Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

In Vivo Visualization of Adventitial Vasa Vasorum of the Human Coronary Artery on Optical Frequency Domain Imaging

– Validation Study –

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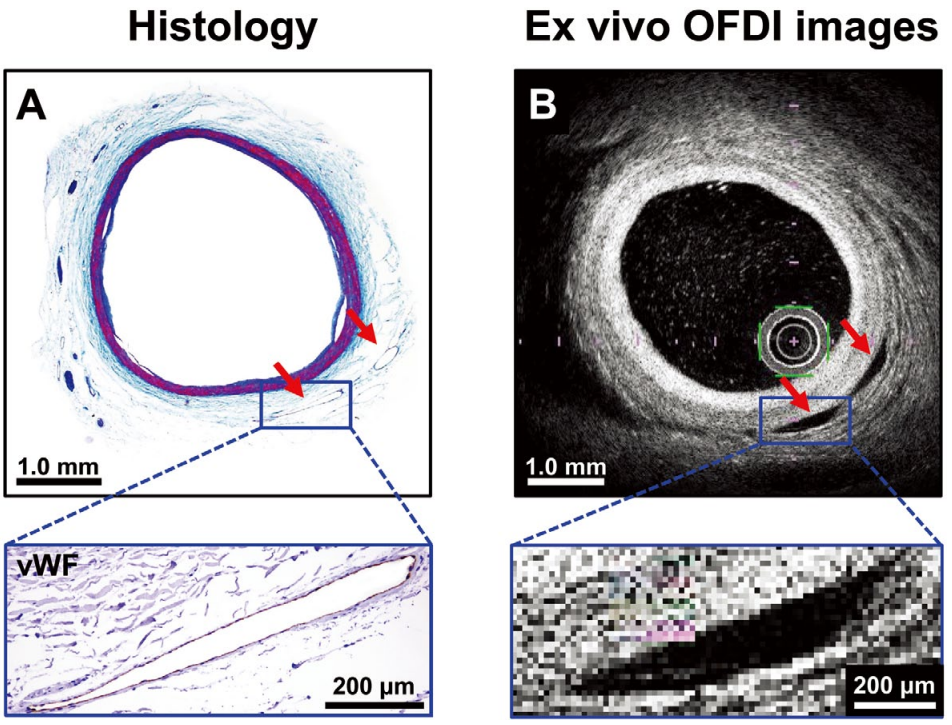

Figure 1. Validation of optical frequency domain imaging (OFDI) of the human coronary artery with histology. Cross-sectional images of (**A**) histology and (**B**) ex vivo OFDI obtained at human autopsy (70-year-old woman). Longitudinal images of von Willebrand factor (vWF)-positive adventitial vasa vasorum was noted in (**A**) histology, which corresponded well to the (**B**) low-intensity micro-lumen structures on OFDI.

We have previously demonstrated that adventitial inflammatory changes including vasa vasorum (VV) development are involved in the pathogenesis of coronary vasospasm in porcine models.[1–3] Given that adventitial VV is a nutrient microvessel of the arterial wall and is known to develop in the atherosclerotic coronary lesion,[4] it could be

Received April 25, 2014; revised manuscript received May 20, 2014; accepted May 21, 2014; released online June 27, 2014 Time for primary review: 19 days
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The Guest Editor for this article was Ken-ichi Hirata, MD.
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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0485

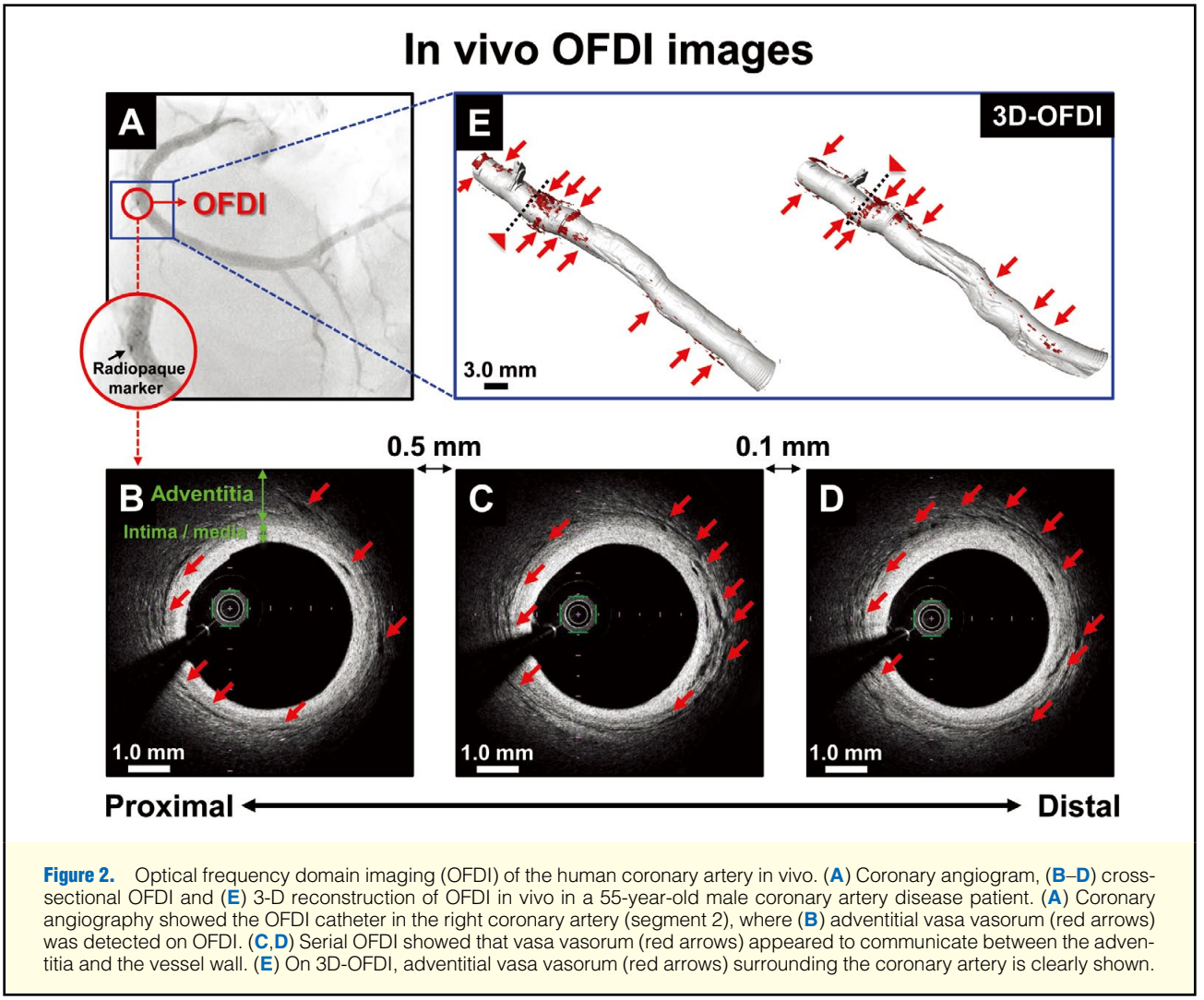

Figure 2. Optical frequency domain imaging (OFDI) of the human coronary artery in vivo. (**A**) Coronary angiogram, (**B**–**D**) cross-sectional OFDI and (**E**) 3-D reconstruction of OFDI in vivo in a 55-year-old male coronary artery disease patient. (**A**) Coronary angiography showed the OFDI catheter in the right coronary artery (segment 2), where (**B**) adventitial vasa vasorum (red arrows) was detected on OFDI. (**C**,**D**) Serial OFDI showed that vasa vasorum (red arrows) appeared to communicate between the adventitia and the vessel wall. (**E**) On 3D-OFDI, adventitial vasa vasorum (red arrows) surrounding the coronary artery is clearly shown.

a novel therapeutic target for coronary artery disease (CAD). Thus, advanced coronary imaging for adventitial VV visualization is warranted to better understand its pathophysiological role in patients with CAD. Current imaging techniques, however, including intravascular ultrasound (IVUS)[5] and first-generation time-domain optical coherence tomography (OCT),[6] are still limited in the in vivo visualization of adventitial VV. Recently, optical frequency domain imaging (OFDI; LUNAWAVE, Terumo, Tokyo, Japan) has been developed as a new-generation OCT with several unique characteristics.[7–9] OFDI enables acquisition of clear cross-sectional images with excellent sensitivity and tissue penetration; also, confirmation of the position of the OFDI core (Fast View, Terumo, Tokyo, Japan) is possible using radiopaque markers during coronary angiography. In the present study, we thus examined whether adventitial VV in humans can be clearly visualized on OFDI in vivo.

First, to validate OFDI of adventitial VV of the human coronary artery, we compared histology and ex vivo OFDI of the left coronary arteries obtained at human autopsy (70-year-old woman who died from breast cancer; **Figure 1**). Masson's trichrome staining showed micro-lumen structures in the coronary adventitia, which were VV because they were positive for von Willebrand factor (a vascular endothelial marker; **Figure 1A**). Notably, cross-sectional ex vivo OFDI was able to clearly visualize adventitial VV as low-intensity lumen structures (**Figure 1B**). Similar findings were also obtained in the remaining 3 cases (data not shown).

We then performed OFDI during coronary angiography in a CAD patient (55-year-old man; **Figure 2**). Briefly, an OFDI catheter was advanced into the right coronary artery (RCA) through a 6-Fr guiding catheter after i.c. isosorbide dinitrate (2 mg). Serial OFDI acquisition was then carried out with an automatic pullback speed (40 mm/s) during i.c. injection of contrast medium mixed with an equivalent volume of saline. Coronary angiography showed a radiopaque marker of the OFDI catheter at segment 2 of the RCA without stenotic lesion (**Figure 2A**). Importantly, cross-sectional OFDI of the RCA clearly visualized adventitial VV as low-intensity lumen structures surrounding the coronary artery wall (**Figure 2B**). Furthermore, VV on OFDI appeared to communicate between the coronary adventitia and the media, indicating micro-channels in the coronary artery wall (**Figures 2C**,**D**). Finally, 3D-OFDI (Avizo 6.3.1, FEI, OR, USA) was reconstructed using adventitial VV and vessel lumen in cross-sectional OFDI, showing the longitudinal VV alignment in vivo (**Figure 2E**). Similar findings were also obtained in the remaining 3 patients (data not shown).

To the best of our knowledge, this is the first report to show

that (1) adventitial VV images obtained on OFDI ex vivo are compatible with histological findings of the human coronary artery; and (2) OFDI enables clear visualization of adventitial VV of the human coronary artery in vivo.

Although previous studies with OCT showed the low-intensity micro-lumen structures as possible adventitial VV,[6] it was unclear whether those structures on OCT corresponded to adventitial VV on histology. The present study demonstrates for the first time that OFDI of the human coronary artery accurately corresponds to histology, although VV visualization by OCT in the porcine carotid artery has been previously reported.[10] Unique properties of the OFDI system, including its excellent sensitivity and tissue penetration,[7–9] allow clear visualization of the coronary adventitia. Thus, the OFDI system could be a new modality for VV visualization as compared with the current imaging techniques (eg, IVUS).[5]

Accumulating evidence has suggested that adventitial inflammation and VV are involved in the pathogenesis of CAD, such as plaque progression and rupture[4] and coronary vasospasm.[1–3] VV has been considered to be a conduit of inflammation between the coronary adventitia and the medial-intimal coronary lesion[1–4] and thus the inhibition of VV formation could be a novel therapeutic strategy for CAD. The OFDI system may be a useful tool for examining the effect of inhibition of VV formation in patients with CAD.

Several limitations should be mentioned for the present study. First, the present study included a small number of patients. Thus, further studies with a larger number of patients are needed. Second, it was difficult to validate VV images on in vivo OFDI and histology in humans. Third, because we examined OFDI only in mild coronary lesions in the present study, it remains to be determined whether OFDI is feasible for adventitial VV visualization in advanced coronary lesions. It has been reported that OCT light sources are prone to be attenuated at the thick atherosclerotic lesions.[11] Finally, it remains to be elucidated in future studies whether OFDI can identify the nature of adventitial VV (arteries vs. veins).

In conclusion, the present study demonstrated that OFDI is capable of visualizing adventitial VV of human coronary artery in vivo. Precise OFDI of adventitial VV may provide important insights into the role of adventitial VV in the pathogenesis of CAD in humans.

Disclosures

None.

References

1. Shimokawa H, Ito A, Fukumoto Y, Kadokami T, Nakaike R, Sakata M, et al. Chronic treatment with interleukin-1β induces coronary intimal lesions and vasospastic responses in pigs in vivo: The role of platelet-derived growth factor. *J Clin Invest* 1996; **97:** 769–776.
2. Kandabashi T, Shimokawa H, Miyata K, Kunihiro I, Kawano Y, Fukata Y, et al. Inhibition of myosin phosphatase by upregulated Rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1β. *Circulation* 2000; **101:** 1319–1323.
3. Nishimiya K, Matsumoto Y, Takahashi J, Uzuka H, Shindo T, Hanawa K, et al. Important role of adventitia in the pathogenesis of coronary hyperconstricting responses after drug-eluting stent implantation in pigs in vivo. *Circ J* 2014; **78**(Suppl I)**:** I100.
4. Barger AC, Beeuwkes R III, Lainey LL, Silverman KJ. Hypothesis: Vasa vasorum and neovascularization of human coronary arteries: A possible role in the pathophysiology of atherosclerosis. *N Engl J Med* 1984; **310:** 175–177.
5. Moritz R, Eaker DR, Anderson JL, Kline TL, Jorgensen SM, Lerman A, et al. IVUS detection of vasa vasorum blood flow distribution in coronary artery vessel wall. *JACC Cardiovasc Imaging* 2012; **5:** 935–940.
6. Uemura S, Ishigami K, Soeda T, Okayama S, Sung JH, Nakagawa H, et al. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J* 2012; **33:** 78–85.
7. Yun SH, Tearney GJ, Vakoc BJ, Shishkov M, Oh WY, Desjardins AE, et al. Comprehensive volumetric optical microscopy in vivo. *Nat Med* 2006; **12:** 1429–1433.
8. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59:** 1058–1072.
9. Muramatsu T, García-García HM, Onuma Y, Zhang YJ, Bourantas CV, Diletti R, et al. Intimal flaps detected by optical frequency domain imaging in the proximal segments of native coronary arteries: An innocent bystander? Insights from the TROFI Trial. *Circ J* 2013; **77:** 2327–2333.
10. Cheng KH, Sun C, Vuong B, Lee KK, Mariampillai A, Marotta TR, et al. Endovascular optical coherence tomography intensity kurtosis: Visualization of vasa vasorum in porcine carotid artery. *Biomed Opt Express* 2012; **3:** 388–399.
11. Kubo T, Tanaka A, Kitabata H, Ino Y, Tanimoto T, Akasaka T. Application of optical coherence tomography in percutaneous coronary intervention. *Circ J* 2012; **76:** 2076–2083.