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Epiaortic Ultrasound for Assessment of Intraluminal Atheroma; Insights from the REGROUP Trial

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Abstract

Objectives: To assess the use of epiaortic ultrasound in contemporary cardiac surgery, as well as its impact on surgical cannulation strategy and cerebrovascular events.

Design: Epiaortic ultrasound data was prospectively collected in the Randomized Endovascular Graft Prospective (REGROUP) trial (VA Cooperative Studies Program #588, [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01850082), NCT01850082), which randomized 1,150 coronary artery bypass graft patients between 2014 and 2017 to endoscopic or open-vein graft harvest.

Setting: Sixteen cardiac surgery programs within the Veterans Affairs Healthcare System with expertise at performing endoscopic vein-graft harvesting.

Participants: Veterans Affairs patients, greater than 18 years of age, undergoing elective or urgent coronary artery bypass grafting with cardiopulmonary bypass and cardioplegic arrest with at least one planned saphenous vein graft were eligible for enrollment.

Interventions: Epiaortic ultrasound was performed by the surgeon using a high frequency (>7 MHz) ultrasound transducer. Two-dimensional images of the ascending aorta in multiple planes were acquired before aortic cannulation and cross-clamping.

Measurements and Main Results: Epiaortic ultrasound was performed in 34.1% (269 of 790) of patients in REGROUP. Among these patients, simple intraluminal atheroma was observed in 21.9% (59/269), and complex intraluminal atheroma comprised 2.2% (6 of 269). The aortic cannulation or cross-clamp strategy was modified based on these findings in 7.1% of cases (19 of

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Disclosures

The authors have no conflicts of interest.

269). There was no difference in stroke between patients who underwent epiaortic ultrasound and those who did not (1.9% v 1.2% $p = 0.523$).

Conclusions: Despite current guidelines recommending routine use of epiaortic ultrasound (IIa/B) to reduce the risk of stroke in cardiac surgery, in this contemporary trial, use remains infrequent, with significant site-to-site variability.

Keywords

ultrasonography; echocardiography; transesophageal; stroke; ascending aorta; plaque; atherosclerotic; coronary artery bypass grafting

STROKE RISK continues to be the Achilles' heel of cardiac surgery. Perioperative stroke is a particularly devastating complication and portends significantly increased patient morbidity, mortality, hospital costs, hospital length of stay, and decreased functional status.¹ Despite advances in surgical technique, periprocedural neurologic events during cardiac surgery remain prevalent, with contemporary studies reporting stroke rates of approximately 1.3% to 4.0%.^{2–6} These general estimates likely increase in elderly populations, with cited contemporary rates between 4.1% and 5.9% in octogenarians and up to 8.6% in nonagenarians.^{7–10} In the SYNTAX trial, coronary artery bypass graft (CABG) participants suffered a 3 times higher risk of stroke at 12 months compared with participants undergoing percutaneous coronary intervention (2.2% v 0.6%; $p = 0.003$),³ and similar rates were observed in the more recent EXCEL trial at the 3-year timepoint (2.9% CABG v 2.3% percutaneous coronary intervention; $p = 0.77$).⁶ Importantly, the incidence of stroke after CABG reported in the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database has been largely unchanged over the past 10 years.^{2,11}

Transesophageal echocardiography (TEE) is routinely used in cardiac surgical procedures for monitoring, assessment of pathology, assessment of biventricular and valvular function, and imaging of the aorta. However, the mid and distal segments of the ascending aorta are often obscured by interposition of the air-filled trachea-bronchial tree.¹² Unfortunately, this TEE “blind spot” is the portion of the ascending aorta that is most often manipulated, clamped, and cannulated during routine cardiovascular surgery. In the majority of cases, the specific location and composition of atheroma in the aortic blind spot cannot be adequately characterized using TEE. Although many surgeons still rely on manual aortic palpation, this approach has very low sensitivity.¹³ Epiaortic ultrasound (EAU) provides a simple solution to accurately screen the entire ascending aorta for presence of intraluminal atheroma (ILA) with superior sensitivity to both TEE and palpation.

The Randomized Endovascular Graft Prospective (REGROUP) Trial analyzed the rate of major adverse cardiac events in patients undergoing CABG in the Veterans Health Administration who were randomly assigned to receive at least one saphenous vein harvested endoscopically or using an open technique; the primary outcome of the REGROUP trial was recently published.¹⁴ Information on the use of EAU was prospectively collected as part of the parent trial. The objective of this planned subanalysis was to assess the prevalence of use of EAU in the REGROUP trial, as well as to evaluate its impact on rates of postoperative

stroke. The authors hypothesized that EAU and altered cannulation strategies owing to EAU would be associated with lower rates of stroke.

Methods

REGROUP is a prospective trial that randomized 1,150 CABG patients at 16 North American medical centers in the Veterans Health Administration to endoscopic or open vein harvest (OVH) between 2014 and 2017. The REGROUP study design and the CONSORT diagram were previously published.^{14,15} The primary outcome was the first occurrence of a major adverse cardiac event (a composite of death from any cause, nonfatal myocardial infarction, or repeat revascularization) in a time-to-event analysis over the active follow-up period of the trial. As the study design for the parent trial has been published previously, and this is a subanalysis, no separate trial protocol has been published. The parent REGROUP study was funded by the Cooperative Studies Program (CSP), Office of Research and Development, Department of Veterans Affairs, Washington, D.C. REGROUP (CSP #588) [Clinicaltrials.gov NCT01850082](https://clinicaltrials.gov/ct2/show/study/NCT01850082).

Data Gathering

Information regarding EAU was gathered prospectively within REGROUP using the following question set:

“Was epiaortic scanning performed prior to cannulation?” (Yes/No)

- a. If yes, indicated EAU findings using scale below (0–2);
 - 0 = No ILA seen by EAU
 - 1 = Simple ILA (<4 mm protrusion into lumen) or focal calcification
 - 2 = Complex ILA (>4 mm protrusion, mobile; including Katz¹⁶ atheroma score 4 and 5)
- b. “Was the surgical plan for aortic cannulation/clamping modified based on EUS (EAU) results?” (Yes/No)

The Katz grading scale is provided in Table 5.

Patients

The clinical characteristics of the patients are described in Table 1. Inclusion and exclusion criteria and additional operative details were previously published.¹⁴ Guideline-directed medical therapy for secondary prevention of cardiovascular events was recommended for all patients.¹⁷

Epiaortic Ultrasound

Before initiation of the REGROUP study, individual sites were educated regarding standard protocols and procedures, including the study chair’s preference for EAU to be performed routinely. However, owing to concerns about availability of appropriate ultrasound probes, the use of EAU was not mandated, and EAU was performed by placing a high frequency (>7 MHz), linear, phased- or matrix-array ultrasound transducer on the ascending aorta and

acquiring two-dimensional images in multiple planes of aortic lumen and aortic walls. Sites were educated using existing guidelines for epiaortic ultrasound published by Glas et al., and examinations were performed based on these guidelines.¹⁸ Based on the acquired images, ILA was graded on a 0 to 2 scale, as described above. Modification of technique was performed based on convincing EAU findings, at the discretion of the attending cardiothoracic surgeon. These modifications included site of cannulation, cross-clamping, or both. The prevalence of TEE use was not collected as part of REGROUP.

Vein Harvest Technique

The use of any endoscopic vein harvest (EVH) device approved by the Food and Drug Administration was allowed in the study; the equipment was purchased by the participating hospitals. OVH was performed according to each center's preference.

Vein Harvester Experience

Only providers (ie, surgeons or physician assistants, but not trainees in either field) with documented experience of >100 EVH and low (<5%) conversion rates within an established EVH Program for >2 years were eligible to be evaluated by a study-harvester selection committee chaired by an academic cardiac surgery physician assistant. Based on the submitted credentials certified by each center's Principal Investigator, the ad hoc committee voted to allow 33 providers at 16 cardiac surgery centers to participate in REGROUP. Similar levels of experience for OVH were required.

Statistical Analysis

Means and frequencies were calculated for patient characteristics and for clinical measures, collectively and by harvesting technique (OVH v EVH). Bivariate analyses were employed to assess underlying differences and differential outcomes between harvesting and SSI groups. χ^2 analysis was used to compare categorical characteristics, and student's independent t test (or nonparametric Wilcoxon rank-sum test) was used to compare continuous outcomes across groups and with outcomes. Analyses were performed using SAS statistical software, (Version 9.4 SAS Institute), assuming a type I error of $\alpha = 0.05$. All statistical analyses were performed by a dedicated statistician employed by the Cooperative Studies Program and assigned to the REGROUP Trial (CSP #588).

Results

In REGROUP, the median active follow-up was 2.78 years (interquartile range 1.99–3.48 years). The primary outcome of major adverse cardiac events occurred in 89 patients (15.5%) randomized to the open-harvest group and 80 patients (13.9%) randomized to the endoscopic-harvest group (hazard ratio 1.12; 95% confidence interval, 0.83–1.51; $p = 0.47$). Other secondary and tertiary outcomes were reported previously.¹⁴

Epiaortic Ultrasound Data

EAU data was available for 68.7% of cases performed (790 of 1,150), and of these patients, the authors' data demonstrate that only 34.1% (269 of 790) underwent documented EAU during their procedure. Furthermore, significant variability was identified between

participating centers in terms of how often EAU was performed. The Boston Veterans Affairs had the highest rate of EAU at 98%, 11 of 16 participating centers performed EAU in <5% of cases, and 4 sites reported EAU rates of 0%. There was no difference in rates of EAU between the OVH and EVH groups (130 of 574, 139 of 576 $p = 0.266$) (Table 2). Though there is no expected impact of OVH and EVH on EAU, this data has been included as this was the primary point of randomization for the parent REGROUP trial. Any atheroma (including both simple or complex) was identified in 24.1% (65 of 269) of all patients who underwent EAU, and cannulation strategy was modified in 7.1% (19 of 269) of the EAU group (Table 2). As shown in Table 3, there was no difference in the rate of stroke between patients who underwent EAU, 1.9% (5 of 269), and those who did not 1.2% (6 of 521), $p = 0.523$. None of the 19 patients who had a modified surgical technique after EAU experienced stroke, and all 5 of the strokes in the EAU group had an unmodified technique, but this was not statistically significant ($p = 0.534$) (Table 4). When the data was more closely analyzed, only 1 patient in the EAU group had a stroke that was in close temporal proximity to the surgery itself (on postoperative day 0), and all others had identified stroke much later in their postoperative course. The severity of ILA by EAU appears to influence the surgeon's decision to modify technique. Five of the 6 patients in which complex or mobile atheroma was identified by EAU underwent modification of clamping or cannulation (Table 6).

Discussion

Most perioperative strokes in cardiac surgery are embolic in origin, and the major source of this atheroembolization is the manipulation (cannulation, clamping) of the ascending aorta. Aortic atherosclerotic disease has long been identified as a critical risk factor for perioperative stroke after cardiac surgery.^{19–22} To mitigate the risk of stroke in cardiac surgery, the 2011 multisociety guidelines recommend: (1) routine EAU examination to assess the severity of intraluminal aortic atheroma, and (2) modification of the procedure in case of complex or mobile aortic atheroma (eg, choosing an alternate cannulation site or performing a CABG off-pump) (class IIa, level of evidence B).²³ The routine use of EAU imaging and TEE to identify and manage aortic atheromatous disease may allow for individualization of the surgical technique and may potentially reduce the incidence of embolic stroke.

The largest study to date looking at EAU and surgical outcomes is a retrospective analysis of 6,051 cardiac surgical patients by Rosenberger et al.²⁴ In this analysis, the authors demonstrated that EAU led to a change in surgical management 4.1% of the time, in the form of no-touch technique, clamp location, cannulation site, aortic intervention, and no cross-clamp or circulatory arrest. Additionally, they found that the incidence of both stroke and TIA was significantly lower in patients who underwent EAU. Most striking was their multivariable logistic regression controlling for the type of surgery, which revealed an odds ratio of 0.27 (95% confidence interval, 0.14–0.38) for the risk of stroke in patients with EAU. Hangler et al. used EAU data to change surgical technique and compared their results to a historical control group. Patients whose therapy was modified on the basis of the EAU examination had a lower stroke rate (2.9%) than their control group (4.4%).²⁵ Other authors have published conflicting results, with many demonstrating higher rates of change in

surgical management (ranging from 4%–31%) as a result of EAU.^{13,26,27} Two randomized, controlled trials have been performed in which patients were randomized to undergo EAU versus manual palpation, with both demonstrating a decrease in cerebral embolic load in the EAU group.^{27,28} Of note, only the study by Djaiani et al. assessed neurologic outcomes, and though cerebral embolic load was different, overall clinically significant neurologic outcomes were not. A more recent subanalysis of a larger trial by Iribarne et al. associated moderate-to-severe ascending aortic atherosclerosis with overall worse outcomes in patients undergoing surgical aortic valve replacement, but did not show any significant difference in composite death, stroke, or cerebral infarction on MRI when comparing mild to moderate-to-severe atheromatous disease.²⁹

In REGROUP, the surgical strategy was changed in 7.1% of patients who underwent EAU (19 of 269). Although relatively low in frequency, the authors' results corroborate the low end of previously published data. The authors did not show a difference in stroke rates between patients who underwent EAU and those who did not, as demonstrated in Table 3. It is important to note, however, that in the group of patients who underwent EAU and had a perioperative stroke, all had an unmodified surgical technique, but this also did not reach statistical significance (Table 4). Additionally, in EAU group patients who had a stroke, only one occurred immediately postoperatively on postoperative day 0, and all the others were identified much later. This raises the question of whether these strokes can be truly attributed to aortic manipulation, or whether they are related to events in the postoperative period. To date, a large, high-quality, randomized, controlled trial comparing neurologic outcomes with and without EAU as the primary intervention has not been performed.

Although many physicians still rely on direct surgical palpation, EAU and TEE imaging have been consistently shown to be far superior at identification of atheromatous disease in the ascending aorta.³⁰ As early as 1989, Marshall et al.³¹ described how 58% of patients undergoing CABG had atherosclerotic ascending aortic disease when assessed by EAU, whereas surgical inspection and palpation only identified atheromatous disease in 24% of these patients. Since then, numerous studies have confirmed these findings and have consistently identified palpation as having a very low sensitivity for the detection of aortic atheroma, likely only 25%.^{21,31} In REGROUP, 24.1% of patients who underwent EAU were found to have aortic atherosclerotic disease, which falls within the range of prevalence that has previously been published.³² Of note, compared with older studies such as the 1989 Marshall report, the authors' findings of only 24.1% atheromatous burden on intraoperative examination likely reflect improved preoperative screening by computed tomography of the chest, magnetic resonance imaging, and transthoracic echocardiography/TEE. Improved perioperative counseling and patient selection in this era of vastly improved imaging likely also plays a role in diminished intraoperative discovery of atheromatous burden.

Reasons cited for nonadoption of EAU include: (1) EAU lengthens surgical time; (2) requires training in its use; (3) can only provide information intraoperatively after an incision has already been made; and (4) requires specialized equipment. Though factually accurate, these concerns are likely less impactful in the modern cardiac suite. It is estimated that a comprehensive EAU examination of the heart and great vessels takes on average 5.5 minutes,³² and if one is evaluating the ascending aorta alone, such an examination is

significantly shorter. Furthermore, although 2 to 5 minutes does increase surgical time, it is likely clinically insignificant when considering the length of an average cardiac surgery. Additionally, little training is required for the acquisition and interpretation of EAU. The American Society of Echocardiography (ASE) has produced guidelines for performing an epiaortic examination, in which they state that trainees in perioperative echocardiography should participate in the evaluation of 25 EAU examinations, at least 5 of which must be personally directed by the individual under the direct supervision of an echocardiographer with advanced level training. Though EAU can only be performed after incision, the equipment required (high frequency >7 MHz linear, matrix or phased array ultrasound transducer) is readily available in most anesthesia departments and is often integrated as an attachment to the TEE machine.

Perhaps owing to the aforementioned concerns, the authors observed significant site-to-site variability in the use of EAU. Few sites had high utilization (98% at Boston Veterans Affairs) and 11 of the 16 participating centers performed EAU in <5% of their cases, with 4 of these 11 sites reporting EAU rates of 0%. This drastic variability, despite an existing Ila recommendation, speaks to the need for a large-scale, randomized, controlled trial to better inform surgeons and anesthesiologists, and perhaps accelerate routine use of this technique.

Of relevance, the present study was subject to a few limitations, specifically, data on the use of EAU was documented for only 790 of the 1,150 patients in trial overall, and the study was not specifically powered to detect differences in stroke rates. Though participating sites were educated on the use of EAU and provided with written guidelines for performing this examination, the degree of adherence to the written guidelines was not assessed within the larger REGROUP trial. Additionally, modification of surgical technique, as well as the specific modifications made, were left to the discretion of the attending cardiothoracic surgeon and were not protocolized.

In this study, the authors present some of the only prospectively collected EAU data from a large-scale, methodologically rigorous randomized controlled trial. Though the authors did not detect a difference in stroke rates between EAU and non- EAU groups, the guidelines for EAU are clear and the potential for reduction in patient harm appears to outweigh the possible disadvantages. Despite these guidelines and available literature, the utilization of this technology remains limited, with EAU only being utilized in 34.1% of cases in REGROUP.

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Table 1

Characteristics of the Patients Randomized to OVH and EVH in REGROUP

	OVH (n = 574)	EVH (n = 576)	Total (n = 1150)	p Value
Age at randomization, y	66.6 ± 7.10	66.2 ± 6.68	66.4 ± 6.89	0.575
Male sex, no./total no. (%)	571/574(99.5)	572/575 (99.5)	1,143/1,149 (99.5)	>0.999
Smoking status, no. (%)				0.347
Never smoked	123 (21.4)	137 (23.8)	260 (22.6)	
Current smoker (last use < 1 y)	151 (26.3)	164 (28.5)	315 (27.4)	
Former smoker (last use 1 y)	296 (51.6)	274 (47.6)	570 (49.6)	
Missing	4 (0.7)	1 (0.2)	5 (0.4)	
Race or ethnic group, no. (%)				0.850
American Indian or Alaskan Native	2 (0.3)	4(0.7)	6 (0.5)	
Asian or Pacific Islander	4 (0.7)	6(1.0)	10 (0.9)	
Black, not of Hispanic origin	50 (8.7)	41 (7.1)	91 (7.9)	
Hispanic	31 (5.4)	31 (5.4)	62 (5.4)	
White, not of Hispanic origin	484 (84.3)	490 (85.1)	974 (84.7)	
Other	3 (0.5)	3 (0.5)	6 (0.5)	
Missing	0 (0.0)	1 (0.2)	1 (0.1)	
Body mass index, kg/m ²	30.6 ± 5.17	30.3 ± 5.16	30.4 ± 5.17	0.369
Diabetes, no. (%)				0.550
No history	277 (48.3)	295 (51.2)	572 (49.7)	
Insulin-dependent diabetes	137 (23.9)	125 (21.7)	262 (22.8)	
Noninsulin-dependent diabetes	160 (27.9)	155 (26.9)	315 (27.4)	
Missing	0 (0.0)	1 (0.2)	1 (0.1)	
Hypertension, no./total no. (%)	515/574(89.7)	521/ 575 (90.6)	1036/1,149 (90.2)	0.613
Hyperlipidemia, no./total no. (%)	502/574 (87.5)	491/575 (85.4)	993/1,149 (86.4)	0.307
Peripheral vascular disease, no./total no. (%)	80/574 (13.9)	80/575 (13.9)	160/1,149(13.9)	0.991
Previous cerebrovascular accident, no./total no. (%)	48/574 (8.4)	48/575 (8.3)	96/1,149 (8.4)	0.993
Previous myocardial infarction, no./total no. (%)	207/573 (36.1)	219/575 (38.1)	426/1,148 (37.1)	0.492
Previous PCI, no./total no. (%)	158/574 (27.5)	160/575 (27.8)	318/1,149 (27.7)	0.910
NYHA functional class, no. (%)				0.677

	OVH (n = 574)	EVH (n = 576)	Total (n = 1150)	p Value
No congestive heart failure	285 (49.7)	284 (49.3)	569 (49.5)	
Class I	68(11.8)	60(10.4)	128(11.1)	
Class II	151 (26.3)	167 (29.0)	318(27.7)	
Class III	65 (11.3)	54 (9.4)	119(10.3)	
Class IV	4 (0.7)	4 (0.7)	8 (0.7)	
Missing	1 (0.2)	7(1.2)	8 (0.7)	
CCS angina class, no. (%)				0.570
No angina present on admission	57 (9.9)	57 (9.9)	114(9.9)	
Class I	92 (16.0)	82 (14.2)	174(15.1)	
Class II	224 (39.0)	238 (41.3)	462 (40.2)	
Class III	130 (22.6)	141 (24.5)	271 (23.6)	
Class IV	46 (8.0)	35 (6.1)	81 (7.0)	
Missing	25 (4.4)	23 (4.0)	48 (4.2)	

NOTE. Plus-minus values are means $\pm$ standard deviation. Data were missing as follows: age for 1 patient in the EVH group, height and body mass index for 2 patients in the EVH group, and 1 patient in the OVH group, weight for 1 patient in the EVH group, and 1 patient in the OVH group. No significant difference of <0.05 was found between groups.

Abbreviations: CCS, Canadian Cardiovascular Society; EVH, endoscopic vein harvest; NYHA, New York Heart Association; OVH, open vein harvest; PCI, percutaneous coronary intervention.

Table 2

Epi-aortic Scanning in REGROUP Trial, Summary Data

	Statistic	OVH (n = 574) n (%)	EVH (n = 576) n (%)	Total (n = 1150) n (%)	p Value
Epi-aortic scanning performed					
No	n (%)	392	398	790	0.601
Yes	n (%)	262 (66.8)	259 (65.1)	521 (65.9)	
	n (%)	130 (33.2)	139 (34.9)	269 (34.1)	
Findings					
No ILA is seen by EAU	n (%)	130	139	269	0.266
Simple ILA (<4 mm protrusion into lumen) or focal calcification	n (%)	97 (74.6)	106 (76.3)	203 (75.5)	
Complex ILA (>4 mm protrusion, mobile)	n (%)	28 (21.5)	31 (22.3)	59 (21.9)	
Missing data	n (%)	5 (3.8)	1 (0.7)	6 (2.2)	
	n (%)	0 (0.0)	1 (0.7)	1 (0.4)	
Surgical plan for aortic cannulation/clamping modified					
No	n (%)	130	139	269	0.299
Yes	n (%)	123 (94.6)	127 (91.4)	250 (92.9)	
	n (%)	7 (5.4)	12 (8.6)	19 (7.1)	

Abbreviations: EAU, epi-aortic ultrasound; EVH, endoscopic vein harvest; ILA, intraluminal atheroma; OVH, open vein harvest.

Table 3

Comparison of Stroke Rates Between Patients Who Underwent EUA and Those Who Did Not in the REGROUP Trial

	Epi-aortic Scanning			p Value
	Yes (n = 269) n (%)	No (n = 521) n (%)	Total (n = 790) n (%)	
Stroke	5(1.9)	6(1.2)	11 (1.4)	0.523

Abbreviation: EUA, epi-aortic ultrasound.

Table 4

Comparison of Stroke Rates Between Patients Whose Surgical Plan Was Modified After Undergoing EUA and Those Whose Plan Was Not Modified

	Surgical Plan Modified			p Value
	Yes (n = 19) n (%)	No (n = 250) n (%)	Total (n = 269) n (%)	
Stroke	0 (0.0)	5 (2.0)	5 (1.9)	0.534

Abbreviation: EUA, epi-aortic ultrasound.

Table 5

Katz's Intraluminal Atheroma Grading Scale

Grade	Examination Findings
I	Minimal intimal thickening
II	Extensive intimal thickening
III	Sessile atheroma
IV	Protruding atheroma
V	Mobile atheroma

Adapted from Ribakove et al.¹⁶

Table 6

Degree of Intraluminal Atheroma in Patients Who Had Surgical Modification

	Total (n = 19) n (%)
Atheroma Severity Grade	
No ILA is seen by EAU	3 (15.8)
Simple ILA (<4 mm protrusion into lumen) or focal calcification	11 (57.9)
Complex ILA (>4 mm protrusion, mobile)	5 (26.3)

Abbreviation: ILA, intraluminal atheroma.