RESEARCH LETTER

Vessel Calcification Patterns Should Determine Optimal Balloon Size Strategy in Below the Knee Angioplasty Procedures

Chronic limb threatening ischaemia is strongly related to diabetes mellitus, which leads to characteristic tibial and pedal pathology. Different from coronary and femoral arteries, medial calcification prevents positive remodelling of the diseased artery by forming a physical barrier against expansion. Long term patency after endovascular treatment of these lesions remains suboptimal, despite the application of additional drug coated balloons, debulking devices, or stenting[1].

Standard angiography techniques use a contrast agent to show the vessel lumen. However, this measurement does not reflect the original vessel size, owing to the severely thickened medial layer and vessel wall calcification restricting the original lumen. Alternatively, using ultrasound, one can measure the area enclosed by the external elastic layer (EEL). These measurements are less affected by the inward vessel wall thickening, and thus more closely resemble the original vessel diameter.

Choosing the proper balloon size may differ considerably between measurement strategies, and this inadvertently results in either balloon undersizing, with low technical success and high restenosis rates, or oversizing with dissections in up to 30% of procedures. In turn, these dissections are associated with reduced patency both when treated by bailout stenting or when left untreated.[2] During oversized balloon inflation, the additional wall stress applied might also result in more severe barotrauma to the vessel wall.

In this letter, a small sample, hypothesis generating study is presented, wherein the combined histological effects of vessel wall calcification patterns, and *ex vivo* oversized balloon angioplasty on vessel wall damage were analysed. Also presented is a renewed strategy for balloon diameter selection.

In this cadaver study, six lower limbs from human donors aged >70 years were included. Donor medical information was not available in accordance with local regulations. A total of 12 dissected vessel segments per balloon size were used, while two segments were randomised to serve as controls (anterior tibial, $n = 12$; posterior tibial, $n = 8$; peroneal, $n = 6$). Measurements of the lumen diameter at 100 cmH_2O pressure before and after dilation were performed using a 7.5 MHz L40 linear transducer ultrasound system equipped with Artlab vessel tracking software (Esaote BV, Maastricht, The Netherlands). Vessels were randomised to undergo angioplasty with either a 3.0 or 4.0 mm balloon (Jade non-compliant; OrbusNeich, Hoevelaken, the Netherlands), intraluminally inflated to nominal pressure. Luminal gain between balloon diameters was calculated by unpaired Student's *t* test. Pearson's correlation coefficients were determined between the relative balloon oversizing (balloon diameter/pre-inflation lumen) and luminal gain. All segments were histologically analysed using Elastica van Gieson and von Kossa calcium specific staining.

Calcification was assessed via the medial layer von Kossa mean pixel intensity using ImageJ (National Institutes of Health, Bethesda, MD, USA). Vessel samples were subsequently grouped in "no calcification" (pixel intensity $< 15\%$); "evenly distributed calcification" when stained circumferentially, including focal calcifications (pixel intensity $\geq 15\%$); or "spot calcification" when focal calcifications were seen, without circumferential calcium. Post-dilation dissections were scored using the iDissection classification that includes the depth (A = intima, B = media, C = adventitia) and circumferential extend of vessel wall injury (1 indicates $< 180^{\circ}$, 2 indicates $\geq 180^{\circ}$).

After dilation, vessel lumen increased from a mean $\pm$ standard deviation diameter of 1.9 $\pm$ 0.3 mm to 2.3 $\pm$ 0.2 mm. No significant difference in luminal increase between the 3 mm and 4 mm balloon was found (0.3 $\pm$ 0.2 mm *vs*. 0.5 $\pm$ 0.4 mm; $p = .21$). Relative balloon oversizing correlated moderately with vessel lumen increase (Pearson's $R = 0.73$; $p < .001$). Uncalcified vessels showed type B1 dissections, irrespective of 36%, 76%, or 100% oversizing. Vessels with evenly distributed calcium consistently showed localised damage to the adventitial layer (C1) at 30%, 74% and 100% oversizing. Spot calcifications showed full circumference dissections through the adventitia (C2) at 50%, 74%, and 100% balloon oversizing. Dissection severity consistently increased from no calcification (iDissection B1), to evenly distributed calcium (C1) and spot calcification vessels (C2). The most extreme oversizing, 100% balloon to lumen ratio, for evenly distributed, and spot calcifications are presented here (see Fig. 1). Full histological comparisons are available via the corresponding author.

The Global Anatomic Staging System dichotomises the presence of calcification, as it is recognised as a negative predictor of technical treatment success.[3] Herein, severe calcifications are described as "> 50% of circumference, diffuse, bulky or coral reef plaques". In this hypothesis generating human cadaveric study, although not designed for quantitative analysis, a significant difference was found between these aggregated calcification patterns. In arteries with spot calcifications, severe dissections occurred after oversizing, which should thus be avoided. Future studies might investigate the effects of selective stenting in these high risk lesions. However, in vessels with circumferential calcium, balloon oversizing showed limited vessel damage and will most probably be beneficial by maximised luminal gain. For these lesions, balloon sizing according to the diameter of the EEL will maximise treatment effect, while limiting damage to the EEL, which in itself is associated with loss of patency. Adequate imaging is therefore paramount

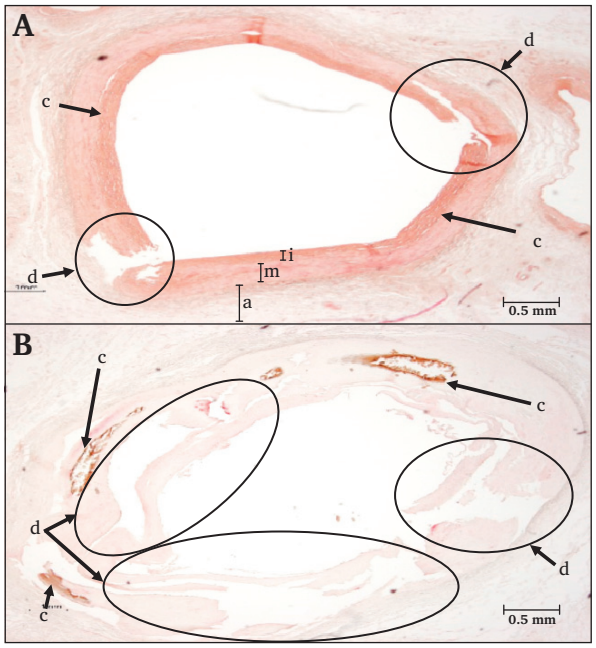

Figure 1. Examples of histological results after 100% balloon oversizing in two human cadaver tibial arteries (A, B) in the von Kossa staining (calcium deposits brown; c). The iDissection classification is based on the circumferential extend (1 = <180°, 2 = ≥180°), and depth of vessel damage in intima (i), media (m) or adventitia (a). Circumferentially distributed calcium (A) in the vessel wall results in less severe dissection patterns (d) (iDissection classification C1) compared to spot calcium deposits (B, iDissection class C2).

in this balloon size strategy, with intravascular ultrasound providing the possibility for both plaque determination, and EEL detection. Whether this is feasible or might even be replaced by extracorporeal ultrasound needs to be tested in future *in vivo* studies.

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CONFLICT OF INTEREST

None.

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