hyper-echogenicity in the scaffolded segment over time appears to be also correlated to the recovery of normal vasoreactivity. The vasoreactive behaviour of the distal edge of the scaffold does not substantially differ from the physiological reaction observed in the scaffolded segment. The clinical and prognostic implications of the present findings remain to be determined.

Conflict of interest: C.D., S.V., and R.R. are employees of Abbott Vascular. The ABSORB Trials are sponsored and funded by Abbott Vascular, Santa Clara, CA, USA.

References


