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TAILORED SIZES OF CONSTRICTIVE EXTERNAL VEIN MESHES FOR CORONARY ARTERY BYPASS SURGERY

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ABSTRACT

External mesh-constriction of vein grafts was shown to mitigate intimal hyperplasia by lowering circumferential wall stress and increasing fluid shear stress. As under-constriction leaves vein segments unsupported and thus prone to neointimal proliferation while over-constriction may cause wall folding optimal mesh sizing holds a key to clinical success. Diameter fluctuations and the occurrence of wall folding as a consequence of external constriction with knitted Nitinol meshes were assessed in saphenous vein grafts from 100 consecutive coronary artery bypass (CABG) patients. Subsequently, mesh dimensions were identified that resulted in the lowest number of mesh sizes for all patients either guaranteeing tight continual mesh contact along the entire graft length (stipulation A) or preventing wall folding (stipulation B). A mathematical data classification analysis and a statistical single-stage partitioning approach were independently applied alternatively prioritizing stipulation A or B. Although the risk of folding linearly increased when constriction exceeded 24.6% (Chi squared test p=0.0004) the actual incidence of folding (8.6% of veins) as well as the degree of lumenal encroachment (6.2±2.1%) were low. Folds were always single, narrow longitudinal formations (height: 23.3±4.0% of inner diameter / base: 16.6±18.1% of luminal circumference). Both analytical methods provided an optimum number of 4 mesh sizes beyond which no further advantage was seen. While the size ranges recommended by both methods assured continual tight mesh contact with the vein the narrower range suggested by the mathematical data classification analysis (3.0 to 3.7mm) put 20.6±12.5% of length in 69% of veins at risk of folding as opposed to 21.3±25.9% being at risk in the wider size range (3.0 to 4.2mm) suggested by the statistical partitioning approach. Four mesh sizes would provide uninterrupted mesh contact in 98% of vein grafts in CABG procedures with only 26% of their length being at risk of relatively mild wall folding.

Keywords: Vein grafts; External support; Coronary artery bypass graft; Luminal folding; Luminal constriction

INTRODUCTION

External mesh-support of vein grafts was shown to mitigate pathological processes leading to graft occlusion [1-6]. The fact that vein graft diameters are mostly too large for their run-off vessels emerged as a main principle of mesh-protection [5, 7]. In coronary artery bypass grafts (CABG), for instance, the average cross sectional ratio (Q_c) between run-off artery and internal thoracic artery grafts is almost $Q_c \approx 1.0$ whereas that of an average vein graft is $Q_c \approx 0.25$ [5], highlighting the fourfold dimensional discrepancy between saphenous vein grafts and coronary arteries. By constricting the diameter of a vein graft to better match that of its target artery, circumferential wall stress decreases and fluid shear stress increases. As such, mesh constriction deals with two main biomechanical triggers of diffuse intimal hyperplasia namely, high circumferential wall stress [8] and low shear forces [9]. Furthermore, constriction also eliminates diameter irregularities and thereby eddy blood flow [10]. As the latter is a main trigger for focal intimal hyperplasia [11-13], mesh constriction also counteracts the formation of localized stenoses – the main reason for the mid- to long-term failure of vein grafts [14-16].

Over time, a deeper understanding of some principles behind optimal constriction conditions for vein grafts had gradually emerged highlighting the challenges of clinical translation. One of these principles is that mesh constriction needs to be present from the time of grafting. In a non-human primate model mimicking the dimensional conditions of clinical bypass grafts, a lack of a tight contact between the outer vein wall and a support mesh at implantation inevitably led to diffuse intimal hyperplasia [5]. At the same time, human saphenous veins vary in diameter and therefore any mesh dimension exceeding the narrowest outer diameter of the vein will lead to 'unsupported' vein segments without tight mesh contact. Yet, constriction to the smallest outside diameter of a given vein carries risks. From a certain degree of constriction onwards, wall redundancy can be expected to lead to longitudinal folding. Likewise, clinical reports of poor performance of very-small diameter vein grafts defined a diameter of 3mm as the unwritten lower size-limit for many surgeons [17-19]. To complicate matters further, clinical routine application cannot

provide an indefinite number of mesh sizes. Any standardization to a few mesh sizes, however, increases the margins by which vein segments deviate from ideal constriction conditions.

Therefore, size-optimization of external vein graft meshes needs to weigh the biological benefits of constriction against the potential hazards of a too rigorous diameter reduction. In an attempt to reconcile the conflicting demands on mesh sizing in the context of clinical application, we established the likelihood of undesirable consequences of mesh-sizing, namely folding of the vein wall and the presence of 'unsupported' vein segments on the basis of data obtained from 100 consecutive patients undergoing coronary artery bypass grafting (CABG).

As a first step we correlated the anatomical dimensions of the saphenous veins of these patients with their propensity for folding when externally constricted. In a second step, we used these patient data to determine the likelihood with which all of the partially opposing framework conditions of mesh sizing are implementable. Finally, we alternatively prioritized two main paradigms of mesh sizing - namely to provide continually constrictive mesh support across the entire length of a vein or to avoid folding from over-constriction - and used both a mathematical and a statistical approach to determine the smallest number of mesh sizes that would comply with the respectively stipulated framework conditions.

MATERIALS AND METHODS

Underlying Paradigms for Mesh Constriction

The first stipulation was that no vein segment must remain without tight mesh contact. In other words, the outer diameter of any segment of the arterially distended vein (D_V) must not be less than the inner diameter of the arterially distended mesh (D_M) thereby guaranteeing continuous tight contact between vein and mesh. Recognizing the widely held conviction that vein grafts of less than 3mm diameter have a poor prognosis [17-19], we further stipulated that D_V of any arterially distended vein segment must not be constricted to less than 3mm. Therefore, veins with segments having an outer diameter of less than 3mm were initially censored before undergoing attempts to excise the narrow segments. Correspondingly, constriction was restricted to 50% of the widest outer diameter of veins (D_{Vmax}) once this value had emerged as a natural limit of constriction requirements in the first part of the study.

Data Acquisition of Human Saphenous Veins

The study was approved by the human ethics committee of the University of Cape Town with informed consent obtained from all patients.

In 100 patients [mean age 58.9±8.7 years / range: 38 to 75 years; mean weight 78.5±16.6Kg; 63.3% male/36.7% female] undergoing coronary artery bypass grafting (CABG) 108 saphenous veins were harvested (bilateral in 8 patients; average length 29.3±9.9 cm). Routine surgical syringe inflation had been used for vein distension during the harvest procedure but the inflation pressure was monitored. As it was previously shown that diameter fluctuations occur over relatively long distances (8.1cm for ≤10% / 22cm for ≤ 50%) [20] it was sufficient to measure the outer diameter (D_V) of the saphenous veins every 2cm from the malleolar cannulation site using a vernier. Veins were harvested by six different surgeons.

Mesh-constriction

In 70 of the harvested saphenous veins segments of sufficient length for mesh constriction experiments were available. After transport in saline (4ºC), the outer diameter of the arterially distended vein segment was re-measured and the saphenous vein samples were inserted into a knitted Nitinol mesh (inner diameter 3.34 mm, wire thickness 0.05 mm, Lamb Inc., Chicopee, MA), clipped at the end and distended with 10% buffered formalin to 120mmHg internal pressure. The inner diameter of the pressure-distended (120mm Hg) external Nitinol mesh was determined to be 3.45mm on the basis of volumetric displacement testing in distilled water at 37ºC (DCT3 compliance tester, Dynatek Dalta, Galena, MS, USA).

Histology

Sustained distension pressures of 120 mmHg during the 24 hours of formalin fixation were achieved by using a custom built perfusion rig. After fixation, the entire samples were embedded in resin (Methyl Methacrylate, Sigma-Aldrich, Steinheim, Germany). Cross-sections (Isomet Precision Saw, Buehler; Dusseldorf; Germany) were stained with haematoxylin and eosin (H&E). A Nikon E 1000M light microscope and a Nikon Coolscope (Nikon, Tokyo, Japan) were used for morphometric analyses.

Image Analysis

Image analysis was performed using Adobe Photoshop® version 7.0 (San Jose, CA, USA) and IPTK version 5 (Reindeer Graphics, Asheville, NC, USA) on tiled images assembled from an array of digital frames captured individually at 10x magnification using Eclipse Net software (Laboratory Imaging, Prague, Czech Republic). Macro procedures of the IPTK software were used to delineate and quantify cross-sectional lumenal area and equivalent lumenal diameter as well as cross-sectional area and thickness of wall (tissue inside and outside of stent excluding side branches), lumen to stent (tissue between lumen and inside edge of stent wires) and media. For the calculation of the inner vein diameter prior to mesh constriction the measured wall thickness of the control sample was subtracted from the outer radius. The inner diameter of mesh-constricted samples was calculated from the lumenal cross-sectional area. Dimensions of folds of the vein wall were assessed by determining

their height measured from a point along an extrapolated lumenal surface and perpendicular to the fold peak to the maximum extension of the fold. The proportion of luminal circumference affected by the fold base, defined as the arc along which the wall exceeded the extrapolated lumen, was also derived. Intimal cushions were evaluated both by their cross-sectional areas and their maximum heights.

Optimization of mesh sizing

Using the dimensional saphenous vein data of all 100 patients the optimization of mesh diameters aimed at the lowest number of mesh sizes that could fulfill the respectively stipulated criteria for the highest proportion of patients.
The two methods applied in our quest to optimize mesh sizes complemented each other in the sense that the statistical method requires a sufficiently large number of veins to generate reliable data for the mesh diameter selection but may be used for inferential statistical assessment of the proposed solutions whereas the mathematical method can be utilized for mesh diameter selection for any number of veins but is not able to statistically validate the probability of the proposed solutions for a larger patient population. The mathematical method facilitated a two-stage approach (P 70), namely data selection (D_{Vmin} and D_{Vmax}) and analysis for each vein and interactive identification of mesh diameters and data classification based on D_{Vmin} and D_{Vmax}. Mesh sizes were intuitively chosen on the basis of clinical data before being tested against these data in 2-, 3- and 4-size solutions. Mesh constriction was expressed as the reduction of the largest outer diameter of the vein (D_{Vmax}) to the inner diameter of a given mesh (D_M). The 'smoothing constriction' C_S was defined as the minimum constriction required to completely eliminate diameter irregularities and maintain a continual tight-fit across the entire vein length.
'Classification' is part of the mathematical method and represents the assignment of a vein to the (most) suitable mesh size. In contrast, the statistical method followed a single-stage partitioning approach without prior data reduction, hence utilizing the full outer diameter data set of each vein without user interaction for mesh diameter identification. This involved defining D_{Vmin} (for Symbols see 'Notations') cut points which categorized veins into statistically distinct subsets based on their D_{Vmax}/D_{Vmin} ratios and thereby also proposed a selection of mesh sizes with IDs equivalent to the

value of the D_{Vmin} cut points. This method then considered the extent of reduction at each measurement point along the length of each vein following hypothetical application of a mesh whose ID coincided with the cut point appropriate to the D_{Vmin} for each vein and presented the average value as the 'actual constriction' (C_A).
In both approaches, two constriction criteria were alternatively prioritized:
A) No vein segment was to remain without tight mesh contact.
B) Constriction was to be restricted to the range within which no folding had been observed.

Priority: Continual Constrictive Mesh Support throughout the Vein

The method for the mathematical data analysis has been described in detail previously [21]. In brief, the degree of constriction (C_S) required to reduce the largest (D_{Vmax}) to the smallest (D_{Vmin}) outer diameter of a vein was $C_S = \frac{D_{V\max} - D_{V\min}}{D_{V\max}}$ [21]. By limiting the actual constriction C_A to maximally 50%, the smallest and largest diameter of an external mesh for a vein was 0.5 x D_{Vmax} and D_{Vmin}, respectively. Thus, the range δ of the mesh diameter was $D_{Vmin} \leq \delta \leq 0.5 \times D_{Vmax}$ for a single vein and $\max [D_{Vmin}]_i \leq \delta \leq \max [0.5 \times D_{Vmax}]_i$ with i = 1 to n for a cohort of n veins. One single mesh can be used for all n veins only if the mesh diameter ranges (δ) of these veins overlap and a common mesh diameter exists. If this is not the case, two or more mesh sizes are required. With the aim of minimizing the number of mesh sizes, four mesh diameters $D_{M1} < D_{M2} < D_{M3} < D_{M4}$ were proposed based on the data analysis described above as well as following practical considerations. Using a classification algorithm, the largest possible mesh size suiting the mesh diameter range (δ) was assigned to a vein, thereby ensuring that the stipulation of complete mesh support was fulfilled with the least amount of constriction required.
For the statistical approach, the extent of constriction individually required for each vein was determined on the basis of $C = \frac{D_V - D_{V\min}}{D_V}$. In a 'one-size-fits-all' mesh with an inside diameter equal to the single narrowest outer diameter of the entire cohort of veins the extent of constriction was calculated according to: $C = \frac{D_V - 2.1mm}{D_V}$

where D_V represents the outer diameters measured and the value 2.0mm the minimum outer diameter recorded for all veins in the study cohort. In order to define the diameter specifications and numbers of meshes optimally suited to the observed saphenous vein profile distribution, the technique of recursive partitioning was applied to the vein data using the JMP® statistical software package (version 6.0.3, Cary; NC). This method proposed a relationship between the D_{Vmin} and D_{Vmax}/D_{Vmin} ratio for each vein, and created a tree of optimal D_{Vmin} cut-points thereby maximizing mean D_{Vmax}/D_{Vmin} ratio differences between the resulting clusters. The software employed an iterative process whereby all possible vein groupings were evaluated to arrive at an optimal cut point. This process was manually repeated until no further significant benefit was observed through additional partitioning. The suggested cut-points were then hypothetically combined in the same sequence as the partitioning solutions to simulate application of single, to up to four, mesh sizes across the cohort of veins with the choice of mesh being determined by each vein's D_{Vmin} and with the extent of constriction determined as before.

Priority: Prevention of Wall Folding

The mathematical method described above, was adjusted with respect to the constriction limit and the limits for the mesh size for each vein. The maximum constriction was limited to C_F = 27%, found to be associated with the onset of the risk of folding (see results section 2). The lower limit of the mesh diameter was $(1\text{-}C_F) \times D_{Vmax}$, i.e. $0.73 \times D_{Vmax}$, whereas the upper limit was defined by the largest vein diameter D_{Vmax}, instead of the smallest vein diameter D_{Vmin} used for the continuous support approach. The mesh diameter range δ for a single vein thus became $0.73 \times D_{Vmax} \leq \delta \leq D_{Vmax}$. Of four mesh sizes $D_{M1} < D_{M2} < D_{M3} < D_{M4}$ proposed, the smallest size possible was assigned to each vein with a classification algorithm. The mesh sizes were affected by the adjusted constriction limit and were not necessarily the same as those for the priority of continuous mesh support.

Data Analysis for Outlier Veins

The few outlier veins that failed to satisfy the criteria for generalised numerical analysis ($D_{Vmin} < 3.0$mm or $D_{Vmax} \geq 2D_{Vmin}$) for continuous mesh support were separately and individually assessed along their entire length to allow for their use

with the proposed mesh solutions, even if subdivision of the vein was necessitated. Resulting vein segments shorter than 12cm were not considered for the dimensional analysis due to insufficient surgical length.

Statistical Methods

All continuous numerical data were expressed as means ± standard deviation. Student's t test and Chi squared test for binomial post-hoc inference testing and partition modeling was performed using JMP statistical software (version 6.0.3, Cary; NC). A two-tailed p-value of less than 0.05 was assumed for statistical significance.

RESULTS

Clinical Vein Dimensions and resulting Constriction Requirements

The overall minimum (D_{Vmin}) and maximum (D_{Vmax}) outer diameter across all 108 veins was 2.0 and 7.0mm with an average D_{Vmin} of 3.59 ± 0.63mm and D_{Vmax} of 4.84 ± 0.75mm, respectively. The relationship between D_{Vmax} and D_{Vmin} was $D_{Vmax} = 2.24 + 0.72D_{Vmin}$ (see Fig. 1). To completely eliminate diameter irregularities in all 108 individual veins, a mean constriction of only 13.7±7.5% (range: 0 – 42.3%) was required. This corresponded with a mean 25.3±10.8% (range: 0 – 57.1%) constriction requirement of D_{Vmax} for all veins. As only two veins (1.8%) required more than 50% constriction, see Fig. 2, mesh support could be continuous in >98% (95% confidence) of veins without exceeding a 50% reduction of their widest diameter (D_{Vmax}). Conversely, only 8/108 veins contained segments smaller than 3mm. The remaining 93% of veins did not require more than 46.4% constriction of their maximum diameter (D_{Vmax}) to obtain continuous mesh support. Therefore, the overwhelming majority of veins required only a moderate constriction relative to their widest diameter to eliminate diameter irregularities (74% of veins requiring less than 30% constriction) while guaranteeing that no vein segment remained un-constricted.

Mesh-Constriction and Wall Folding

Conservatively exceeding the required mean constriction by a factor two, the chosen mesh size resulted in a mean reduction in outer vein diameter of 25.1±7.4% corresponding with a lumenal reduction by 43.8±10.9%. In almost one third of veins (29.7%) a mean constriction of more than 30% was observed. Overall, 62.9% of mesh-constricted veins showed a perfectly circular, smooth luminal surface (Fig. 4). Longitudinal folding, as a consequence of vein wall redundancy, occurred in 8.6% of veins but never encroached the cross sectional area of the lumen by more than 6.2±2.1%. The folds were always single, narrow longitudinal formations with a height equivalent to 23.3±4.0% of the respective inner diameter and a base corresponding with 16.6±18.1% of luminal circumference. There was a significant linear increase in the risk of folding with increasing constriction (Chi squared test; $p=0.0004$). No folds were observed in veins where constriction was less than 21.6%. Partition modeling suggested a significant prevalence of folds only when constriction exceeded 24.6%. This corresponded with actually observed folding in only one (2.7%) vein that did not exceed this hypothetical limit. Yet, only 15.2% of veins requiring more than 24.6% constriction (47.1% of all veins / average constriction 27.7±3.8%) actually exhibited folding. There was no correlation between wall thickness and folding or the presence of intimal cushions and fold formation.
As adventitial tissue was not deliberately denuded, external vein wall compression by adventitial tissue bulks was observed in 17.1% of veins. In 75% of these veins (12.9% of all mesh supported veins), excess adventitial tissue caused a modest elliptical encroachment of the cross sectional area (20.8±9.0%) over an arc extending over 29.8±12.1% of the lumenal surface. In the remainder a small 'bulge' protruding beyond the blood surface could be distinguished. The presence of adventitial tissue between vein wall and mesh neither correlated with the harvesting surgeon nor with dimensional parameters such as outer diameter ($p=0.63$) or wall thickness ($p=0.47$).

Optimized Mesh Sizing

Priority: Continuous Mesh Support throughout the Vein

In the mathematical approach, the hypothetical application of external meshes equivalent in diameter to the corresponding D_{Vmin} of each vein resulted in 27 different mesh sizes for 108 veins (based on an accuracy limitation of 0.1mm). The hypothetical application of a single external mesh size with an internal diameter equivalent to the smallest diameter within the entire cohort (D_{Vmin} = 2.0mm) would have failed the '50% constriction limit' in 84.3% with 32.4% of veins being constricted by more than 60%. Additionally, in 7.4% of veins the diameter limitation to ≥3mm would have been violated. After censoring the veins containing segments of less than 3mm, a 'one size fits all' solution of a 3mm mesh would have exceeded the 50% constriction limit in 8.3% of veins. However, in none of these veins constriction would exceed 60% of the widest diameter.

Postulating the availability of two (3.0, 3.5mm), three (3.0, 3.3, 3.5mm), or four (3.0, 3.3, 3.5, 3.7mm) mesh sizes for the mathematical solution (see Fig. 3), the resulting degree of constriction is summarized in Table 1. Complete elimination of diameter irregularities, i.e. $C_A/C_S \geq 1$, within the constriction limit was ensured in all proposed solutions. Values of $C_A/C_S > 1$ indicated that the mesh reinforcement constricted a vein more than required. The closest match between actual constriction and the minimum constriction required to eliminate diameter irregularities while providing continual external support was obtained with the four-mesh solution (grand mean C_A/C_S: 1.34 ± 0.80), followed by the three-mesh (C_A/C_S: 1.45 ± 0.94) and two-mesh solutions (1.48 ± 0.93). The distribution of mesh sizes was: 34.3% and 65.7% for two sizes; 25%, 10% and 65% for three sizes; and 25%, 10%, 17% and 48% for the four-size solution.

Similarly, a 4-size solution emerged from the statistical partitioning approach beyond which no further advantage was seen. After those 7.4% of veins had been censored that contained segments of less than 3mm diameter (D_v) partitioning proposed mesh diameters of 3.8, 3.5, 4.2 and 3.1mm in that order. By increasing the number of mesh sizes from one to four, partitioning points were added to existing ones rather than redefining the entire set for each size solution anew. To avoid areas of non-

constricted unsupported vein, however, the 3.1mm stent size was replaced with a 3.0mm size, coinciding with the lower size-limit for vein grafts that had emerged from clinical experience. For the one-size solution (3.0mm) constriction beyond 50% of the widest segment (D_{vmax}) was only required in 9.0% with an average maximum constriction of 37.5±9.2% and a mean constriction of 27.7±8.6% (Fig. 5). The 2-size solution (3.8mm for 41.4% and 3.0mm for 58.6% of veins) required constriction of >50% of D_{vmax} in only 3% of veins with a mean maximum constriction of 31.0±9.6% and a mean overall constriction of 20.4±7.5%. The 3-size solution (3.8mm for 41.4%; 3.5mm for 25.1% and 3.0mm for 33.5% of veins) and 4-size solution (4.2mm for 19.8%; 3.8mm for 21.7%; 3.5mm for 25.1% and 3.0mm for 33.5% of veins) each required >50% constriction in only 1% of veins, resulting in a mean maximum constriction of 28.6±9.6% and 27.2±9.7% and a mean overall constriction of 17.6±7.0 and 16.1±6.5%, respectively. Figure 6 illustrates the constriction across the lengths of the 100 saphenous veins with $D_{Vmin} \geq 3.0$mm based on recursive statistical partitioning.

Priority: Prevention of Wall Folding

When using the previously determined four mesh sizes, 69% (3.0, 3.3, 3.5, 3.7mm) / 59% (3.0, 3.5, 3.8, 4.2mm) of the veins would require a maximum constriction of ≥24.6% over 20.7±12.5% / 21.3±25.9% of their length. Related to the grand sum of harvested vein lengths, however, this represented a risk of folding of 26.1% / 22.8%. For three and two mesh sizes, the incidence of $C_A \geq 24.6\%$ increased moderately to 35.2% / 27.4% and 37.3% / 40.0% of the overall vein length with 77% / 67% and 78% / 75% of the veins being affected over 23.3±14.7% / 25.9±27.0% and 24.3±15.2% / 37.6±32.3% of their length. Thus, when sizing was prioritized along the stipulation of maximum constriction not exceeding 24.6% larger mesh sizes of 3.0, 4.0, 4.5 and 5.5mm (four-mesh solution), 3.0, 4.0 and 5.0mm (three-mesh solution), and 3.5 and 4.5mm (two-mesh solution) were identified in the mathematical approach. The four and three mesh size solutions accommodated all 108 and 106 (Table 2) veins, respectively, while 13 of the 108 veins were excluded in the two-mesh solution. The maximum / mean

constriction was 14.4 ± 6.9% / 0.1 ± 10.5% for four mesh sizes, 14.1 ± 7.1% / -0.1 ± 10.9% for three mesh sizes and 13.5 ± 6.0% / -0.1 ± 10.2% for two mesh sizes. For the four- and three-mesh solutions the constriction limit of 24.6% resulted in unsupported segments in 80 and 78% of the veins, representing 18.5 ± 15.1% and 18.4 ± 15.1% of the harvested length, respectively. For the two-mesh solution, on average 18.0 ± 15.9% vein length was unsupported in 77% of the accommodated veins.

In the statistical partitioning approach, 46% of veins precisely and hypothetically matched to constrict no more than the limit imposed due to folding risk (24.6% of D_{Vmax}; C_F) nevertheless failed to avoid oversizing along 29.3±24.9% (9.7±9.0cm) of their length. The area of peak failure corresponded anatomically to a point midway between the ankle malleolus and the knee. Only in the region above the knee where the vein diameter increased was this problem avoided. Conversely, hypothetical application of individually matched stents equivalent in diameter to D_{Vmin} avoided oversizing but exceeded C_F over 8.6±7.4cm (27.6±21.5%) of the failed veins. The maximum constriction in these failed veins was 27.6±21.5%. Availability of increasing numbers of discrete stent sizes asymptotically approximated C_F (Figure 5) but only to a point where close to one out of two veins would remain at risk for folding. The mean maximum vein constriction (and 95% tolerance intervals for 90% of veins) were 37.5% (20.1-54.8%), 31.0% (12.4-49.5%), 28.6% (10.6-46.5%) and 27.2% (9.1-45.3%) for one, two, three and four stent solutions respectively.

Analysis of Outlier Veins

The mean harvested length of the 8 outlier veins with segments of <3mm was 28.5±11.6cm and their degree of constriction required to eliminate irregularities was 41.1±10.2%. For 3/8 veins, narrowing to less than 3.0mm occurred within the proximity of one end. These veins qualified for external meshing after removal of an end segment of 2cm (9.1%), 4cm (18.2%) and 8cm (36.4%) of the harvested length, respectively. In the other 5/8 veins, segments with an outer diameter of less than 3.0mm occurred throughout the length of the vein. Two veins qualified for an

external mesh after removing between 2cm (4.3%) and 22cm (64.7%) of the harvested length. For the remaining three veins, censoring resulted in segments shorter than the 12cm minimum length. In total, mesh-supported vein segments of surgically useful length could still be obtained from 5 of the 8 veins and 47% of the total harvested length of these 8 veins could be used. The length of the mesh-supported segments after excision of the narrow parts was 18.0 ± 4.2cm. Their degree of 'smoothing constriction' was 22.3 ± 7.1%.

DISCUSSION

The present study aimed at identifying optimal sizes for external vein graft meshes in order to facilitate their clinical routine application.

Three underlying framework conditions were defined on the basis of conventional clinical perceptions [17-19] as well as experimental evidence [1-7]: vein diameters of 3mm should represent the absolute lower limit of constriction; tight continuous contact between the vein and the mesh should be guaranteed throughout the entire length of the vein graft and constriction should remain within a range that does not lead to wall folding.

In view of the often distinct diameter irregularities of saphenous veins [20] though, simultaneous compliance with all three stipulations represents an irreconcilable condition. Clearly, optimal mesh sizing will require a compromise that prioritizes that frame work condition where non-compliance has the most detrimental impact on graft performance. As only clinical long-term experience will conclusively allow such ranking, we alternated between prioritizing both the prevention of 'incomplete mesh contact' and the prevention of 'vein folding' in our present analysis. In both scenarios a vein diameter of 3mm was seen as the absolute lower limit of constriction. This arbitrary cut-off dimension was based on the clinical perception that outer diameters smaller than 3mm have a poor prognosis [17-19] in spite of some studies reporting excellent results with vein grafts of <3mm diameter [22-25]. Yet, the reluctance of surgeons to cross this line would only theoretically expand the spectrum of mesh sizes but have no practical consequences. Given the potential of

external mesh support to fundamentally change the pathobiology, and in its wake the performance of vein grafts, however, even this presumed limit of mesh constriction may wane with time. Alternatively, cross-sectional size match between the run-off artery and the vein graft may turn out to be the most important diameter limitation in the mesh support of vein grafts. Taking the wall thickness of saphenous veins into account, this alternative prioritization may even increase the minimum outer diameter to 3.5mm. As such, our study needs to be seen as a first preliminary attempt to optimize mesh sizing on the basis of today's insights. Notwithstanding, in spite of these limitations a number of unambiguous conclusions could be drawn:

i) Only 7.4% of veins contained segments of less than 3mm diameter of which two third would still provide sufficiently long vein grafts after excision of the narrow parts. Therefore, more than 97% of saphenous veins harvested for coronary artery bypass surgery would qualify for continual, tight mesh support.
ii) There was a linear increase in the risk of folding with increasing constriction. As a significant prevalence of folding only occurred from 24.6% of constriction onwards, only 11.4% of total vein length would be at risk.
iii) Both the mathematical and the statistical approach led to an optimum number of 4 mesh sizes beyond which no further advantage was seen.
iv) By providing an additional mesh size between 3.0 and 3.5mm in the mathematical solution, only one quarter of veins needed a small 3.0mm mesh as opposed to a third in the statistical solution. This additional 3.3mm mesh size reduced the mean maximum constriction occurring in 3.0mm meshes from 31.6±9.9% to 30.0±9.9% and the percentage of veins and their affected length at risk of folding in this group from 85.3% to 80.0% and 22.5±11.5% to 19.9±11.4%, respectively.
v) If those 25% of veins still requiring a 3.0mm mesh received a 3.3mm mesh instead, one quarter of veins would contain 1.8±0.9 unsupported segments over 10.8±6.8% of the length.
vi) By providing an additional 4.2mm mesh size beyond 3.8mm in the statistical solution, the risk of folding in the >3.8mm veins decreased from 67 to 59%.
vii) In absolute terms, the narrower size-range of meshes suggested by the mathematical approach (3.0 to 3.7mm) puts 69% of veins over 20.6±12.5% of

their length at risk of folding as opposed to 59% of veins over 21.3±25.9% of their length in the broader range of mesh sizes (3.0 to 4.2mm) suggested by the statistical approach.

viii) While prioritizing continual tight mesh support over the risk of folding would lead to 69% of veins being at risk of folding (with mild lumenal encroachment of <10%), prioritizing the prevention of folds over tight external support would result in 80% of veins containing non-supported segments.

By mesh-constricting the left-over segments of 100 consecutive CABG patients to almost half their cross sectional area, we addressed the natural concern of surgeons that constriction may lead to flow-obstructive folding of the vein wall. Although we could demonstrate that the risk of folding linearly increased from 25% diameter-constriction onwards, the actual incidence of folding was low with only 8.6% of veins showing longitudinal folding. Moreover, these folds were shallow and narrow-based only modestly encroaching the lumen by 6.2±2.1%. No folds at all could be detected in any veins that were diameter-constricted by less than 21% corresponding with a lumenal constriction of 38%. Furthermore, as the distended vein segments were collected at the end of the operation followed by transport- and experiment-related delays the contractile responsiveness of medial smooth muscle cells at the time of the experiments may have been largely exhausted aggravating the extent of folding. In view of the vigorous spastic response veins can undergo during harvest procedures where circumference rather translates into increased wall thickness than folds, the threat of folding of the vein wall seems even more remote. This also confirms previous reports where more than 50% diameter-constriction did not lead to the formation of folds [26]. Similarly, extreme constriction of varicose veins from an average of 13mm to 6mm only showed moderate folds in as few as 13% of veins [27]. Moreover, those veins experiencing folds were extremely varicose at mean diameters of 17mm resulting in an average diameter-constriction of 65%, equivalent to 88% lumenal reduction [27]. Thus, it seems that our prioritization of 'prevention of folding' was more based on intuitive anticipation than actual occurrence.
In contrast, the alternative prioritization of 'continual tight mesh support' in our analysis was based on the previous demonstration that even minor degrees of

oversizing where the tight contact between mesh and vein was lost led to the complete loss of the suppression of intimal hyperplasia [5]. Furthermore, only tight external support relieves circumferential wall strain – one of the major biomechanical triggers of intimal hyperplasia [8]. Additionally, compliance with this main stipulation concurrently leads to an elimination of lumenal irregularities, a main source of eddy blood flow and thereby of focal intimal hyperplasia. As a 50% diameter constriction suffices in 98% of saphenous veins to achieve this goal [20] it seemed sensible to limit constriction to 50% of the diameter of the largest vein segment. In general, 93% of all veins harvested for coronary artery bypass surgery turned out to be amenable to continual tight mesh support despite a limitation of constriction to 50% of the widest diameter. The remaining 7% required the surgical excision of vein segments. A detailed mapping of these segments clearly demonstrated that apart from being scarce and short, the narrow portions were either so close to the proximal or distal end of the vein that they could easily be discarded or suitably distributed across the length of the vein to leave sufficiently long segments for grafting after their excision. It is obvious that this only applies to coronary surgery and not to peripheral bypass surgery where a major portion of the saphenous vein is needed as one continuous conduit. However, inasmuch as a separate anatomical analysis of the much longer vein segments usually taken during peripheral bypass surgery will be needed to reach an equally firm conclusion regarding mesh sizing, it is anticipated that the mildly larger diameter and more even dimension of the proximal saphenous vein [20] may partially compensate for the proportion of censored veins. At the same time, applying the meshes to peripheral bypass surgery will highlight another challenge: as the difficulty to insert veins into small mesh sizes increases with the graft length, ways may need to be found to close the constricting circumference of the mesh after the atraumatic insertion of the vein.

Given the principally different yet complementary nature of the two methods applied, it significantly strengthened the confidence in the size recommendations emerging from our analysis that almost identical results emerged for mesh sizes. We showed with two independent theoretical methods that two sizes of an external support mesh are sufficient to guarantee continual external mesh support and thereby fully eliminate diameter irregularities in 97% of the harvested saphenous

veins. The similarity of the solutions at which the two dissimilar analysis methods arrived underlines the validity of the results. Furthermore, the algorithms used lend themselves to the development of an easy-to-use guide for mesh size selection in the operation room. Moreover, such a 'dial-in-calculator' may utilize the finding that the outer diameter of a saphenous vein rarely varies more than two-fold along the harvested length. This would additionally reduce the number of diameter measurements required to identify the individually most suitable mesh size for a vein during the harvest procedure. Similar results of the two methods were also obtained with regard to the reduction in overall constriction as a consequence of extending the number of mesh sizes from two to three and four (mathematical: 8.9% and 14.7% vs statistical: 9.0% and 16%). This coincidence again confirms the robustness of the two methods and their solutions.

CONCLUSIONS

Our analysis alleviated concerns that constriction may lead to distinct inward folding of the vein wall detrimentally encroaching on the lumen. Not only could we demonstrate that such folds are rare and typically of low profile, their longitudinal alignment with the blood stream makes it unlikely that they would significantly disturb laminar flow patterns. Complying with strong experimental evidence [5, 7] for the need to continually provide tight mesh-contact with the vein, the four mesh sizes suggested by the mathematical approach of our study would provide such uninterrupted mesh contact in 98% of veins harvested for coronary artery bypass surgery. Only 26% of the length of these veins would require constriction that carries the potential of folding.

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NOTATIONS

Symbol	Unit	Description
C	%	Degree of constriction
C_S	%	Degree of constriction required to reduce largest to smallest diameter of a vein
C_A	%	Degree of actual maximum constriction per vein
$C_{A,mean}$	%	Degree of actual mean constriction per vein
C_F	%	Degree of constriction associated with onset of risk of folding
D_M	mm	Inner diameter of mesh (*)
n	-	Total number of veins considered for the analysis
D_V	mm	Outer diameter of a vein (*)
D_{Vmax}	mm	Maximum outer diameter of a vein ('largest vein segment') (*)
D_{Vmin}	mm	Minimum outer diameter of a vein ('narrowest vein segment') (*)
L	cm	Length of harvested vein
L_{UNS}	%	Proportion of total length of vein that remains unsupported by the mesh
Q_c	-	Ratio of luminal cross-sectional area of run-off artery to luminal cross-sectional area of vascular graft
R^2	-	Coefficient of determination
x_j	-	Position of measurement of D_V along a vein measured from the malleolar reference point
δ	mm	Range of mesh diameter for a single vein
Δ	mm	Range of mesh diameter for a set of veins

(*) assuming arterial distension pressures

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TABLE AND FIGURE LEGENDS

Table 1. Percentage of constriction required to eliminate all luminal irregularities while limiting the maximal constriction to 50% for the majority of veins that did not contain segments with an outer diameter of less than 3mm (100/108). The two-, three- and four-mesh solutions of the mathematical approach were compared with regard to size prevalence and accompanying degree of constriction at the site of the largest vein graft diameter while receiving the largest possible mesh that complied with the stipulations 'continual tight mesh support' and 'constriction limited to $\leq$50% of the widest diameter of a given vein. The ratio C_A/C_S indicates how much the actual maximum constriction obtained with the best suited mesh size exceeded the individual constriction required to reduce the maximum outer diameter to the minimum outer diameter of the vein. For the two-mesh solution, one vein could not receive a mesh due to dimensional incompatibility.

Table 2. Percentage of constriction and vein length not supported by the mesh as well as distribution of veins with the constriction limited to a maximum of 24.6% to avoid the risk of luminal folding. Two-, three- and four-mesh solution were compared. Mesh sizes were selected from six sizes of 3.0, 3.5, 4.0, 4.5, 5.0 and 5.5mm so as to minimize the proportion of unsupported vein length for each solution.

Figure 1. Relationship between the minimum and maximum outer diameters of 108 harvested human saphenous veins. In all but two exceptions (encircled), D_{Vmin} was never more than half of D_{Vmax} highlighting that a constriction to half of the widest diameter of a vein graft was sufficient in 98% of saphenous veins harvested for coronary artery bypass surgery.

Figure 2. Distribution of the 108 saphenous veins according to their degree of constriction required to guarantee uninterrupted, continual tight mesh contact (C_S).

The majority of veins required between 20 and 30% constriction to eliminate diameter irregularities.

Figure 3. Permissible mesh diameter range δ_i for those 100 veins that did not contain segments with an outer diameter of less than 3.0mm. The mesh diameter ranges are ranked according to 1) maximum mesh diameter and 2) minimum mesh diameter. The dashed horizontal lines indicate the proposed mesh diameters D_{M1} = 3.0mm, D_{M2} = 3.3mm, D_{M3} = 3.5mm and D_{M4} = 3.7mm.

Figure 4. Haematoxylin/Eosin stains of resin saw-ground cross-sections of all veins reinforced with an external Nitinol mesh. Red boxes highlight veins where folding of the wall occurred. Green boxes highlight veins where humps, mostly associated with excess adventitial tissue or sometimes due to size mismatching, and blue boxes where elliptical encroachment due to adventitial tissue were observed. Percentages indicate the degree of diameter-constriction.

Figure 5. Maximum vein constriction (C_A) was confined below 50% and avoidance of oversizing ensured throughout while the risk for wall folding, defined as constriction greater than 24.6% (red line), marginally diminished through the application of an increasing array of discrete mesh sizes.

Figure 6. Hypothetical constriction across lengths of 100 saphenous veins ($D_{Vmin} \geq$ 3.0mm) based on recursive statistical partitioning into subgroups with distinct OD ranges and following the virtual application of mesh diameters (3.5, 3.8 and 4.2mm) suggested by this method as well that of a 3.0mm mesh size determined by the overall D_{Vmin} to avoid oversizing. The final selection of the mesh diameter for each vein was based on the minimum outer diameter for that vein. Both criteria of avoidance of areas of unsupported vein (oversizing) and maximal constriction of 50% were achieved for the first 43cm of vein, even with a two mesh-size solution. Red lines indicate the threshold above which there is risk for folding.

TABLES AND FIGURES

Table 1

	Priority: Continual, tight mesh contact		
	No of mesh sizes assumed		
	2	**3**	**4**
	Excluded		
n	9/108	8/108	8/108
D_{M1} [mm]	3.0		
n	34	25	25
C_A [%]	31.6±9.9	30.0±9.9	30.0±9.9
C_A/C_S	1.17±0.36	1.12±0.40	1.12±0.40
D_{M2} [mm]	3.3		
n	N/A	10	10
C_A [%]		31.6±9.4	31.6±9.4
C_A/C_S		1.06±0.05	1.06±0.05
D_{M3} [mm]	3.5		
n	65	65	17
C_A [%]	30.3±8.7	30.3±8.7	24.9±7.2
C_A/C_S	1.65±1.09	1.65±1.09	1.05±0.12
D_{M4} [mm]	3.7		
n	N/A	N/A	48
C_A [%]			28.4±8.9
C_A/C_S			1.62±1.06
	Overall		
n	99	100	100
C_A [%]	30.8±9.0	30.4±9.0	28.5±9.0
C_A/C_S	1.48±0.93	1.45±0.94	1.34±0.80

Table 2

	Priority: Prevention of Folding		
	No of mesh sizes assumed		
	2	**3**	**4**
		Excluded	
n	13	2	0
D_{M1} [mm]	**3.5**	**3.0**	**3.0**
n	42	9	9
C_A [%]	16.1±6.5	16.6±5.6	16.6±5.6
$C_{A,mean}$ [%]	5.3±9.2	7.9±8.4	7.9±8.4
C_A/C_S	0.83±0.52	1.39±1.26	1.39±1.26
L [cm]	27.2±9.6	23.6±7.5	23.6±7.5
L_{UNS} [%]	10.5±12.1	5.5±9.2	5.5±9.2
D_{M2} [mm]	**4.5**	**4.0**	**4.0**
n	53	77	77
C_A [%]	11.5±4.7	13.7±7.6	13.7±7.6
$C_{A,mean}$ [%]	-4.4±8.9	1.0±10.1	1.0±10.1
C_A/C_S	0.56±0.51	0.73±0.82	0.73±0.82
L [cm]	32.0±9.8	29.5±9.9	29.5±9.9
L_{UNS} [%]	24.0±16.1	17.1±14.4	17.1±14.4
D_{M3} [mm]		**5.0**	**4.5**
n		20	11
C_A [%]		14.3±5.7	18.8±2.2
$C_{A,mean}$ [%]		-7.9±10.8	-1.8±9.0
C_A/C_S		0.49±0.26	0.61±0.21
L [cm]		36.2±8.5	37.3±8.0
L_{UNS} [%]		29.5±13.2	19.8±14.9
D_{M4} [mm]			**5.5**
n			11
C_A [%]			13.3±4.2
$C_{A,mean}$ [%]			-10.6±8.7
C_A/C_S			0.44±0.16
L [cm]			34.4±8.6
L_{UNS} [%]			37.9±9.7
		Overall	
n	95	106	108
C_A [%]	13.5±6.0	14.1±7.1	14.4±6.6
$C_{A,mean}$ [%]	-0.1±10.2	-0.1±10.9	0.1±10.5
C_A/C_S	0.68±0.53	0.74±0.82	0.75±0.81
L [cm]	29.9±10.0	30.3±10.0	30.3±9.9
L_{UNS} [%]	18.0±15.9	18.4±15.1	18.5±15.4

Figure 1

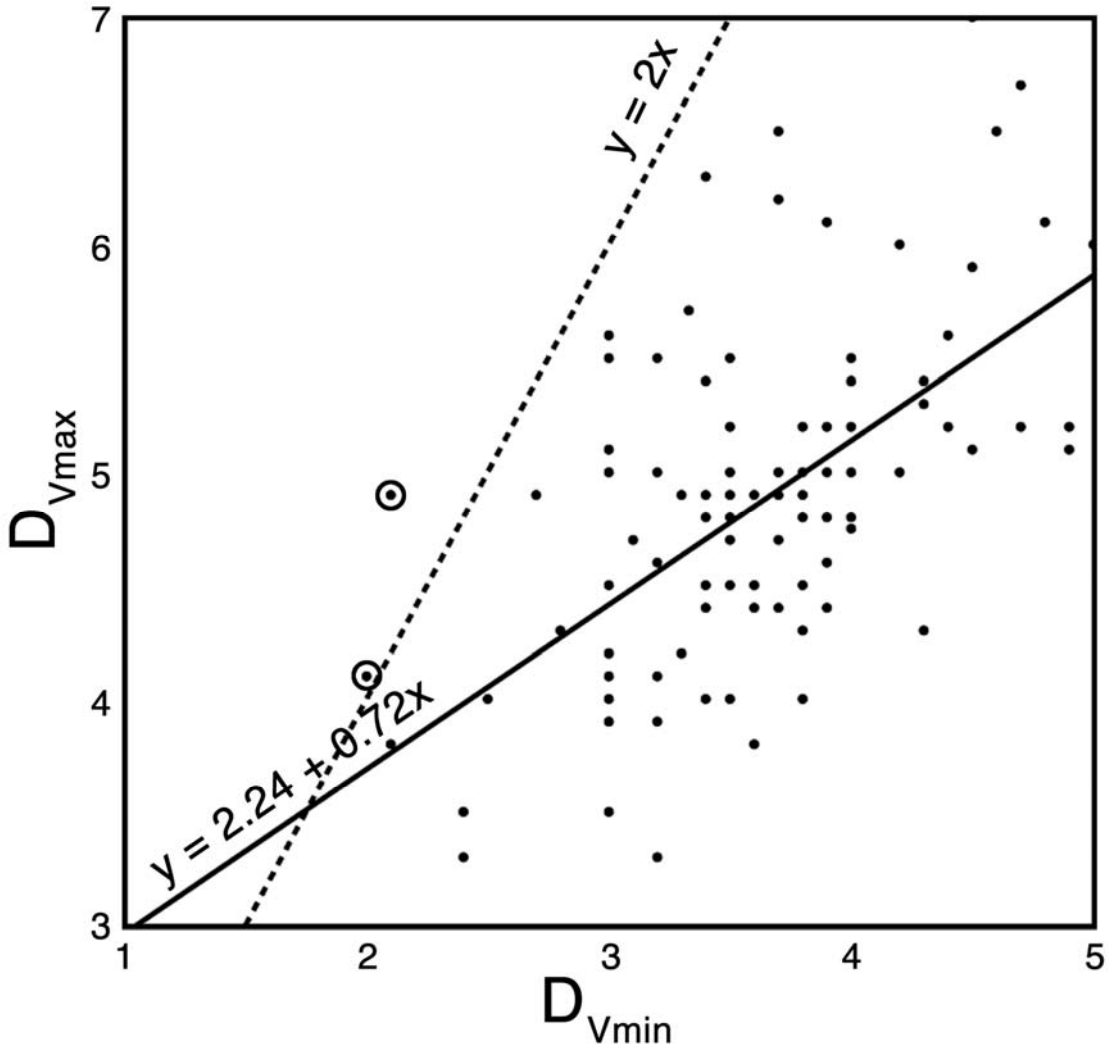


Figure 2

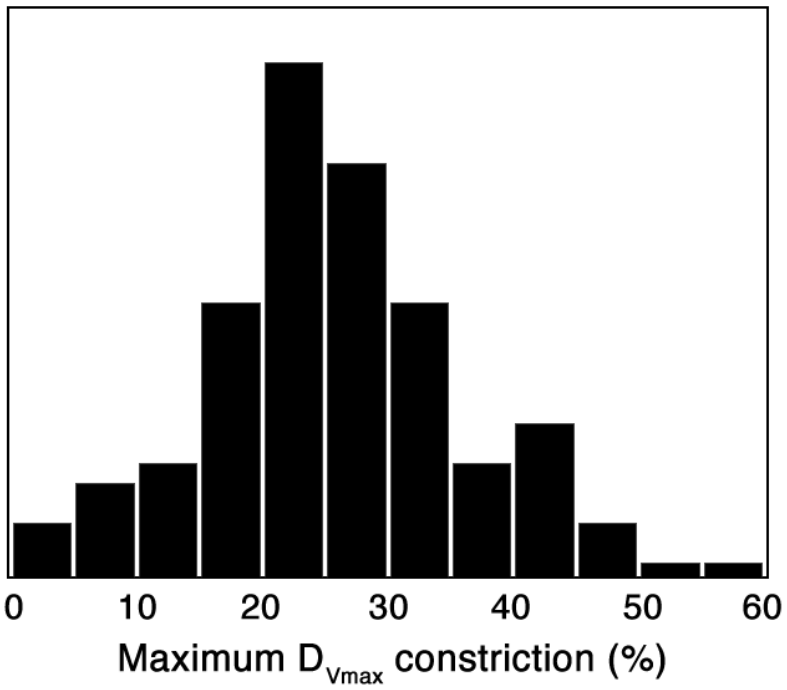


Figure 3

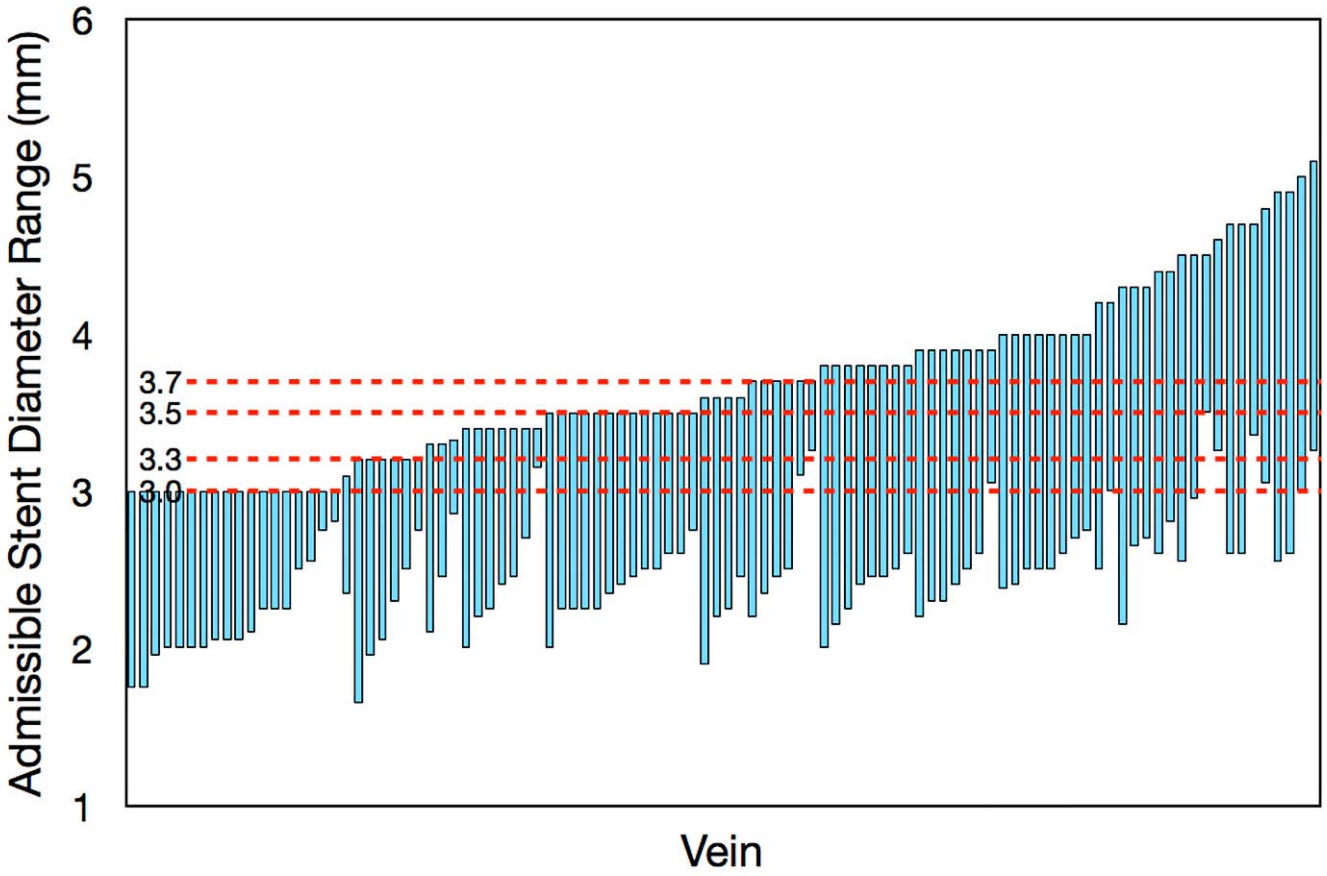
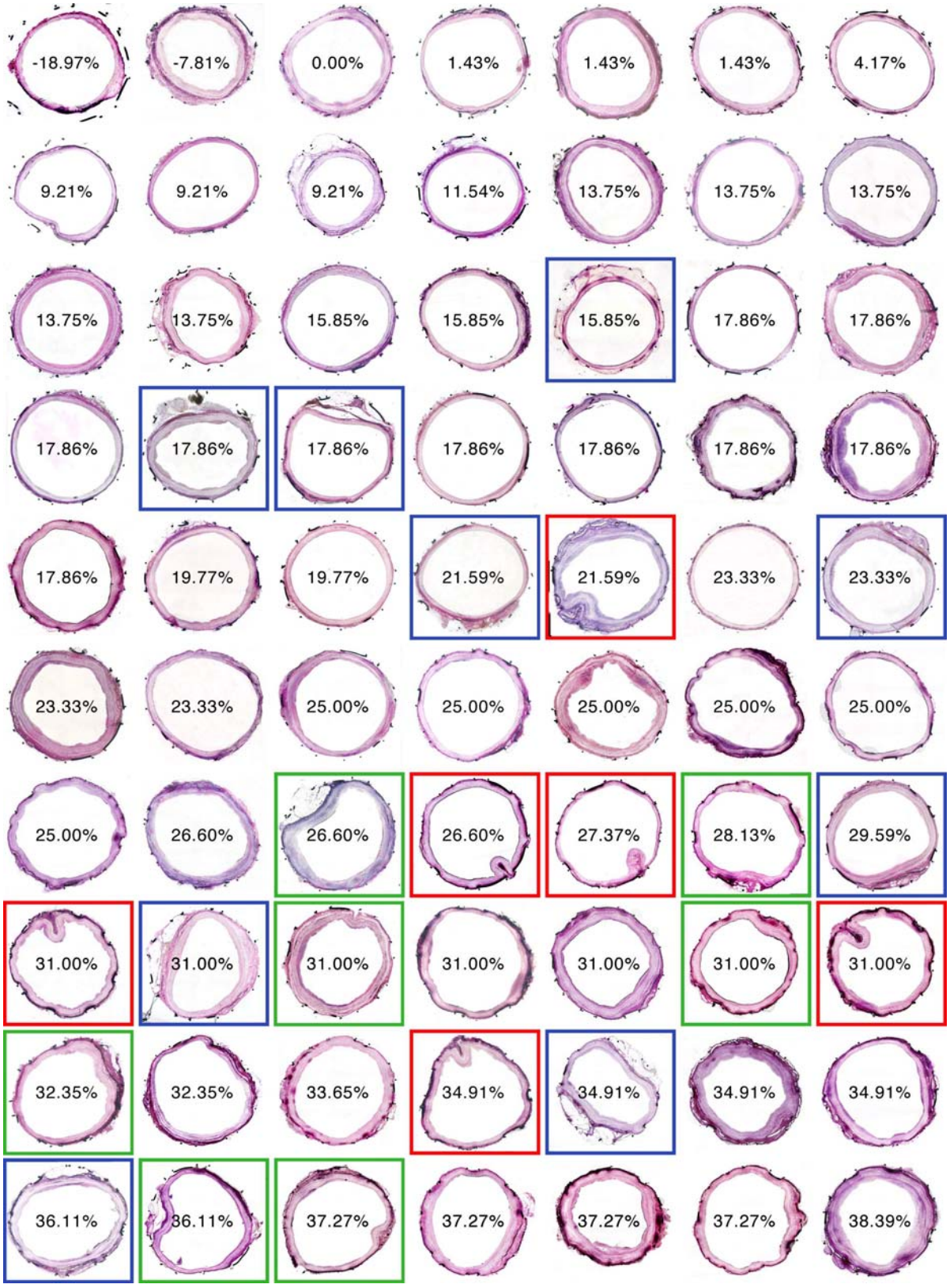


Figure 4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0.00%
1.43%
1.43%
1.43%
4.17%
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37.27%
37.27%
37.27%
38.39%

Figure 5

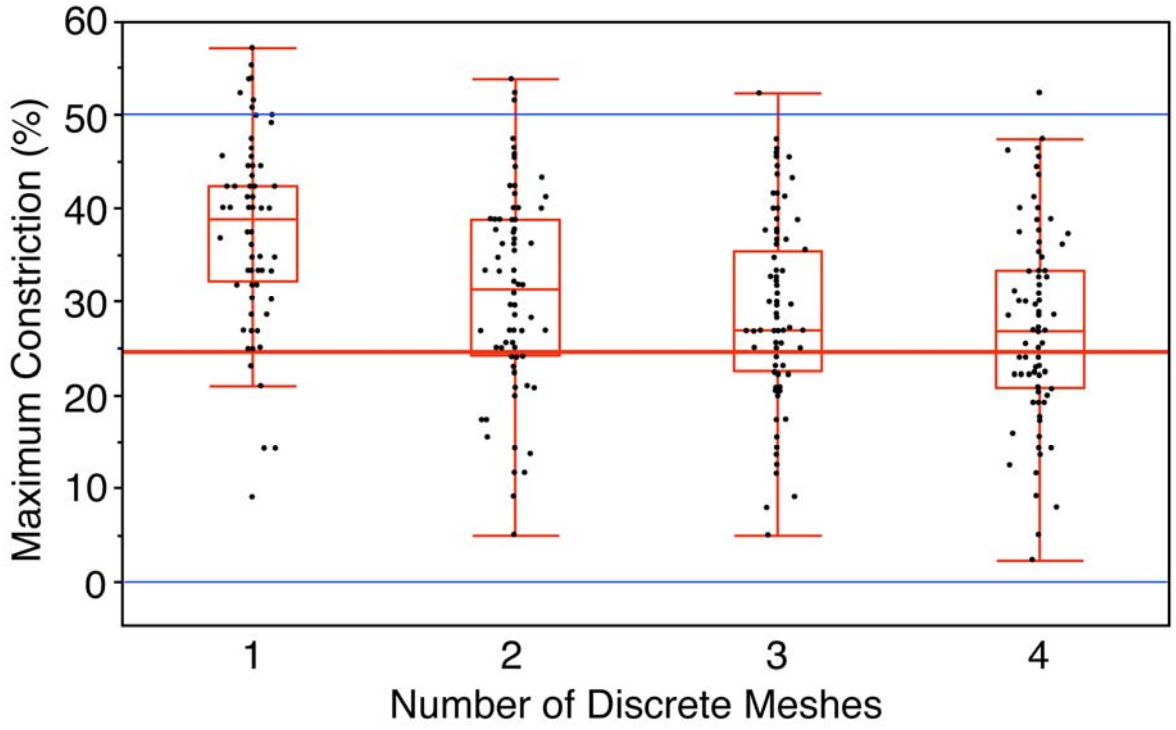
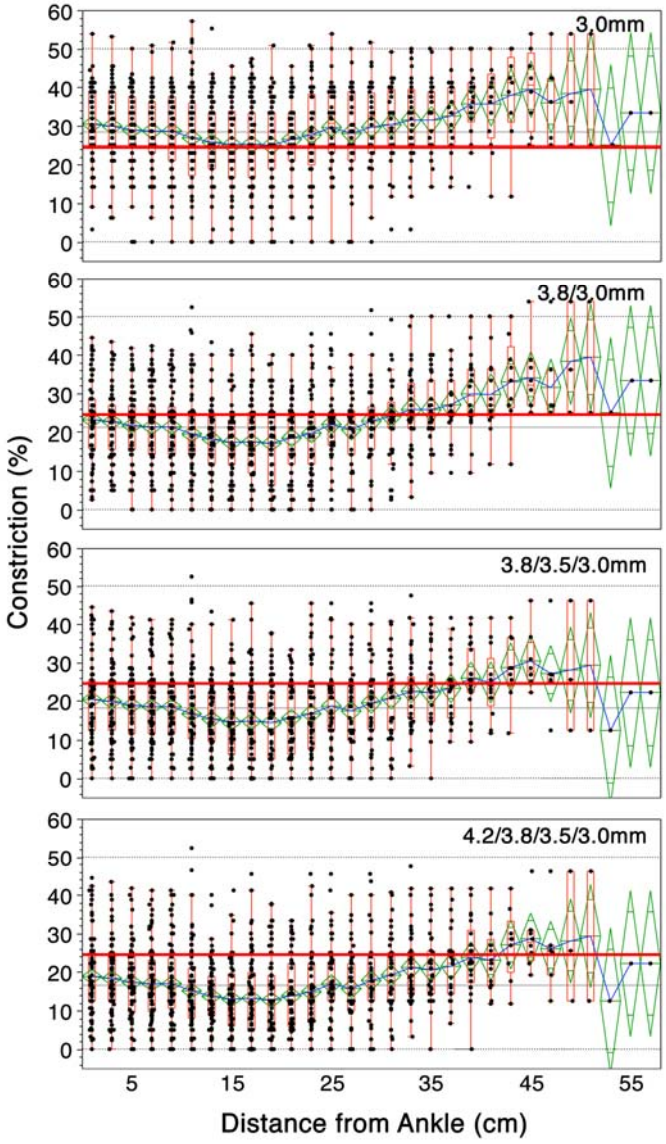

60
50
40
30
20
10
0
Maximum Constriction (%)
1
2
3
4
Number of Discrete Meshes

Figure 6


3.0mm
3.8/3.0mm
3.8/3.5/3.0mm
4.2/3.8/3.5/3.0mm
Constriction (%)
Distance from Ankle (cm)
0
10
20
30
40
50
60
5
15
25
35
45
55