Comparison of alternate preparative techniques on wall thickness in coronary artery bypass grafts: the HArVeST randomised controlled trial

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Abstract

Background: The success of coronary artery bypass grafting surgery (CABG) is dependent on long-term graft patency, which is negatively related to early wall thickening. Avoiding high-pressure distension testing for leaks and preserving the surrounding pedicle of fat and adventitia during vein harvesting may reduce wall thickening. Methods: A single-centre, factorial randomised controlled trial was carried out to compare the impact of testing for leaks under high versus low pressure and harvesting the vein with versus without the pedicle in patients undergoing CABG. The primary outcomes were graft wall thickness, as indicator of medial-intimal hyperplasia, and lumen diameter assessed using intravascular ultrasound after 12 months. Results: 96 eligible participants were recruited. With conventional harvest, low-pressure testing tended to yield a thinner vessel wall compared to high-pressure (mean difference MD (low minus high) -0.059mm, 95%CI -0.12, +0.0039, p=0.066). With high pressure testing, veins harvested with the pedicle fat tended to have a thinner vessel wall than those harvested conventionally (MD (pedicle minus conventional) -0.057mm, 95%CI -0.12, +0.0037, p=0.066, test for interaction p=0.07). Lumen diameter was similar across groups (harvest comparison p=0.81; pressure comparison p=0.24). Low pressure testing was associated with fewer hospital admissions in the 12 months following surgery (p=0.0008). Harvesting the vein with the pedicle fat was associated with more complications during the index admission (p=0.0041). Conclusions: Conventional saphenous vein graft preparation with low pressure distension and harvesting the vein with a surrounding pedicle yielded similar graft wall thickness after 12 months, but low pressure was associated with fewer adverse events.

INTRODUCTION

Saphenous vein remains the most commonly used conduit for coronary artery bypass because of its predictable handling qualities and ready availability.[1] However, as many as 40% of vein grafts become occluded at 12 years post-surgery.[2, 3] Early thrombosis occurs in up to 10% of vein grafts due to spasm or technical error.[4, 5] Late vein graft failure occurs as a consequence of early neointimal hyperplasia with later superimposed atherosclerosis.[5] Therefore, the clinical implications of any intervention to improve long-term graft patency are significant.

Surgical preparation of the harvested vein is often overlooked but may be an important contributor to

vein graft failure. Typically, the harvested vein is distended at uncontrolled high pressure with blood or fluid using a syringe to test for leaks and relieve spasm prior to grafting; this has been shown to result in endothelial loss and medial disruption.[6, 7] Our group proposed an alternative protocol that tests for leaks by connecting the harvested vein to a side branch of the aortic return cannula on the cardiopulmonary bypass circuit.[8] In this way, the grafts are then distended at the patient's own systemic pressures. We hypothesised that this should attenuate medial disruption, platelet adherence, the release of mitogenic growth factors and subsequent neointima formation, as supported by our observations that avoiding high pressure distension reduces medial damage and preserves release of prostacyclin and nitric oxide (NO), both of which have potential antiproliferative actions.[6-8] Our technique has also been shown to reduce neointima formation in cultured human saphenous vein grafts in vitro compared to conventional harvest.[9] However, while avoiding pressure distension increases graft patency in vivo in a porcine saphenous vein to carotid artery interposition model, this appears to be due to a reduction in early thrombosis rather than an effect on neointima formation.[10] Furthermore, it is not known whether avoiding high-pressure distension by our method improves long-term graft patency.

Souza and colleagues described a non-traumatic vein harvesting technique that combines avoidance of pressure distension with preservation of the surrounding adventitia and fat or 'pedicle', which is stripped during conventional vein harvesting.[11] The pedicle has been shown to preserve wall architecture and endothelial function in vitro and experimental studies have shown that the preserved fat tissue is a rich source of NO.[12, 13] It has been hypothesised that preservation of the adventitial microcirculation may reduce subsequent atherogenesis by improving wall oxygenation and reducing oxidative stress.[14]

Until recently clinical trials of therapies designed to prevent vein graft disease were limited by the large sample sizes required to measure changes in the lumen (i.e. new lesions) or patency rates by postoperative angiography. Intravascular ultrasound (IVUS) accurately and reproducibly measures vein graft wall dimensions and quantifies levels of plaque and wall fibrosis.[15-17] Using this technology, we set out to determine the effects of the vein graft harvesting technique and pressure distension on the development of vein graft wall thickness in a factorial randomised controlled trial (RCT), which allowed both techniques to be evaluated in the same trial.

METHODS

Trial Design

A single-centre, parallel group, factorial RCT with blinding of participants and clinical and research staff not involved in the operation. Participants were randomly allocated in a 1:1:1:1 ratio to one of four treatment groups; conventional harvest and high-pressure test, conventional harvest, and low-pressure test, pedicled harvest and high-pressure test, or pedicled harvest and low-pressure test.

The study was approved by a National Health Service Research Ethics Committee (Wiltshire ref. 09/H0104/28). The trial was registered as ISRCTN10567790. Patients and the public did not contribute to the design or conduct of the trial.

Participants

Adults aged 18 and over undergoing first time non-emergency CABG (either on or off-pump) at the Bristol Heart Institute, with at least one saphenous vein graft and not requiring valve replacement/repair or an aortic procedure were eligible to take part.[18, 19] Patients with congestive heart failure, ejection fraction <30%, pre-operative serum creatinine >104μmol/L, peripheral vascular disease, allergy to iodinated contrast media, participating in another interventional study, or unwilling to participate in follow-up were excluded. All participants provided written informed consent.

Interventions

Harvest technique : vein grafts were harvested either *with*(pedicle harvest) or *without* (conventional harvest) the pedicle of surrounding fat and adventitia, as described by Souza.[11] All grafts were harvested using a no-touch technique and were left in-situ until systemic heparinisation.

Pressure test for leaks : vein grafts, excised following systemic heparinisation, were either flushed with heparinised blood from a syringe (conventional high pressure test) or attached to a side arm of the aortic canulae in patients undergoing on-pump surgery, or anastomosed first to the ascending aorta in off-pump surgery, and flushed with blood at systemic pressure (low pressure test).[8]

Outcomes

The protocol-defined primary outcomes were vein graft disease as measured by i) wall thickness and ii) lumen diameter assessed using IVUS at 12 months post-surgery. Multiple IVUS measurements were taken per graft and the patient-level mean for each measurement was used. Wall thickness at baseline was measured by histological analysis of a short segment of the harvested vein from the end of each graft retrieved prior to completion of the proximal anastomoses.

Secondary outcomes were lumen diameter and graft patency assessed by quantitative angiography at 12 months; serious adverse events (SAEs); wound infection using the ASEPSIS scoring system; duration of postoperative stay; leg wound pain or dysaesthesia at 3 and 12 months assessed using the neuropathic pain symptom inventory (NPSI) scoring system; and readmissions to hospital within 12 months.[20, 21] SAEs not listed in the study protocol were coded using the Medical Dictionary for Regulatory Activities (version 19.0;McLean, Va).

Sample Size

The sample size was set at 96 patients (24 per group), which is sufficient to detect an effect size of 0.5 standard deviations (SD) with 80% power and 5% statistical significance, assuming no interaction between the method of harvesting the graft and the method of testing for leaks, a correlation of 0.7 between the one pre- and one post-randomisation measurement and allowing for 25% loss to follow-up.

An effect size of 0.5 SD equates to differences of [?]1.2mm in the mean graft wall thickness and [?]2.4mm^2 in lumen area between pedicled and conventional harvest groups, or between high- and low-pressure test groups, assuming estimated within-group SDs of 2.33 and 4.69 respectively.[16] The sample size calculation assumes only one graft per patient whereas, in practice, some patients received two or more vein grafts.[18] Therefore, the study was powered to detect differences somewhat smaller than 0.5 SD.

Randomisation

Allocations were generated by computer using block randomisation with varying block sizes in advance of the study. A password-controlled secure database concealed the allocation until data had been entered to confirm identity and eligibility. Randomisation took place as close to the start of surgery as possible. The team member responsible for randomisation was not involved in data collection for the study.

Blinding

Participants were blinded to treatment allocation. The surgical team involved in the operation were unblinded. Research nurses collecting post-operative data, and assessors measuring wall thickness and lumen diameter with IVUS and quantitative angiography were blinded to treatment allocation. Laboratory staff conducting histological analyses of short segments of prepared vein could not be blinded to the harvest technique used.

Follow-up

Postoperative management was in accordance with hospital protocols. Participants were followed up at 3 and 12 months by questionnaire to assess wound infection, leg wound pain and dysesthesia, and readmissions to hospital; and attended hospital for IVUS and angiographic imaging at 12 months.

Statistical Methods

Analyses were based on a pre-specified statistical analysis plan, were performed on an intention-to-treat basis and are reported in line with the CONSORT reporting guidelines. Patient level means of the multiple IVUS measurements per graft were calculated for wall thickness, lumen diameter, lumen area and wall area. Binary outcomes were compared using logistic regression, counts using Poisson regression, time to event outcomes using Cox proportional hazards models and continuous longitudinal outcomes using hierarchical mixed effects models, to account for participants with multiple grafts and IVUS frames of each graft. Analyses were adjusted for IVUS frame number as a continuous fixed covariate and patient and graft number as random effects. Multiple imputation by predictive mean matching using chained equations was used to impute missing data for the primary outcomes and angiographic assessment of lumen diameter. Data missing due to graft occlusion was not imputed. See Appendix for further details. All analyses used the conventional harvest and high pressure as the reference groups and included harvest technique, pressure test and the interaction between two (if significant at the 10% level) and were adjusted for baseline measurements where available. If a significant interaction is indicated, pressure testing is compared and reported for each harvest technique separately (and harvest technique is compared and reported for each pressure test separately) otherwise the main effects of harvest technique and pressure test are reported. There was no adjustment for multiple comparisons. All analyses were performed in Stata version 14.0 (StataCorp LP, College Station, Tex) and SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Recruitment

Trial recruitment was from December 2009 until October 2013. A total of 712 patients were assessed for eligibility. Of 195 patients who were approached, 109 consented, and 97 were randomised into the trial. Overall, 46 patients were allocated to receive conventional harvest, and 51 to receive pedicled harvest; 49 to receive low pressure, and 48 to receive high pressure (**Figure 1**).

The primary analysis included 96 randomised patients, excluding one patient who was withdrawn during surgery as no vein grafts were harvested. Protocol deviations occurred in 37 grafts from 21 patients (**Table 1** , **Appendix Table A1**). In total, 17 patients randomised to pedicled harvest received conventional harvest, 6 patients randomised to low-pressure received high-pressure. Unblinding of treatment allocation occurred for one patient randomised to the pedicled harvest and high-pressure group.

A total of 20 of the 96 patients did not attend for the 12-month IVUS and angiography assessment, 12 of whom returned at least one questionnaire at 12 months. Seventeen patients formally withdrew from the trial, 15 from 12-month IVUS and angiography assessment only and 2 from all follow-up (**Figure 1** , **Appendix Table A2)** .

Baseline data

The mean age of participants was 66.0 years (SD 8.9), and 87/96 (91%) were male. By chance, patients randomised to pedicled harvest were slightly older than those randomised to the conventional harvest group (mean 67.3 years vs. 64.5 years), and the low-pressure group had proportionally more males than the high-pressure group (96% vs. 85%). From histology of veins after surgical preparation, the median wall thickness was greater in the low-pressure (0.39 vs. 0.32mm) and pedicled harvest (0.39 vs. 0.31mm) groups and

the median lumen diameter was smaller in these groups (pressure comparison 2.87 vs. 3.30mm; harvest comparison 2.87 vs. 3.35mm) (**Table 2, Appendix Table A3**).

Operative details

The median duration of surgery was 3 hours and was similar across groups. Overall, 28/96 (29%) procedures were performed on-pump. Study participants received a total of 275 grafts (mean 2.9 grafts per patient), of which 160 (58%) were vein grafts. The most common vein graft sites were RCA-PDA (n=50, 31%), Diag (n=21, 13%), OM1 (n=39, 24%) and OM2 (n=19, 12%), while the majority of arterial grafts were LAD (n=90, 80%). Most vein graft conduits were judged good quality (n=90, 56%), with a higher proportion of good quality conduits in the conventional harvest group compared to the pedicled harvest group (61% vs. 52%). Most vein grafts were taken from the left leg long saphenous vein (n=132, 83%, **Table 3, Appendix Tables A4 and A5**).

Primary Outcomes at 12 months

Wall thickness

Grafts assessed using IVUS had, on average, thicker walls than the surgically prepared veins assessed by histology. There was a trend towards a difference in mean wall thickness according to the harvest technique and pressure test used (test for interaction between the pressure test and harvest technique, p=0.070). In patients randomised to conventional harvest, those in the low-pressure group had, on average, a thinner vessel wall compared to those in the high-pressure group (mean difference MD (low minus high) = -0.059mm, 95%CI -0.12, +0.0039, p=0.066). By contrast, in patients randomised to pedicled harvest the wall thickness was similar irrespective of distension pressure (MD (low minus high) = +0.019mm, 95%CI -0.038, +0.075, p=0.51).

Comparing the results by harvest method in patients randomised to a high pressure test, grafts with a pedicle had a thinner vessel wall than those in the conventional harvest group (MD (pedicle minus conventional) = -0.057mm, 95%CI -0.12, +0.0037, p=0.066). For those randomised to a low-pressure test, wall thicknesses were similar for the two harvest techniques (MD (pedicle minus conventional) = +0.021mm, 95%CI -0.038, +0.081, p=0.48, **Figure 2, Table 4, Appendix Table A6**).

Lumen diameter

There was no interaction between the pressure test and harvest technique for lumen diameter assessed using IVUS (p=0.49). Consistent with this, comparing the harvest techniques, the average lumen diameter was similar in the two groups (geometric mean ratio, GMR (pedicled:conventional) = 1.01, 95%CI 0.95, 1.07, p=0.81). It was also similar in the two pressure test groups (GMR (low:high) = 0.97, 95%CI 0.91, 1.02, p=0.24,**Figure 2, Table 4, Appendix Table A6**).

Secondary Outcomes

Angiography at 12 months

Lumen diameter results assessed using quantitative angiography were consistent with the IVUS results. Fewer grafts became occluded within 12 months in patients randomised to the low pressure test compared to high (4/62; 6% vs. 8/67; 12%; odds ratio OR (low:high) = 0.53, 95%CI 0.15, 1.88, p=0.32) and with pedicled harvest compared to conventional (4/66; 6% vs. 8/63; 13%; OR (pedicled: conventional) = 0.46, 95%CI 0.13, 1.62, p=0.22, **Figure 3, Appendix Table A7, Figure A1**).

In hospital outcomes

The median postoperative hospital stay was 6 days irrespective of harvest technique groups. However, in the low-pressure group the median was 5.5 days, representing a non-significant higher chance ('hazard') of being

discharged in the first 5 days. There were similar numbers of participants with one or more post-operative complications during the index admission in the two pressure test groups (41/48, 85% vs. 40/48, 83%; OR (low:high) = 1.23, 95% CI 0.39, 3.90, p=0.72), but a higher number in the pedicled compared to the conventional harvest group (48/51, 94% vs. 33/45, 73%; OR (pedicled:conventional) = 5.86, 95% CI 1.53, 22.4, p=0.0041, **Figure 3, Appendix Tables A8 and A9, Figure A2**).

Serious adverse events during follow-up

There were significantly fewer patients being readmitted to hospital within 12 months of surgery and fewer patients experienced SAE(s) in the low pressure group compared to the high pressure group (admissions: 9/44; 20% vs 15/44; 34%; incidence rate ratio IRR (low:high) = 0.31, 95%CI 0.15, 0.65, p=0.0008; one or more SAE: 9/48, 19% vs. 18/48, 38%;. OR = 0.39, 95%CI 0.15, 0.98, p=0.040), but the rate of admissions and SAEs did not vary by harvest technique (admissions: IRR (pedicled:conventional) = 0.84, 95%CI 0.44, 1.58, p=0.59; one or more SAE: OR = 1.13, 95%CI (0.45, 2.82), p=0.79, **Figure 3, Appendix Tables A10 and A11**).

Wound infection and pain

Two patients had an ASEPSIS score>20 within their index hospital admission, increasing to 5 patients at any time from surgery to 12 months post-operatively (**Appendix Table A8**). Fewer patients randomised to the low-pressure group reported pain (NPSI pain score>0) at 3 months compared to the high-pressure group (11/40, 28% vs. 16/33 48%; OR (low:high) = 0.40, 95%CI (0.15, 1.04), p=0.061, but at 12 months similar numbers reported pain (16/39, 41% vs. 12/35, 34%; OR (low:high) = 1.29, 95%CI 0.50, 3.29, p=0.60). Pain was similar in the pedicled and conventional harvest groups (OR (pedicled:conventional) = 0.98, 95%CI 0.45, 2.14, p=0.96,**Figure 3, Appendix Tables A12 and A13)** .

DISCUSSION

Study design

The use of no-touch techniques during preparation of saphenous veins for CABG has been advocated for decades based on evidence from experimental studies.[5] However, efficacy in terms of reduced early graft occlusion and less neointimal thickening has not been evaluated in clinical trials, except for the studies of Souza and colleagues using grafts surrounded by a pedicle.[11, 22] The HArVeST trial is the first adequately powered RCT comparing the efficacy of low vs. high-pressure testing of saphenous vein and of harvesting with and without a pedicle. Histological measurements of lumen size and wall thickness in samples of prepared veins were taken to examine the acute effects of distension. Wall thickness is a more sensitive measure of neointima formation after grafting than luminal encroachment.[6, 10] In time course experiments, lumen area increases by 33% between one and six months of implantation, whereas graft wall thickness increases 2-3 fold.[23] Vein wall thickening occurs rapidly within the first 2 months, stabilising at 6-9 months.[5, 24] Hence, by 12 months early fluctuations have abated, establishing the choice of primary endpoint, although atherosclerosis within 12 months is rare.[2, 3, 5] Owing to its effect on bulk fluid transfer and lipoprotein retention, total wall thickness is thought to be a key predisposing factor for subsequent graft atherosclerosis and late occlusion. Wall thickness may be considered a surrogate for long-term patency, although this remains to be investigated directly.

Main findings

Histological examination of prepared vein samples demonstrated an increase in lumen diameter and decrease in wall thickness after high-pressure distension of veins without a pedicle. This is consistent with nonelastic distension of the veins at high pressure and has been shown to result in injury to the vein endothelium and medial layer. By contrast, the veins with a pedicle were protected, implying less overdistension and by implication less damage. The increases in wall thickness and values obtained at 12 months are consistent with other recent studies.[16, 25] Low pressure veins without a pedicle tended to suffer less wall thickening than high pressure ones, consistent with a reduction in neointima formation. Pedicled grafts showed similar

thickening irrespective of distension pressure. Importantly, low pressure grafts without a pedicle had similar wall thicknesses to pedicled grafts at either pressure. Low pressure grafts without a pedicle were associated with fewer post-operative complications and less pain compared to pedicled grafts. Our results imply that the simpler, less complicated low-pressure vein distension protocol is at least as effective at reducing wall thickening as vein harvesting with a fat pedicle.

Clinical implications

The success of CABG is dependent on long-term graft patency because vein graft occlusion is associated with a return of cardiac symptoms, an increase in myocardial infarction and death.[5, 26] Aspirin therapy reduces early vein graft thrombosis, but no treatment, with the exception of aggressive lipid lowering has been shown to attenuate the incidence of vein graft atherosclerosis and improve long-term graft patency.[4, 5, 27] The E2F antisense oligonucleotide, Edifoligide, reduced neointima formation in pre-clinical experiments, showed clinical efficacy in a first in human study, but failed to benefit graft patency in a phase 2 study.[28] A method for external vein graft stenting also reduced wall thickness in pigs, but proved impractical in patients.[24, 29] These failures prompted us to re-evaluate simple surgical techniques for vein graft harvesting that might improve patency. Such interventions do not increase operative costs and require no laboratory or manufacturing resources.

Souza, in a RCT with veins harvested using the pedicled technique reported a superior patency compared to veins harvested conventionally (90% versus 76% at a mean of 8.5 years post-grafting, p=0.01).[30] Assessment of a subset of vein grafts using IVUS (18 patients) showed less intimal hyperplasia and atherogenesis in grafts harvested with the surrounding pedicle (mean intimal thickness 0.42±0.07mm versus 0.53±0.08mm, p<0.01).[16] Similar excellent long-term results were reported by this group in a comparison of pedicled vein grafts with radial artery grafts.[22] Although the improved graft patency with the pedicled technique is encouraging the results derive from a single surgeon study and have not been confirmed by others.

Compared to low pressure distention of conventionally harvested veins, pedicle grafting requires more extensive dissection (which led to a number of protocol deviations) and increases the frequency of leg wound morbidity.[11] Our data demonstrate that it is possible to achieve similar benefits in terms of reduced wall thickening to pedicled grafts by using low pressure distension of conventionally harvested veins.

Strengths and limitations

Strengths include the inclusive eligibility criteria, with few patients being ineligible and minimisation of bias through concealed allocation. Personnel conducting the analyses, participants and staff not involved in the surgical procedure were blinded to the group allocation. The factorial study design allows two interventions to be evaluated in one study.

Limitations include that participants were recruited from a single centre, limiting the generalizability of the findings. There were protocol deviations, mostly in the pedicle harvest group, which reduces the power of the study to detect differences between the interventions. Some patients withdrew and did not attend the follow-up at 12 months, although the impact of this missing data was minimised by estimating the missing data using multiple imputation.

In conclusion, conventional saphenous vein graft preparation with low pressure distension and harvesting the vein with a surrounding pedicle yielded similar graft wall thickness after 12 months, but low pressure distention was associated with fewer short and long-term adverse events.

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LEGENDS TO FIGURES

Figure 1 Flow of participants

Angio/IVUS = Angiogram/ Intravascular ultrasound; NPSI = Neuropathic pain symptom inventory

Notes: [1]Some patients may be ineligible for more than one reason

Figure 2 Primary outcomes

Blue circles represent the point estimate of the treatment effect and the red line depicts the 95% confidence interval

GMR = geometric mean ratio; MD = mean difference

Figure 3 Secondary outcomes

Blue circles represent the point estimate of the treatment effect and the red line depicts the 95% confidence interval

GMR = geometric mean ratio; IRR = incidence rate ratio; HR = hazard ratio; NPSI = Neuropathic pain symptom inventory; OR = odds ratio

Table 1 Protocol deviations

	Patients Randomised to Conventional Harvest & High Pressure (n=22) *Grafts/ Patients*	Pa *%[1]*
Any protocol breach	**0/0**	**0%**
Did not receive allocated pressure treatment	0/0	0%
Did not receive allocated harvest treatment	0/0	0%
Unblinded*	0/0	0%

[1] Percentage of patients

* Operation ran late, and randomisation details were stored in patient notes rather than being collected immediately after the operation as per the protocol**.**

Table 2 Patient demography and previous history

		Randomised to vein distension pressur High (Conventional) (n=48) n
BASELINE CHARACTERISTICS	**BASELINE CHARACTERISTICS**	
Age (years)	Mean (SD)	65.9
Gender (Male)		41/48
BMI	Median (IQR)	27.8
Urgent procedure		11/48
NYHA class	I/Asymptomatic	23/48
	II	24/48
	III	1/48
	IV	0/48
CCS class	Asymptomatic	9/48
	I	8/48
	II	20/48
	III	7/48
	IV	4/48
EuroSCORE	Median (IQR)	3.0
CARDIAC HISTORY	**CARDIAC HISTORY**	

LV function	Good (>50%)	42/48
	Moderate (30-50%)	6/48
>50% disease in left main stem		12/48
Coronary disease, number of vessels:	Single	1/48
	Double	14/48
	Triple	33/48
RISK FACTORS	**RISK FACTORS**	
Family history (IHD)ˆ		30/47
Hypertension		38/48
Hypercholesterolemia		44/48
Hypothyroidism		3/48
Smoking status:	No	15/48
	Ex-smoker (>1 month)	25/48
	Smoker	8/48
Diabetes:	None	38/48
	Diet	2/48
	Oral	5/48
	Insulin	3/48
HISTOLOGICAL ANALYSIS	**HISTOLOGICAL ANALYSIS**	
Wall thickness (mm)*	Median (IQR)	0.32
Lumen diameter (mm)*	Median (IQR)	3.30

Details on missing data (High pressure, low pressure, conventional harvest, pedicled harvest): *(1,2,1,2), ˆ(10,14,11,13)**.**

BMI = body mass index; CCS = Canadian Cardiovascular Society; IHD = ischaemic heart disease; IQR = interquartile range; LV = left ventricular; NHYA = New York Heart Association; SD = standard deviation

Table 3 Intraoperative characteristics

		Randomised to vein distension pressure (n=96)	**Rand**
		High (Conventional) (n=48)	**High**
		n	**%**
BYPASS DATA			
Duration of operation (minutes)	Median (IQR)	180.0	(160.5
Type of operation:	On Pump	16/48	33%
If On Pump:			
Bypass duration (mins)	Median (IQR)	79.0	(55.5,
Cross clamp duration (mins)	Median (IQR)	46.0	(34.0,
Temperature:	Warm	14/16	88%
	Cooled	2/16	13%
Grafts			
Mean number of grafts		2.9	0.8
Saphenous vein successfully harvested? *		44/47	94%

Details on missing data (High pressure, low pressure, conventional harvest, pedicled harvest): *(1,0,0,1). IQR = interquartile range

Table 4 Primary outcomes: quantitative intravascular ultrasound assessments at 12 months

	Vein grafts of patients (n=160) High (Conventional) (n=81)	**Vein grafts of patients (n=160) High (Conventional) (n=81)**	**Vein grafts of patients (n=160) Low (Systemic) (n=79)**	**Vein grafts of patients (n=160) Low (Systemic) (n=79)**	**Vein grafts of patients (n=160) Conventional (n=72)**	**Vein grafts of patients (n=160) Conventional (n=72)**	**Vein grafts of patients (n=160) Pedicled (n=88)**	**Vein grafts of patients (n=160) Pedicle (n=88)**
	Mean/ Median	**SD/IQR**	**Mean/ Median**	**SD/IQR**	**Mean/ Median**	**SD/IQR**	**Mean/ Median**	**SD/IQ**
PRIMARY OUTCOMES:								
Lumen Diameter (mm)	3.6	(3.1, 4.2)	3.4	(3.0, 3.8)	3.5	(3.0, 3.9)	3.5	(3.0, 4.0)
Wall Thickness (mm)	0.74	0.15	0.76	0.17	0.74	0.15	0.77	0.16
Other IVUS Measurements:								
Lumen Area (mm^2)	10.2	(7.8, 13.9)	9.3	(6.9, 11.5)	9.5	(7.3, 12.2)	9.9	(7.2, 12.6)
Wall Area (mm^2)	9.9	(8.3, 12.5)	10.1	(7.7, 12.2)	9.7	(7.9, 11.6)	10.3	(8.3, 12.7)
Plaque burden Area (mm^2)	9.9	(8.3, 12.4)	10.1	(7.7, 12.5)	9.7	(7.9, 11.5)	10.3	(8.3, 12.6)
Area of Stenosis	49.6	8.8	52.0	8.7	50.3	7.9	51.3	9.6
Diameter of Stenosis	28.6	(24.0, 31.6)	31.2	(26.2, 35.3)	29.2	(26.3, 34.2)	30.6	(24.7, 33.9)
Minimum Lumen Diameter (mm)	3.1	0.8	2.9	0.6	3.0	0.6	3.0	0.7

Time between randomisation and 12-month primary outcome assessment (months)	13.2	(12.3, 13.9)	13.0	(12.6, 14.0)	13.1	(12.4, 13.6)	13.1	(12.4, 14.5)

IVUS = intravascular ultrasound; IQR = interquartile range; SD = standard deviation. Note: Numbers in the table are summaries of the patient level means e.g. for each patient the mean wall thickness of all IVUS measurements was calculated; summary statistics of these individual patient level means are presented. *Missing data on 50 vein grafts (High pressure, low pressure, conventional harvest, pedicled harvest): Withdrew from IVUS (14,14,11,17). Occluded (8,4,8,4), IVUS Problems (4,0,0,4), Missing (3,3,1,5).

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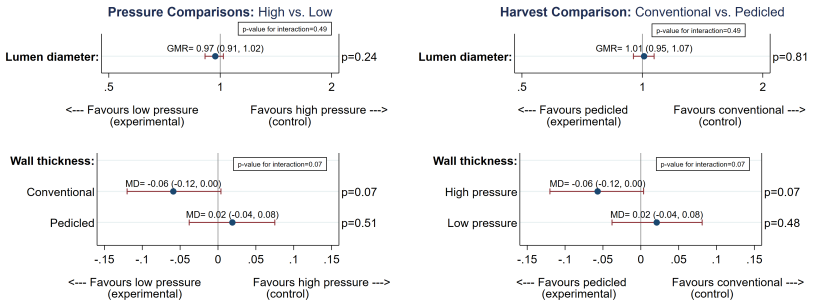
`Figure 1 - flow chart.pdf` available at https://authorea.com/users/311183/articles/504343-comparison-of-alternate-preparative-techniques-on-wall-thickness-in-coronary-artery-bypass-grafts-the-harvest-randomised-controlled-trial



Secondary outcomes