IMAGING OF THE DISTAL ASCENDING AORTA USING MODIFIED TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN CARDIAC SURGERY

Imaging of the distal ascending aorta using modified transesophageal
echocardiography in cardiac surgery

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Beeldvorming van de distale aorta ascendens doormiddel van aangepaste transoesophageale echocardiografie in cardiale chirurgie

(met een samenvatting in het Nederlands)

Proefschrift

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Voor Lottie en Tom

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GENERAL INTRODUCTION

1

Annually about 1 million patients worldwide undergo cardiac surgery. One of the most severe complications after cardiac-surgery is ischemic stroke. The overall incidence of major ischemic stroke after cardiac surgery is about 3%, accounting for 20% of postoperative deaths(1-5). As the occurrence of atherosclerosis increases sharply with age, from 10% in patients aged 50-60 years to 35% in patients older than 75 years, the post-cardiac-surgery stroke rate also increases to 7% in older patients(5-10). Taking into account advances in cardiac surgery and the ageing society, patients undergoing cardiac surgery will become increasingly older and more vulnerable, thus being at higher risk of aortic atherosclerosis and neurologic complications.

Post-operative stroke is often caused by emboli merging from atherosclerosis in the ascending aorta to the brain, as the ascending aorta is the place of cannulation and clamping(2-4,8,11-14). In the presence of severe atherosclerosis, use of alternative surgical strategies that avoid or reduce manipulation of the ascending aorta is indicated. To enable adjustment to such alternative strategies a diagnostic test that can visualize the ascending aorta, particularly the distal part and preferably as early as possible, e.g. before sternotomy, is needed.

Usual care

Current methods to potentially visualise and detect atherosclerosis of the ascending aorta in cardiac surgery patients include chest X-ray, transesophageal echocardiography, manual palpation, and epiaortic ultrasound scanning. Compared to epiaortic ultrasound scanning, all former methods have proven to be not sensitive and specific enough, not for pre- or peroperative detection of atherosclerosis(15-23). Epiaortic ultrasound scanning has thus become the gold standard for detecting atherosclerotic changes in the ascending aorta, but it can only be used during the operation after sternotomy(15-18,20-22). Therefore, if its findings show severe aortic atherosclerosis, decisions regarding change in surgical strategy have to be made at a late stage, which is often less feasible and more complicated. Preferably, such decisions are made pre-operatively, requiring a method that detects aortic atherosclerosis at an earlier moment, before sternotomy(24).

Modern MRI and CT-scanners have diagnostic accuracy comparable with epiaortic ultrasound scanning, but they come with several disadvantages. First, their (yet) relatively low availability does not allow for routine evaluation of every cardiac surgery patient. Second, high costs make them less cost-effective. Third and most importantly, both are not (yet) capable of providing real-time images of the ascending aorta to direct changes in surgical strategy.

The most widely used diagnostic imaging technique in cardiac surgery patients(25), i.e. transesophageal echocardiography is indeed capable of visualizing the extent of atherosclerosis before and during cardiac surgery. Since, it can be used before sternotomy changes in surgical strategy are earlier and easier to implement. But transesophageal echocardiography is not capable of imaging the distal part of the ascending aorta, due to the so-called blind spot(18). The blind spot is caused by the interposition of air, located in the trachea and main bronchi, between the echo-transducer and the ascending aorta. To overcome this limitation of transesophageal echocardiography, the A-View method was developed to image the distal ascending aorta using conventional transesophageal echocardiography and a specially designed intra-tracheal balloon-catheter(26,27). The evaluation of this diagnostic device is the topic of this thesis.

Potential effects on health of the A-View method

Improved diagnostic classification leads to improved treatment indications, and thus improved patient outcomes. Diagnostic tests in itself commonly have no direct impact on health improvement but they do via the therapies indicated or chosen based on the test results(28). Thus, enabling improved and early detection of ascending aorta atherosclerosis in cardiac surgery patients at a moment (preoperatively) that extensive manipulations of the ascending aorta (i.e. the major cause of emboli generation) can be prevented, will likely induce changes to less invasive cardiac surgery techniques. This reduces manipulations of a sclerotic ascending aorta and thus the incidence of post-operative stroke. In various studies it has been shown that the use of epiaortic ultrasound scanning of the ascending aorta combined with changes to less manipulative techniques in case of severe ascending aorta atherosclerosis indeed reduces the incidence of post-operative ischemic stroke(29-32). Hence, it can be expected that, if the A-View method is capable of adequately imaging atherosclerosis in the ascending aorta before sternotomy, the positive effects on patient outcome can (at least) be comparable to epiaortic ultrasound scanning, where the latter surely is more cumbersome to use and often applied too late to allow for relevant changes in surgical technique.

Central theme of this thesis

It is widely acknowledged that in the scientific evaluation of a new diagnostic device, like the A-View method, a phased approach should be followed(33-38). After technical development and safety evaluation (first phase), but before investigating whether the test may replace current diagnostic techniques and actually improves the (cost)-effectiveness in terms of patient outcome, the test's reproducibility and potential discriminative accuracy as compared to current reference standards, must be quantified. Hence, the second and third phases of the evaluation of the A-View method consist of the quantification of the inter- and intra-observer variation of the A-View method and whether it can discriminate between evident cases with and without aortic atherosclerosis as determined by the current reference standard (diagnostic accuracy). Subsequent research should focus on quantifying the test's diagnostic accuracy beyond or additional to conventional diagnostics, in a prospective manner and consecutive series of patients in whom the test is to be applied. Finally, it should be studied whether the test actually improves the cost-effectiveness in terms of patient outcome. On a longer term, if the (incremental) diagnostic accuracy of the A-View method will indeed be proven, it is very likely that use of the A-View method will contribute in resolving the problem of inadequate imaging of aortic atherosclerosis with the current available techniques. This in turn will reduce - in case of prevalent ascending aorta atherosclerosis - the number of ascending aorta manipulations, thus reducing the incidence of post cardiac surgery stroke and increase cost-effectiveness of current care. This thesis describes the first three phases of the scientific evaluation process of the A-View method.

Outline of this thesis

In Chapter 2 *Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery,* we retrieved all available literature on the diagnostic accuracy of conventional transesophageal echocardiography compared to epiaortic ultrasound scanning as reference standard, to perform a diagnostic meta-analysis. The aim was to quantify the overall accuracy of conventional transesophageal echocardiography and whether it is capable to assess the presence and severity of atherosclerosis of the ascending aorta in patients undergoing cardiac surgery.

The technical and safety evaluation of the A-View method is described in chapter 3 *Resolving the blind spot of transesophageal echocardiography: A new diagnostic device for visualizing the ascending aorta in cardiac surgery.* The technical evaluation addresses to what extent the A-View method is capable of imaging the distal ascending aorta, and the safety evaluation whether the method leads to unexpected complications due to the use of the device.

In chapter 4 *Visualization of the distal ascending aorta with improved transesophageal* *echocardiography* we describe the application and indications for use of the A-View method. Furthermore we define the standard views that can be obtained with the method so that future communications on the A-View method can easily be compared.

In single test diagnostic accuracy studies, besides sensitivity and specificity, the positive and negative predictive values with their 95% confidence intervals are calculated. When a so-called nested case-control design is used to estimate these accuracy parameters, correction for the sampling fraction has to be incorporated into the equation to estimate the correct positive and negative predictive value(39,40). But, estimation of the standard error of these predictive values, which is needed to estimate their 95% confidence interval, is less straightforward. Until now it is unclear what the best method is to calculate the standard error of the positive predictive value when using a nested case-control design. In Chapter 5 *Comparison of methods to estimate confidence intervals of predictive values of diagnostic test results in a nested case-control design* we describe six solutions to calculate the standard error and thus the confidence intervals of the positive and negative predictive values of a diagnostic test, when using a nested case-control study. In a simulation study we compare these six methods with the "true" standard error of the positive predictive value as obtained from the full cohort of patients.

In chapter 6 *Diagnostic accuracy of modified transesophageal echocardiography for pre-incision assessment of aortic atherosclerosis in cardiac surgery patients* we quantify the diagnostic accuracy (using e.g. sensitivity, specificity, positive predictive value and negative predictive value) of the A-View method. Aim is to assess whether the A-View method is capable of discrimination between patients with atherosclerosis and those without.

Chapter 7 *Inter- and intra-observer variability of modified transesophageal echocardiography for pre-incision detection of distal ascending aorta atherosclerosis in cardiac surgery patients,* describes *the* inter- and intraobserver variation of the reading of the A-View method images, i.e. comparing the results of different A-view readings per observer (intraobserver variation) and across different observers (interobserver variation).

Diagnostic accuracy in itself is insufficient to determine the most efficient diagnostic strategy. The latter can only be achieved by taking into account the clinical outcomes after diagnostic work-up and so-directed therapeutic interventions. Therefore, in chapter 8 *Cost-effectiveness analysis of modified transesophageal echocardiography to assess the distal ascending aorta in cardiac surgery patients before incision* we present a modelling study to compare the balance between costs and effects of manual palpation and the A-View method.

This thesis ends with concluding remarks on our findings, and suggestions for future research in chapter 9.

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2

META-ANALYSIS OF THE DIAGNOSTIC ACCURACY OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR ASSESSMENT OF ATHEROSCLEROSIS IN THE ASCENDING AORTA IN PATIENTS UNDERGOING CARDIAC SURGERY

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Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery.
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Neurological complications, such as ischemic stroke, occur in 3% of all cardiac operations, accounting for 20% of postoperative deaths after cardiac surgery(1-3). Prevention of stroke after cardiac surgery saves on average $13,019 for mild ischemic strokes and $20,346 for severe ischemic strokes per patient, in direct medical costs of the first 30 days(4). This does not even account for savings after the first 30 days in case of disabling strokes. Peri-operative stroke may be caused by emboli emerging from atherosclerosis in the ascending aorta to the brain, as the ascending aorta is manipulated during cardiac surgery for placement of the aortic cannula and (de)clamping as well as by the “sandblasting” effect due to the aortic cannula flow.

Epiaortic ultrasound scanning is the ‘gold’ standard for detecting atherosclerosis in the ascending aorta. Its use combined with appropriate modification of operative technique when severe atherosclerosis is present can effectively reduce the incidence of postoperative stroke(5-9). However, epiaortic ultrasound scanning has not gained widespread use, because there is a lack of optimized ultrasound devices, it would lengthen the surgical procedure, it may endanger the sterility of the surgical field, and there is a false belief by many surgeons that palpation is as sensitive as epiaortic ultrasound scanning(10,11). Finally, there is no clear evidence proving that the use of epiaortic scanning changes outcome in cardiac surgery. Moreover, as it is applied during the operation decisions regarding surgical strategy are to be made at a late stage. Preferably, such decisions are be made pre-operatively(12).

Transesophageal echocardiography (TEE) is a minimally invasive and widely available tool that can be used pre-sternotomy and may overcome these limitations(13). However, the distal section of the ascending aorta is poorly visualized due to interposition of the trachea between the oesophagus and the ascending aorta, the so-called “blind spot”. Various researchers thus investigated the ability of TEE to discriminate between presence and absence of ascending aorta atherosclerosis(10,14-19). Accordingly, it is often acknowledged that TEE has limited value in this, but it has never been supported by a systematic review or meta-analysis estimating the true diagnostic accuracy of TEE based on all available quantitative evidence. We aimed to do this using state of the art methodology of diagnostic meta-analyses, incorporating the correlation between sensitivity and specificity as well as covariates to explore heterogeneity across studies.

Methods

Search strategy and study selection

Medline (Pubmed), Embase, the Cochrane library, the Database of Abstracts of Reviews of Effectiveness (DARE), and Medion (a database of diagnostic test reviews) were searched from 1966 through January 2006 for publications. We used "epiaortic ultrasound scanning", and "transesophageal echocardiography" as keywords (see appendix A for search filters) without language restrictions.

We explicitly used epiaortic ultrasound scanning as the reference standard, since it is most widely accepted as the best available per-operative diagnostic for the detection of ascending aorta atherosclerosis. Magnetic resonance imaging (MRI) and computer-aided tomography scanning (CT-scanning) are believed to be superior to TEE in the detection of ascending aorta atherosclerosis. Despite extensive search efforts, only one study was found that (quantitatively) compared the accuracy of CT scanning with that of epiaortic ultrasound scanning(20). Hence, these modalities could not be included in our meta-analysis. Furthermore MRI and CT have as yet limited application and availability in routine care of cardiac surgery patients, because they are not capable of providing real-time images of the ascending aorta to direct immediate changes in surgical strategy.

Based on titles and abstracts, all studies evaluating TEE for assessment of the ascending aorta in cardiac surgery patients were selected. Reference lists from these retrieved studies and related articles identified by MEDLINE were scanned to identify any additional studies. We contacted the authors of the retrieved studies for additional published or non-published studies. Hand searching of topic-specific journals and conference proceedings was not performed. Non-English publications were assessed by observers who had command of the language to allow data extraction from those studies. We eventually included studies comparing TEE with epiaortic ultrasound scanning for the assessment of ascending aorta atherosclerosis in patients undergoing cardiac surgery that reported the number of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN) and studies from which these numbers could be inferred in our analysis.

Quality assessment

The methodological quality of included studies was independently assessed by 2 observers (BvZ, APN) and in case of doubt by a methodologist (KGMM), using the QUADAS-tool in a slightly adapted version (see table 1 for quality criteria)(21).
The selected items of the QUADAS-tool enabled us to examine potential sources of bias and variation(22). We did not calculate summary scores estimating the overall-quality of included studies since it is been shown that their interpretation is problematic and may be misleading(23).

Data extraction

The two observers independently extracted the raw data from the included studies to construct two by two contingency tables. Other elements that were extracted included the year of publication, sample size, patients mean or median age, proportion of male subjects, prevalence of atherosclerosis, and the cut-off point used for TEE and epiaortic ultrasound scanning to determine the presence of (clinical relevant) atherosclerosis. Data were considered missing if they were not mentioned explicitly in the text. Discrepancies were resolved by discussion or, if agreement could not be reached, by consultation of a third reviewer (KGMM).
To reach a more precise description of the location of atherosclerosis in the ascending aorta, the ascending aorta is often divided into different segments. This can be a simple division between the proximal and the distal ascending aorta, to more complex divisions with multiple (up to 12) different segments. If studies

presented multiple two by two tables for different segments of the thoracic aorta we included the data concerning the ascending aorta only. When studies provided a per-segment analysis instead of a per-patient analysis we attempted to contact the first authors of these studies to obtain the original data on a patient level if this could not be inferred from the paper. If authors did not respond or could not provide the data we included the segmental data in our analysis.

Analysis

We used sensitivity and specificity as our primary measures of association. Sensitivity was calculated by dividing TP by (TP + FN) and specificity by dividing TN by (FP + TN). We first used forest plots to display the precision (95% Confidence interval (CI)) by which sensitivity and specificity had been measured in each study, and to illustrate the variation in the estimates between studies. The exact binomial method was used to calculate the 95% CI's of the sensitivity and specificity. We calculated the Inconsistency (I^2), which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. This measure may range from 0% to 100%, where 0% means no variation due to heterogeneity and 100% means that all variation can be explained by heterogeneity.

Until recently the summary Receiver Operating Characteristic (sROC) was the method of choice for the meta-analysis of studies reporting pairs of sensitivity and specificity. The sROC approach converts each pair of sensitivity and specificity into a single measure of accuracy, the diagnostic odds ratio (DOR). The disadvantage of converting sensitivity and specificity into a single measure of diagnostic accuracy is that it does not discriminate between nor provide insight anymore in the sensitivity and specificity of a test. Distinguishing between these two measures of accuracy is important to determine the optimal use of the test under investigating in clinical practice. With the introduction of the bivariate model it has become possible to meta-analyze estimates of sensitivity and specificity directly, hereby taking into account the inherent correlation between sensitivity and specificity within studies due to differences in threshold(24-26). We thus applied the bivariate model - a random effects model as known from therapeutic meta analysis - to obtain a valid summary estimate for both sensitivity and specificity of TEE (with 95% CI) (SAS statistical packages version 9.1) (26). Two studies reported only test results per segment, and not a two by two table on the patient level(15,19). By using these segmental data, the 95% CI appears narrower than it should be. Therefore we adjusted these 95% CI's by dividing the standard errors of sensitivity and specificity by the number of segments used.

Finally, we intended to include the following covariates in the model to explore the heterogeneity between studies in either sensitivity, specificity or both: sample size, year of publication, patient mean age, prevalence of atherosclerotic disease, cut-off point of TEE for the presence of atherosclerosis, whether or not a segmental analysis was performed, and the methodological criteria from the adapted QUADAS-tool.

Assessment of publication bias

The validity of a meta-analysis largely depends on minimizing the bias in the identification and selection of the relevant studies. Meta-analytical results will be compromised by publication bias if the retrieved studies have results that significantly differ from relevant studies that are missed(27). To explore the effect of small studies and the possibility of publication bias, we constructed a funnel plot by plotting the natural logarithm of the DOR (lnDOR) against the inverse of the square root of the effective sample size ($1/\mathrm{ESS}^{1/2}$), and applied the effective sample size regression test for asymmetry as recommended by Deeks et al(27). The effective sample size regression test uses regression of lnDOR with the $1/\mathrm{ESS}^{1/2}$ weighted by ESS to show asymmetry of the funnel plot. A significant test indicates a potential for the presence of publication bias(27).

Results

Search results

Our searches located 310 potentially eligible articles (Figure 1). After screening titles, 263 studies were excluded. After reviewing the abstracts of the remaining 47 studies, 14 studies remained. Reading these papers and applying the in- and exclusion criteria yielded 7 studies for analysis. One of the 7 studies lacked sufficient reporting of major methodological features and was therefore also excluded (figure 1) (17).

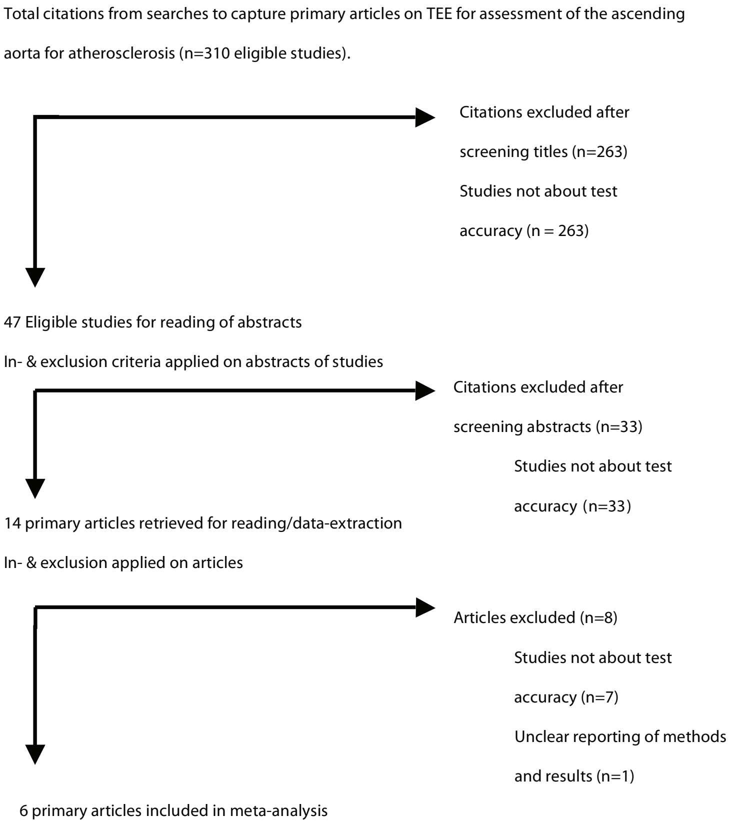

Figure 1: Flowchart of search results and study inclusion

All included studies were published in the English language(10,14-16,18,19). The mean sample size and the number of studied segments of the studies were 52 and 70, respectively. The meta-analysis comprised a total of 346 patients, of whom 419 aortic segments were analyzed, including 100 with atherosclerosis (median prevalence 25% (range 17 – 43%)). The mean age across all studies was 68 years and the proportion of male subjects was 72%. Table 1 lists the methodological characteristics and table 2 lists the demographic characteristics of the included studies. None of the included studies fulfilled all quality criteria. All studies used a prospective cross-sectional cohort design, an adequate reference standard and a representative patient sample. A clear description of selection criteria was found in only 2 studies. In the majority of the studies it remained unclear if the observers were blinded to the index-test results, the reference-test results, or the clinical data.

Authors	Cohort study design	Prospective data collection	Consecutive recruitment	Representative patient sample	Selection criteria clearly described	Adequate reference standard	Cross-sectional design	Complete verification of diagnosis	No differential verification	Adequate index-test description	Adequate reference-test description	Blinding of index-test results	Blinding of reference test results	Clinical data available as in practice	Uninterpretable/ Intermediate results reported	Withdrawals explained
Sylivris(14)	+	+	+	+	+	+	+	+	+	-	+	?	?	?	?	+
Davila-Roman(15)	+	+	-	+	-	+	+	+	+	+	+	+	+	-	?	?
Royse(16)	+	+	?	+	-	+	+	+	+	-	-	?	?	?	?	+
Konstadt(18)	+	+	?	+	-	+	+	-	+	+	+	?	?	?	?	?
Konstadt(10)	+	+	?	+	-	+	+	+	+	+	+	+	+	?	+	?
Wilson(19)	+	+	+	+	+	+	+	+	+	+	+	+	+	?	?	?

Table 1: Summary of methodological quality of 7 studies on the diagnostic accuracy of transoesophageal echocardiography for the assessment of the ascending aorta for atherosclerosis. Columns 4-16 represent 13 of the 16 QUADAS criteria (+ = Yes, ? = Unclearly reported, - = No)

Author	Year of publication	No. of patients	Mean age (Year)	Male (%)	Prevalence (%)	No. of segments in analyses	Location of TEE*	Location of EUS#	Cut-off Point	True positive	False positive	False negative	True negative
Sylivris(14)	1997	100	69	75	28	1	?	PAA/ DAA	Intimal thickening > 4mm	3	0	25	72
Davila-roman(15)	1996	44	69	70	25	2	PAA§/ DAA¶	PAA/ DAA	-	3	0	19	66
Royse(16)	1998	70	66	76	20	1	AA**	AA	Intimal thickening > 4mm	4	0	10	56
Konstadt (18)##	1994	29	67	70	43	1	?	?	Intimal thickening >3mm	0	0	6	8
Konstadt(10)	1995	81	64	70	17	1	AA	AA	Intimal thickening >3mm	4	1	10	66
Wilson(19)	2000	22	66	73	24	3	?	PAA/ DAA	Intimal thickening > 2mm	5	1	11	49

Table 2: Demographic characteristics of included studies. *transesophageal echocardiography; #Epiaortic ultrasound scanning; §Proximal ascending aorta; ¶ Distal ascending aorta; ** Ascending aorta; ## Partial verification.

Meta-analysis

All studies divided the thoracic ascending aorta in two or more segments. Two studies reported the test-result only per-segment and not a two by two table on the patient level(15,19). The authors of both studies could not provide us the original data to reconstruct a per-patient two by two table. Therefore, we included the per-segment data into our analysis for these two studies.

Figure 2 shows the sensitivities and specificities of TEE for the detection of clinically relevant atherosclerosis (as defined by the authors of the included studies) in the distal ascending aorta with their 95% confidence intervals. The I^2 for was 31.3% and 0.0% for sensitivity and specificity respectively, showing small heterogeneity of the included studies, both for the sensitivity and specificity. Furthermore, figure 2 shows that sensitivity varied more across studies and had a lower precision than specificity did.

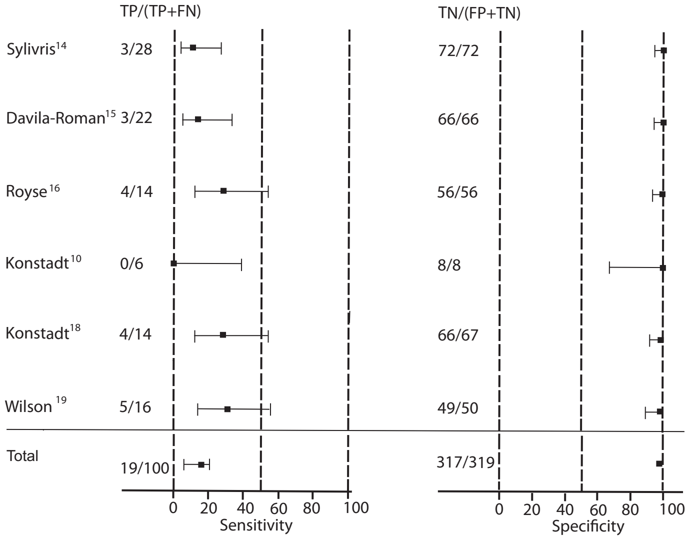

Figure 2: Forrest plot of sensitivities and specificities with 95% confidence interval for transoesophageal echocardiography for the detection of ascending aorta atherosclerosis

The bivariate model yielded a summary estimate for the sensitivity of 21% (95% CI 13 – 32%), and specificity of 99 % (96 – 99 %) (Figure 3). The analysis of the impact of study features on diagnostic accuracy was hampered by poor reporting and by the low number of included studies. Therefore, we could only include whether or not a segmental analysis was performed and the cut-off point of the test as a covariate into our bivariate analysis. This did not significantly change the diagnostic accuracy of TEE, yielding the same overall summary estimates for the sensitivity and specificity.

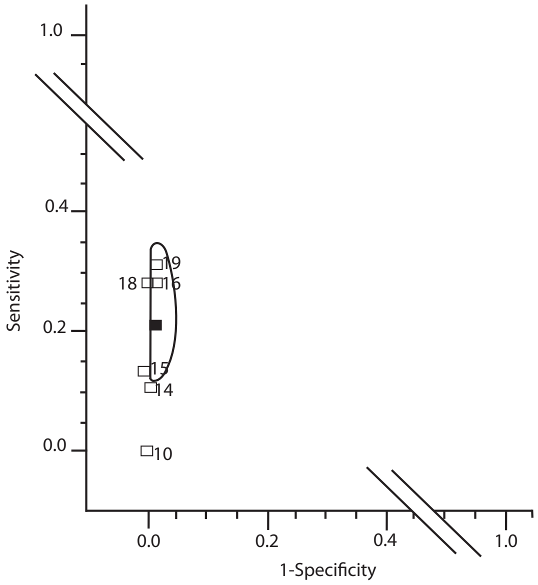

Figure 3: Sensitivity and specificity of individual studies plotted in ROC space. Black square represents summary estimate of sensitivity and specificity with the 95% confidence ellipse from the bivariate model. Numbers represent the reference numbers.

Publication bias

If publication bias is absent in a systematic review, it is expected that the lnDor and 1/ESS$^{1/2}$ points of the individual studies are evenly distributed around the crude mean DOR (vertical line in figure 4), i.e. a symmetric funnel plot. In figure 4 it is shown that 4 of the 6 included studies are at the right side of the crude mean DOR. This is an indication for an asymmetric funnel plot. The diagonal line in the figure indicates the regression line as obtained with the effective sample size regression test. The difference between the two lines is an indication for the presence of some form of sample size effect, most likely due to publication bias(27-29). The p-value of the effective sample size regression test was <0.001, confirming possible publication bias. If the outlier in the left upper corner was excluded from the analysis for publication bias, the test remained significant (p<0.001), although the line changed in direction. Exclusion of this study from the bivariate model, however, did not changed the overall sensitivity or specificity.

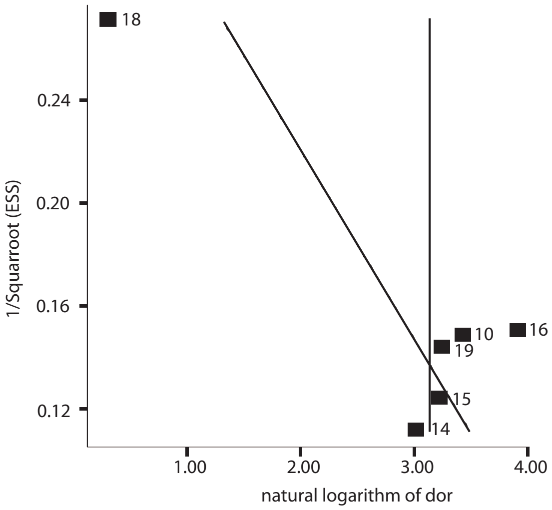

Figure 4: Funnel plot of the natural logarithm of the DOR (lnDOR) against the inverse of the square root of the effective sample size (1/ESS$^{1/}$2) of included studies. Regression line (deviation from vertical) is used as a measure of asymmetry. Numbers represent the reference numbers.

Discussion

We summarized all available quantitative evidence on the diagnostic accuracy of TEE for the detection of clinically relevant atherosclerosis in patients undergoing cardiac surgery with epiaortic ultrasound scanning as reference standard. In most diagnostic meta-analysis, results are summarized using the diagnostic odds ratio or a summary-ROC curve but such measures are hard to translate or apply to practice. By using the bivariate approach we directly obtained an overall estimate of the, clinically better understood, sensitivity and specificity of TEE for the detection of ascending aorta atherosclerosis.

We found that the overall sensitivity of TEE for detection of atherosclerosis of the ascending aorta in patients undergoing cardiac surgery was 21% (95% CI 13 – 32%) and the specificity 99% (96 – 99 %). Hence, routine use of TEE would lead to a false negative test result in 79% of patients with atherosclerosis of the ascending aorta. Accordingly, almost all negative results require additional testing with epiaortic ultrasound scanning to determine the "true" presence or absence of ascending aorta atherosclerosis. As such, TEE cannot simply replace epiaortic ultrasound scanning, although it could be used as a screening or triage tool to detect or include ascending aorta atherosclerosis. If TEE is positive, atherosclerosis is almost certain to be present (given the specificity of 99%). The low sensitivity of TEE is most likely due to TEE being unable to show the entire ascending aorta due to the so-called "blind spot" (18). The use of TEE as a screening tool in all patients is only effective when the incidence of atherosclerosis is high enough. We found the incidence of significant atherosclerosis of the aorta has been reported to vary widely from 1.2% to 28% of the cardiac surgical population, depending on the definition of 'significant' pathology, and on the sensitivity of the diagnostic methods. On average the incidence will be approximately 10-15%, this will be a sufficient incidence to establish some form of screening (epiaortic ultrasound scanning or some alternate technology), certainly when taken into account the devastating complication that might be prevented(5,30-35).

The variation in specificity was small between studies, but the variation in sensitivity considerable. These variations could partly be explained by the low number of patients with clinical significant atherosclerosis in the studies, but could not be attributed to specific study features. Incomplete reporting and the small number and size of the studies hampered the latter analysis.

Limitations of the included studies

The result of a meta-analysis largely depends on the quality of the included studies. Using the QUADAS criteria we found that the overall methodological quality and reporting of the included studies was fair to poor. Reporting was often incomplete or confusing with respect to study design, patient characteristics and study outcomes. This severely limited our efforts to introduce covariates into the bivariate model to explain the difference in diagnostic accuracy across the included studies. Sub-optimal methodological quality and incomplete reporting is not unique for the studies we have retrieved for our review and occurs frequently in diagnostic research(22,36-39). The STAndards for Reporting of Diagnostic accuracy (STARD) steering committee has proposed guidelines for the conduct and reporting of diagnostic research to improve the quality of diagnostic studies(36). Future studies on diagnostic accuracy should adhere to this concept, if only to facilitate the performance of systematic reviews and meta-analyses, and to avoid premature dissemination of diagnostic tests based on overoptimistic results from poorly designed studies(40).

Limitations of the review process

Our review has several limitations. We recognize that our search was limited by the fact that we did not hand-search journals or conference proceedings. As in therapeutic reviews, this could have led to an overestimation of the diagnostic accuracy of TEE. However, there is no empirical data available specific for diagnostic studies that shows this overestimation. Our review might also be limited by publication bias or small sample size effects, since the test for asymmetry of the funnel plot (figure 4) showed a significant result. This asymmetry can be due to various reasons as long as they are related to both sample size and to the observed diagnostic accuracy parameters (sensitivity and specificity). The most important reason is publication bias, i.e. in general small studies with a high estimate of sensitivity and specificity are more likely to be published than large studies with less promising results. Other reasons maybe an inadequate search strategy, differences in study population, poor study quality, and a small number of included studies(41). We are confident that we have minimized the influence by publication bias, by searching multiple databases, and contacting the authors of all included papers. The significant result of the test for asymmetry is therefore more likely to be related to a combination of factors like the between study variation, the low number of included studies and study quality issues. The fact that the slopes with and without the study-outlier are both significant and in a different direction is most likely due to between study variation and the low number of studies. This was also confirmed by the small I^2. Finally, for two studies we included the per-segment rather than patient data in our analysis. However, we believe that this only had a small effect on our results. There was no significant relation between the use of segmental data and the sensitivity or specificity, as indicated by the non-significant change in sensitivity and specificity when the use of segmental data was included in the bivariate model as a covariate. Furthermore, inclusion of segmental data will lead to a narrower 95% confidence interval. We tried to adjust the 95% confidence interval by dividing the standard error by the number of segments used to overcome this limitation.

Conclusion

We formally meta-analyzed all available evidence on the accuracy of TEE in the detection of ascending aorta atherosclerosis. Because of the low sensitivity, a negative TEE result requires verification by additional testing using epiaortic scanning. In case of a positive test result, ascending aorta atherosclerosis can be considered as present, and less manipulative surgical strategies such as off-pump surgery might be indicated. Eventually this may reduce the incidence of post-operative stroke.

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Apendix A: Search filters

Database	Search filter
Medline 1966 to 2005/11	(epiaort* [tiab] OR "epicardial" [tiab]) AND ("Echocardiography, Transoesophageal" [MeSH] OR "TEE" [tiab] OR "transoesophageal echocardiography"[tiab] OR (Echocardiography [tiab] AND ultraso* [tiab]) OR (intraoperative ultraso* [tiab]))
Embase 1966 to 2005/09	epiaort* AND ('transoesophageal echocardiography' OR TEE OR echocardiography OR (intraoperative AND ultraso*))
Medion 5/11/2005	Circulatory [Icpc_Name] AND Medical imaging [Signs_Name]

3

RESOLVING THE BLIND SPOT OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY: A NEW DIAGNOSTIC DEVICE FOR VISUALIZING THE ASCENDING AORTA IN CARDIAC SURGERY

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Resolving the blind spot of transoesophageal echocardiography: a new diagnostic device for visualizing the ascending aorta in cardiac surgery. *British Journal of Anaesthesia* 2007;98:434-41.

Stroke after cardiac surgery is often caused by emboli from atherosclerotic plaques in the ascending aorta (AA). These are produced by cannulation, clamping and (de) clamping during conventional on-pump cardiac surgery(1-5). In the presence of severe atherosclerosis, the use of alternative surgical strategies that avoid or reduce manipulation of the AA is desirable(2,6-8). The best use of such strategies requires a diagnostic test that can visualize the AA, particularly the distal part, preferably before surgery.

The gold-standard for intraoperative detection of atherosclerosis of the AA is epiaortic ultrasound scanning(4). However, since its introduction in the eighties this technique has not gained widespread acceptance. It lengthens the surgical procedure, endangers the sterile field, is time-consuming, and is not available in many hospitals. Most importantly, epiaortic ultrasound scanning is performed after sternotomy, just before cannulation(4,9,10). At that point, changes in surgical strategy are less feasible.

Transesophageal echocardiography (TEE) is a minimal invasive, method to visualize the extent of atherosclerosis, before and during cardiac surgery. TEE overcomes some of the problems of epiaortic ultrasound scanning, is widely available and used during cardiac surgery(11). The major disadvantage of TEE is that the distal part of the AA, i.e. the place where the cannula is introduced, cannot be visualized due to the so-called blind spot(12). The blind spot is caused by the interposition of air, located in the trachea and main bronchi, between the echo-transducer and the AA (figure 1).

We have modified conventional TEE to overcome this limitation(13). This new diagnostic method, referred to as the A-View (Aortic-View) method, uses a saline filled balloon catheter (figure 1) to replace the air in the trachea during the investigation. This fluid creates an ultrasound conducting window and the possibility of imaging the distal part of the AA that is normally invisible. New diagnostic methods should undergo evaluation before introduction into clinical practice(14-17). The present diagnostic study describes the first phase of the evaluation process, i.e. the technical and safety evaluation. The technical evaluation addresses to what extent the A-View method is capable of imaging the distal AA, and the safety evaluation whether the method leads to unexpected complications due to the use of the device.

Methods

Study population

After approval by the institutional medical ethical committee and written informed consent, 41 consecutive patients scheduled for elective cardiac surgery through a sternotomy were included. The study took place in a general teaching hospital (Isala Clinics, Zwolle, the Netherlands). The study was conducted in compliance with the protocol and in accordance with the moral, ethical, and scientific principles

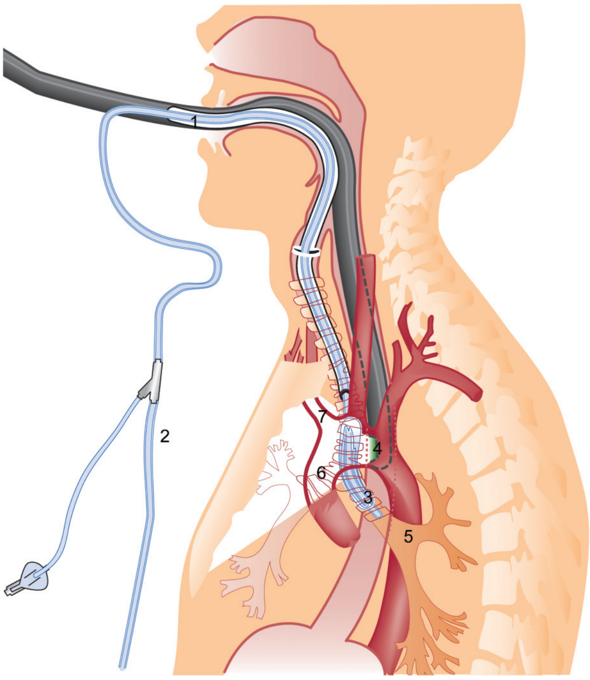

Figure 1: Longitudinal cross section illustrating the anatomic interrelation of structures, the A-View balloon catheter and the transesophageal echocardiography probe. (1 = Endotracheal tube, 2 = A-View catheter, 3 = Balloon of A-View catheter 4 = TEE probe, 5 = Left main bronchus, 6 = Ascending aorta, 7 = Innominate artery)

governing clinical research as set out in the Declaration of Helsinki (1989) and Good Clinical Practice (GCP). Patients were included between September 2005 and January 2006, and are a random sample of the target population in which the device is to be used, i.e. cardiac surgery patients. Only Patients older than 18 years of age were included. Patients scheduled for off-pump surgery or cardiac re-operation were not included. Furthermore, patients with contra-indications to TEE (esophageal dysfunction), or contra-indications for the A-View method (severe COPD, tracheal dysfunction) were also excluded.

Design and measurements

The study followed a cross-sectional diagnostic design. All consecutive patients underwent the same systematic work-up including a standardized conventional TEE, the A-View method, epiaortic ultrasound scanning (reference standard) and hemodynamic monitoring. All ultrasound data were recorded for subsequent off-line analysis.

Heart rate, mean arterial pressure, oxygen saturation, and end tidal CO_2, were continuously recorded. Before and after the A-View method, bronchoscopy was performed to detect possible side effects caused by the A-View catheter.

The study was a systematically designed and conducted diagnostic study and no intervention was performed. Treatment decisions were based upon current guidelines and routine clinical care practice.

Conventional Transesophageal echocardiography

After induction of anesthesia and intubation a standard TEE (Vivid I, General Electronics, Solingen, Germany or Philips HP Sonos 2500, Best, the Netherlands) was performed according to the guidelines of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists(18). The main test result for the present study was whether the AA distal to the right pulmonary artery could be visualized. Visualization was attempted twice, before and after the initiation of cardiopulmonary bypass (CPB). Before CPB, visibility was defined as visualization of the aorta from the right pulmonary artery to the innominate artery. During CPB visibility was defined as the ability to visualize the flow from the aortic cannula of the CPB-circuit. TEE images were digitally stored to enable off-line analysis by one experienced anesthesiologist (APN).

The A-View method

The A-View method was performed using the conventional TEE probe together with the A-View catheter (Cordatec Inc., Zoersel, Belgium). The TEE probe was positioned in the mid esophageal position enabling visualization of the proximal AA and right pulmonary artery. The A-View catheter was then introduced into the trachea via the endotracheal (ET) tube. To facilitate ventilation of the patient, a Y-connecter was used. Since the AA is in close anatomic relation to the left main bronchus, the A-View catheter was placed in the left main bronchus to optimize imaging. This was performed via the semi-rigid shaft of the A-View catheter, which allowed us to create a curve of about 30 degrees in the distal end of the catheter to facilitate easy positioning. The 24 cm marker on the A-View catheter balloon (total distance marker until tip of A-View catheter is 34 cm) was lined up with the 24 cm mark at the ET tube so that the A-View catheter will protrude 10 cm from the ET tube and to prevent too deep insertion. Retraction of the ET tube together with the A-View catheter was used to enhance visualization if the balloon of the ET tube overlapped the distal AA. After checking the correct position of the catheter by auscultation, and interrupting ventilation, the balloon was filled with sterile saline. The A-View method was performed by retracting the TEE-probe from the mid esophageal view until the AA was visualized (20-30 cm from the incisors). When necessary, lateral flexion of the tip of the echo-probe was used to obtain adequate imaging. After completion of the investigation the ET-tube was repositioned if necessary using the catheter as a guide wire. Subsequently, saline was aspirated from the A-View catheter, the catheter was removed, and ventilation was resumed.

We used the same definitions for the test results of the A-View method as for conventional TEE. Furthermore, the presence and severity of aortic atherosclerosis of the visualized part (i.e. distal AA) was described with a five-grade ranking system(19); grade I: normal aorta, grade II: extensive intimal thickening, grade III: protruding atheroma < 5 mm, grade IV: protruding atheroma > 5mm and grade V: mobile plaques. A-View images were digitally stored and off-line interpreted by the same anesthesiologist (APN). Prior to the study, we performed a pilot-study of 15 patients, to exclude the effect of a learning curve of the anesthesiologist in the interpretation of the A-View images(13).

Epiaortic ultrasound scanning

The epiaortic ultrasound scan was performed after sternotomy and opening of the pericardium before cannulation of the AA by the cardiac surgeon. A transthoracic ultrasound probe (M4S, General Electronics, Solingen, Germany) or an epiaortic probe (Philips 15m – 6L, Best, the Netherlands) was placed on to the AA. For optimal imaging of the AA the pericardium was filled with saline at body-temperature. Short and long axis views of the proximal and distal AA were obtained. The epiaortic ultrasound scan was used as the reference test for comparison with the A-View method of examining the presence, severity and location of AA-atherosclerosis. Epiaortic ultrasound scanning was performed by the attending cardiac surgeon and interpreted off-line by the same anesthesiologist (APN).

Outcomes

The primary outcome of this study was the visibility of the AA based on the A-View method compared with conventional TEE, both before initiation of CPB, i.e. visualization of the AA from the right pulmonary artery to the innominate artery and after initiation of CPB, i.e. visualization of the aortic cannula flow. A number of secondary outcomes were examined. Complications due to the use of the device, including cardiopulmonary side effects such as hypoxemia and hypercarbia and damage due to the placement of the A-View catheter into the trachea and main left bronchus were actively sought and recorded. The presence and severity of atherosclerosis in the distal AA, visualized with the A-View method was compared with epiaortic ultrasound scanning as reference standard. Absence of atherosclerosis was defined as grade I – II and the presence as grade III, IV or V of the grading described above(19). Based on a previous report(20), the size of the plaque (cm^2) was also determined by both techniques. Finally, the duration of the three methods examination was compared.

Statistics

As for therapeutic phase 1 studies, there are no formal rules for power calculations of phase 1 diagnostic studies. However, we estimated that 40 patients should be included, assuming that the A-View method enables visualization of the distal AA (the primary endpoint) in 95% of patients with a standard error of 6% (power = 0.80; alpha=0.05, two-sided). This number of 40 patients was more than enough to compare the visibility rates of the A-View method with conventional TEE. For example, assuming that with conventional TEE the AA is visible in 10% of patients, only 6 patients are needed. The number of 40 patients would also suffice for the evaluation of the percentage of unexpected events due to the use of the device, based on an expectation of unexpected events in 10% of patients with a standard error of 7.5% (power=0.80; alpha=0.05, two-sided)

Frequencies of patients in whom the innominate artery (before CPB), and the aortic cannula flow (after initiation of CPB) could be visualized with conventional TEE and with the A-View method were compared. The frequency of adverse effects related to the A-View catheter was quantified.

The degree of agreement between the A-View method and epiaortic ultrasound scanning for grades of atherosclerosis was estimated using the Kappa-statistic. A 2 by 2 table of the presence of AA-atherosclerosis (grade III-V) versus absence (grade I-II) was constructed. A standard correction of adding 0.5 to all cells of the table was applied since the table contained one zero cell. Positive and negative predictive value, sensitivity, specificity and the likelihood ratios with their 95% confidence intervals were calculated. In patients with atherosclerosis the Bland-Altman method was used to study the agreement in plaque-size with the A-View method versus epiaortic ultrasound scanning.

Average measurement duration (in minutes) of the A-View method and epiaortic ultrasound scanning was compared using a paired t-test.

Results

Conventional TEE, the A-View method and epiaortic ultrasound were performed in all patients. The mean age of the patients was 67 (Range 42-94) years. The study population consisted of 28 (68.3%) males and 13 females (31.7%). Sixteen patients underwent isolated coronary bypass surgery, 15 had only valve surgery, and 10 patients had combined bypass and valve surgery.

Visualization of the ascending aorta

Using conventional TEE, the innominate artery was visible in 2 out of 41 (4.9%) patients and after initiation of CPB the aortic cannula flow was visible in 4 out of 41 (9.8%) patients. With the A-View method the innominate artery (figure 2) and the aortic cannula flow (figure 3) was visible in all (100%) patients.

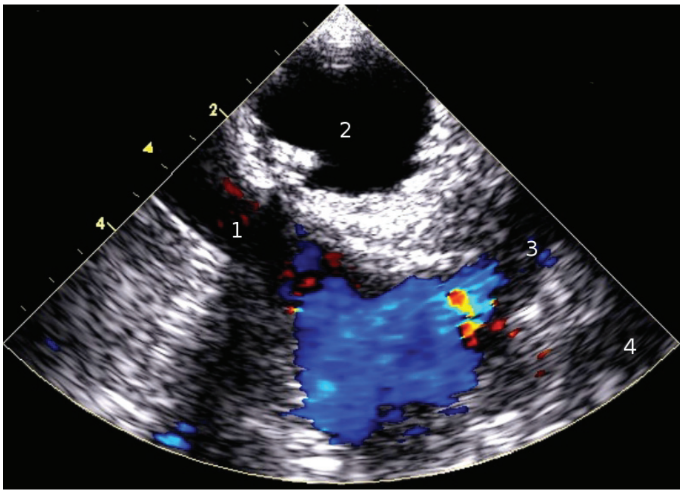

Figure 2: Image of the ascending aorta and the innominate artery as imaged with the A-View method (1 = Innominate artery, 2 = Trachea, 3 = Left carotid artery, 4 = Left subclavian artery).

Safety

We did not observe any clinical significant effects on the hemodynamic and ventilatory status of the patients due to the use of the A-View method (Table 1). We observed one unexpected severe complication. In one patient the ET-tube was accidentally dislocated while retracting it to optimize imaging, leading to a drop of SaO_2 from 99% to 53% without clinical consequences. Bronchoscopy revealed insignificant mucosal bleeding after the A-View procedure in seven (18%) patients without any additional interventions needed.

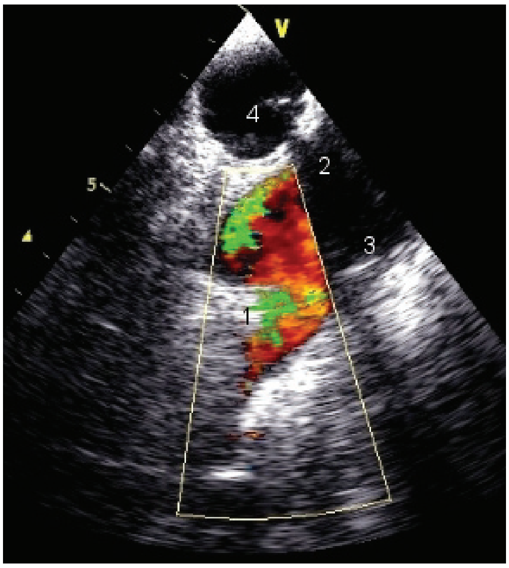

Figure 3: Image of the ascending aorta with the aortic cannula flow as imaged by the A-View method (1 = Aortic cannula, 2 = dorsal wall of ascending aorta, 3 = ventral wall of ascending aorta, 4 = trachea).

	Before use of the A-View method	After use of the A-View method
Saturation, %	100 (1)	98 (3)
End-tidal CO_2, KPa,	3,9 (0,5)	4,5 (0,6)
Heart rate, beats/min	65 (11)	66 (11)
Mean arterial pressure, mmHg	78 (14)	73 (13)

Table 1: Hemodynamic and ventilatory variables before and after the A-View method expressed as mean (SD).

Atherosclerosis

In four patients the A-View method showed clinical relevant atherosclerosis that was not detected with epiaortic ultrasound scanning. In three patients the A-View method showed atherosclerosis of a higher degree than epiaortic scanning. The Kappa statistic was 0.69 (95%CI 0.50 – 0.88). After dichotomization the positive predictive value of the A-View method was 80%, and the negative predictive value was 98%. The sensitivity was 97% and the specificity was 81% (Table 2).

In one of the 18 patients with clinically relevant atherosclerosis the plaque size could not be determined with epiaortic ultrasound scanning as the atherosclerotic plaque was too large to image it at once. Therefore, this patient was excluded from the Bland – Altman analyses. Figure 4 shows that there was a poor agreement between the A-View method and epiaortic ultrasound scanning with wide limits of agreement and an increasing difference between the two methods with increasing plaque size; mean plaque size 0.42 cm^2, bias 0.05 cm^2, limits of agreement -0.63 to 0.74 cm^2.

Duration

The A-View method took a mean(SD) 4.5(1.8) minutes, whereas epiaortic ultrasound scanning took 3.1(1.8) minutes to obtain images of the entire AA. The mean(95% CI) difference in additional time between the two methods was 1.3(0.4 – 2.6)minutes.

		Epiaortic ultrasound scan		
		Presence	Absence	Total
A-View method	Presence	18	4	22
	Absence	0	19	19
	Total	18	23	41

Table 2: Presence (Grade III, IV or V) versus absence (Grade I or II) of AA atherosclerosis visualized with the A-View method compared to the epiaortic ultrasound scanning result. Sensitivity (95% CI) = 97%(90% – 100%), Specificity 81%(66% - 97%), Positive predictive value 80%(64% - 97%), Negative predictive value 98%(91% - 100%), likelihood ratio of a positive test 5.2 (2.3 – 12.0), likelihood ratio of a negative test 0.03(0.002 – 0.50).

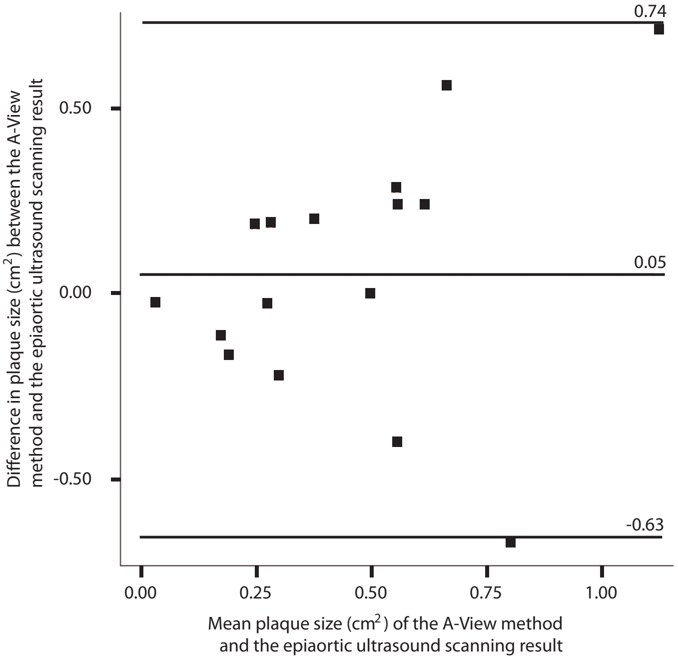

Figure 4: Bland-Altman plot of the A-View method and epiaortic ultrasound results of patients with clinically relevant atherosclerosis (Middle line = Bias 0.05, Upper line = upper limit of agreement 0.74 and lower line = lower limit of agreement -0.63).

Discussion

In the present study it is shown that in patients undergoing cardiac surgery imaging of the distal AA is possible before sternotomy using modified TEE-technology. With the A-View method the innominate artery and the aortic cannula flow was visible in all patients. Our findings confirm the results of a recently published study by Li and colleagues(21). We have demonstrated that the A-View method allows for the acquisition of a series of images of the distal part of the AA without severe unexpected adverse effects. Furthermore, initial results indicate good diagnostic accuracy of the A-View method as compared to epiaortic ultrasound scanning for the detection of presence and severity of atherosclerosis. Mean(SD) duration of both the A-View method and epiaortic ultrasound scanning was short, 4.5 (1.8) and 3.1 (1.8) minutes respectively, and had no impact on the total surgical time.

Clinical relevance of the A-View method

Diagnostic tests in itself commonly have no direct impact on health improvement but they do (in most instances) via the therapies indicated or chosen based on the results(22). Studies in cardiac surgical patients have shown that the use of epiaortic ultrasound scanning of the AA combined with appropriate changes in surgical techniques can reduce the incidence of stroke in case of severe AA atherosclerosis(23-25). We have shown that the A-View method is capable of adequately imaging the distal AA. Initial results also show that the A-View method enables detection of the presence and severity of AA atherosclerosis at a time preoperatively that extensive manipulations of the AA, the major cause of emboli generation, can be avoided. Hence, it can be expected that, the benefits of the A-View method are comparable to epiaortic ultrasound scanning where the latter is more burdensome to use and often applied too late to allow changes in surgical technique.

Interestingly assessing the presence and severity of atherosclerosis by the A-View method as compared to epiaortic scanning showed comparable results, whereas conventional TEE image quality is not sufficient when compared to epiaortic scanning. As expected, we noticed a difference in image quality between the epiaortic scan and the A-View method but this did not hamper the interpretation of the images or the measurements.

The A-View method revealed in seven patients a more severe degree of atherosclerosis than epiaortic ultrasound scanning. There are two potential reasons for this finding. First, since the aorta distal to the innominate artery is not directly exposed to the surgical field the epiaortic ultrasound probe cannot be placed on this part of the aorta. As a consequence epiaortic scanning is only capable of obtaining longitudinal images of the aorta distal to the innominate artery and no transversal images can be obtained. On longitudinal images a different, most likely smaller, cross-section of atherosclerotic plaques is acquired and severity of atherosclerosis is underestimated. Second, the ultrasound beam of epiaortic scanning is less wide then the TEE ultrasound beam used in the A-View method. Therefore, a larger part of the AA is imaged at once with the A-View method and atherosclerotic plaques may then be better visualized.

Overall there was a poor agreement between the A-View method and epiaortic ultrasound scanning in determining plaque size shown. Poor agreement is most likely because of the different imaging planes of the two methods. The A-View method and epiaortic ultrasound scanning obtain different cross-sections of the same plaque and therefore of different plaque sizes. The latter may also be an explanation for the increasing difference between the two methods with increasing plaque size, as a larger plaque has more different cross-sections. However, in clinical practice this will not have relevant implications since in most cases the location rather than the size of the atherosclerotic plaque will guide surgical management.

Methodological issues

The evaluation of a new diagnostic device needs a phased scientific approach where subsequent studies are indicated only in case of good results in previous phases(14-17). The present study addresses the results of the first phase of the evaluation of the A-View method. As the purpose was to study the ability to visualize the AA with the A-View method and its safety we explicitly performed a single observer study. This observer was the person who developed the A-View method (APN)(13). This could lead to an overestimation of the ability of the A-View method to image the distal AA. Given however, the promising results of the present study and following the guidelines(14-17), we conclude it is ethical and safe to conduct additional studies in a larger series of patients to estimate more precisely the intra- and inter observer variation and the diagnostic accuracy of the A-View method. Finally, studies are needed to address the impact of the use of the A-View method on patient outcome and cost-effectiveness.

Due to the fact that we first performed the TEE in each patient and subsequently the A-View method, some learning effect cannot be ruled out as the A-View study will be informed by the previous TEE study and this could favor the A-View method. However, the A-View method 'effect' on visualizing the AA was so large compared to TEE that it is highly unlikely that this could entirely be explained by a learning curve. Moreover, we tried to minimize this error by having the images interpreted in a blinded fashion off line.

As with phase 1 studies for therapeutic interventions, diagnostic phase 1 studies are not intended to obtain highly precise estimates of the unexpected event rate of the device. The aim is rather to study in a small series of patients the safety of the device. Larger and more formal safety evaluations have to be carried out in post-marketing (phase 4) studies.

We used epiaortic ultrasound scanning as reference rather than modern MRI and CT-scanners because epiaortic scanning is at present time the most widely used reference standard for this disorder. MRI and CT have limited application and availability in routine care of cardiac surgery patients. But more importantly, they are not capable of providing real-time images of the AA to direct immediate changes in surgical strategy.

Potential complications of the A-View method

After pre-oxygenation with a FiO_2 of 100% an apnea period of several minutes can be maintained without clinical significant hypoxemia or hypercapnea. Visualizing the AA with the A-View method can be done within this time frame. It is not expected that the temporary apnea will have harmful effects on the patient.

In one patient severe hypoxemia was observed when the ET-tube was accidentally dislocated after retraction of the ET-tube to optimize imaging of the innominate artery. Since the patient was already draped for surgery we had difficulties in reintubating the patient. This led to a short drop of SaO_2 from 99% to 53% without clinical consequences. To prevent these adverse events the A-View method should only be performed before draping, to obtain full and easy airway access to solve these potential ET tube related difficulties. Furthermore, we advise not using the

A-View method when intubation problems are expected or when unexpected intubation difficulty has occurred.

Apart from small mucosal point bleeding caused by the stiff tip of the catheter in seven patients, no patient showed damage of the bronchial or tracheal wall. However, to reduce the incidence of mucosal bleeding an adjustment has been made to the design of the catheter, which is now made of a softer material. In none of the patients was any evidence of barotrauma due to the fluid-filled balloon of the A-View catheter observed. Intratracheal balloons filled with water are in use for several other occasions, during intratracheal laser surgery the endotracheal tube cuff is filled with fluid. This technique has never been associated with severe side effects or an increased incidence of tracheal damage. Pressure on the tracheal wall caused by water has the same physics as air and therefore the same safety guidelines must be used. Although there is some controversy about a 'safe' cuff pressure, most clinicians accept 25 cmH$_2$O up to 35 cmH$_2$O as a safe limit(26). Rupture of the trachea is described at pressures above 120 cm H$_2$O(27), and usually related to over-distension of the tracheal cuff. The A-View catheter consists of a much more compliant balloon than the standard endotracheal balloon. Hence, if the pressure is kept under the safe limit, the risk for tracheal barotrauma is minimal. To prevent over inflation of the balloon, filling of the balloon should be visualized by TEE. As soon as the image of the trachea and/or the distal AA appears the appropriate volume is reached for the individual patient.

Balloon rupture is very unlikely because the balloon is made out of polyurethane, an extremely strong material. In case of balloon rupture, a total of 20-30 ml of sterile saline will enter into the lungs. It can be expected, that this amount of water will be absorbed without clinical implications. In general we think that the risk of clinical significant harmful effects of the A-View method is small and will outweigh the gain of the A-View method.

To conclude, the A-View method offers a fast, easy, safe and minimally invasive approach of resolving the blind spot of TEE. Compared to epiaortic ultrasound scanning, the A-View method yielded adequate results in the detection of AA atherosclerosis and can be used prior to sternotomy. The surgical strategy can therefore be adjusted to reduce or even avoid manipulation of the AA in case of severe aortic atherosclerosis. Accordingly, the A-View method seems a promising tool for patients undergoing cardiac surgery to reduce possible post-operative stroke.

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4

VISUALIZATION OF THE DISTAL ASCENDING AORTA WITH IMPROVED TRANSESOPHAGEAL ECHOCARDIOGRAPHY

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Visualization of the distal ascending aorta with improved transesophageal echocardiography. *Journal of Cardiothoracic and Vascular Anesthesia.* 2008;22(5):766-773

Transesophageal echocardiography (TEE) is a widely used imaging technique for perioperative evaluation of cardiac function and intra-thoracic vascular structures(1). Imaging of the thoracic aorta is part of the standard intra-operative TEE examination as recommended by the society of cardiovascular anesthesiologists(2). Most of the thoracic aorta can routinely be imaged with conventional TEE, because it is adjacent to the esophagus as it passes vertically through the mediastinum. However, major limitation of conventional TEE remains the so-called "blind spot". Because of interposition of the air filled trachea between the esophagus and the distal ascending aorta and proximal aortic arch, these regions usually cannot be visualized with conventional TEE(3).

The distal ascending aorta is the location for aortic clamping and cannulation. Manipulation of an atherosclerotic aorta can dislodge atherosclerotic debris and cause post-operative stroke. In a recent meta-analysis, based on all available quantitative evidence, of the diagnostic accuracy of TEE for the detection of atherosclerosis in the ascending aorta it was shown that conventional TEE is not capable of adequately assessing the ascending aorta for clinically relevant atherosclerosis, most likely due to the 'blind spot'(4).

We recently improved conventional TEE in order overcome the 'blind spot' of TEE. The method, further referred to as the A-View (Aortic-View) method, uses a fluid filled balloon catheter (the A-View catheter, Cordatec Inc, Zoersel, Belgium, Figure 1) in combination with conventional TEE. In a, previously published, cross-sectional diagnostic study evaluating this new method in 41 patients undergoing cardiac surgery, the distal ascending aorta was visible in all (100%) patients with the A-View method and only in 9,8% with conventional TEE. There were no clinical important side effects associated with the use of the A-View catheter. Severity of atherosclerosis visualized with the A-View method compared with epiaortic ultrasound results showed good agreement between the two methods [Kappa of 0.69 (0.50–0.88)](5). Aim of this paper is to describe the use of this new diagnostic method, its potential views, uses and risks of the method via various case reports.

Clinical application of the A-View Method

The patients described in this chapter all gave written informed consent to use their clinical data. The A-View method is approved for clinical use by both CE marking as by the United States Food and Drugs Administration and thus may be used for diagnostic purposes in patients.

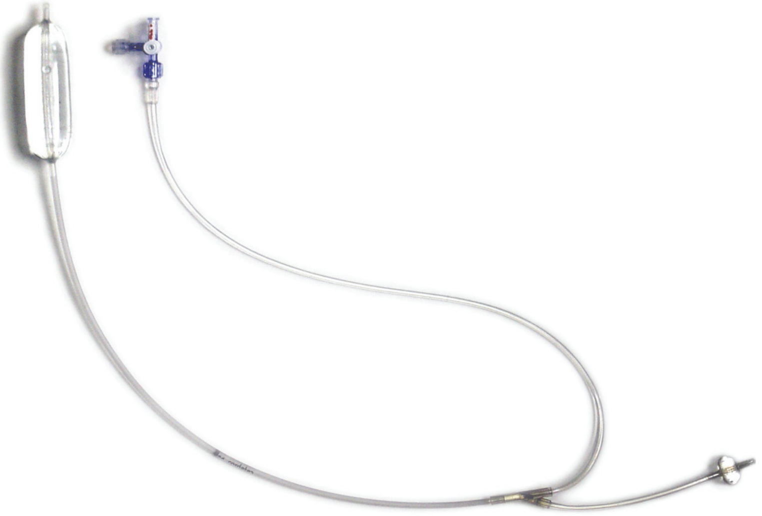

Figure 1: The A-View catheter.

As said the A-View method, uses a saline-filled balloon catheter to replace the air in the trachea during the investigation (Figure 2). This fluid creates an ultrasound-conducting window and the possibility of imaging the distal part of the ascending aorta by conventional TEE in the anesthetized patient, during a short (2-3 minutes) period of apnoea.

The A-View catheter is an endotracheal balloon catheter consisting of an external filling line connected to a highly compliant airway balloon, and an external pressure balloon mounted on a sideline. The airway balloon is oversized, in order to cover the main bronchus and trachea without the necessity to reposition the balloon during the investigation. A marker is placed 24 cm proximal from the balloon (total distance from tip of the catheter until marker is 34 cm), indicating that the balloon is distal from the endotracheal (ET)-tube if the marker is parallel to the 24 marker on the ET-tube.

Potential risks with the use of the A-View Method

The A-View method may lead to potential complications such as: Cardiopulmonary side-effects (most importantly hypoxemia or hypercapnea), tracheal or bronchial wall damage, and fluid leakage from balloon rupture. After pre-oxygenation an apnoea of several minutes can be maintained without clinical significant hypoxemia or hypercarbia. Visualizing the AA with the A-View method can be done within this time frame. Also, intratracheal balloons filled with water are in use for several other occasions, this technique is not associated with reported severe side effects or an increased incidence of tracheal damage if the pressure is kept under the safe limit (25 mmH_2O up to 34 mmH_2O as a safe limit)(6-9).

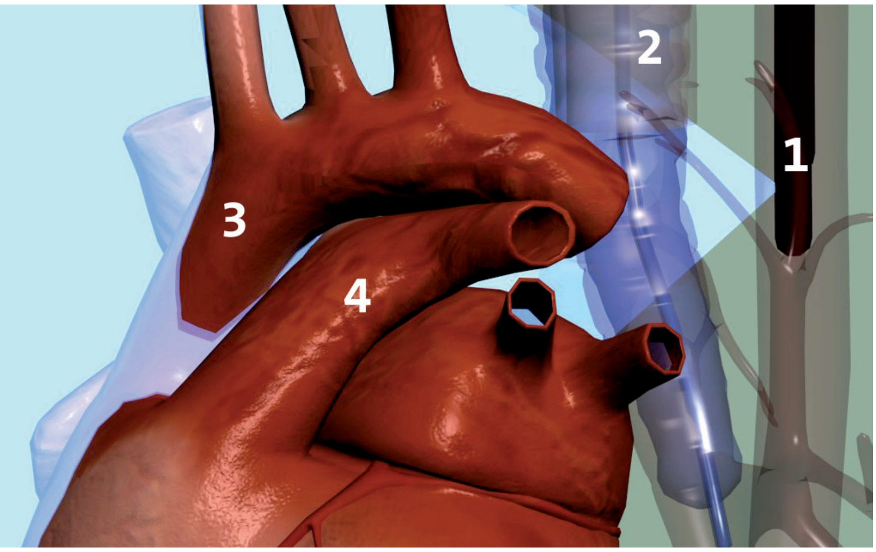

Figure 2: Schematic view of the upper mediastinum: 1. Esophagus with TEE probe and new echowindow through blind spot; 2. Trachea and left main bronchus with A-View catheter; 3. Distal AA; 4. Pulmonary artery.

In our experience so far airway injuries were limited to small mucosal bleedings that did not require any further intervention. Finally, balloon rupture is very unlikely, because the balloon is made out of the extremely strong material poly-urethane. In the rare case of balloon rupture 20-30 ml of sterile saline will enter the lungs, but this will be absorbed immediately without clinical implications.

The method is only for patients older than 18 year and the minimum ET-tube size is seven. In patients with bronchial stenosis, previous tracheobronchial tear or surgery, bronchial arteriovenous malformations, extrinsic bronchial erosion or compression or bronchial or tracheal tumors, and those patients with severe COPD, the use of the balloon catheter is contra-indicated. Furthermore, patients with contra-indications to TEE (esophageal stenosis, or varicosus) make it impossible to use this diagnostic device.

How to perform the A-View Method

Since a period of apnoea is a pre-requisite to perform the A-View method, the patients on whom the method is performed have to be anesthetised and their trachea has to be intubated. So, after applying standard monitoring (electrocardiogram, blood pressure and oxygen saturation), and induction of general anesthesia, the trachea is intubated with a standard ET-tube with special emphasis to position the cuff of the ET-tube immediate distal to the vocal cords. This is important in order to provide maximal space distal to the ET-tube for positioning of the A-View catheter in the trachea. Subsequently, the A-View method is initiated. Before introducing the A-View catheter into the trachea the balloon catheter must be prepared, i.e. checked for fluid-leaks and removing of residual air. Injecting 50 ml of saline into the catheter will show fluid leaks. Withdrawal of this volume back into the syringe, keeping the catheter vertical, will remove the air from the balloon. Lubrification of the A-View catheter with saline or aqua gel will reduce friction during placement through the ET-tube. After appropriate pre-oxygenation of the patient and assuring that the level of anesthesia is deep enough to prevent sympathetic responses on tracheal excitation, the A-View catheter can be introduced into the trachea through the ET-tube, after disconnection from the ventilator and thus interrupting ventilation for a short period. When the balloon is empty it is possible to ventilate the patient when a swivel Y-connecter is used.

The optimal position of the A-View catheter is in the distal trachea and in the left main bronchus, since a part of the ascending aorta is in close anatomic relation to the left main bronchus. Due to the length of 10 cm of the balloon, both the trachea and left main bronchus will be covered at once. The blunt tip of the catheter prevents positioning below the main bronchus. Positioning in the left main bronchus is facilitated by the semi-rigid shaft of the A-View catheter. Due to the introduction through the ET-tube, a curve of about 30 degrees in the distal end of the catheter is created. During introduction of the A-View catheter the pilot balloon is pointing forward. When the 24 cm marker reaches the beginning of the ET-tube the catheter has to be turned 90 degrees anticlockwise to the left side of the patient. Slowly moving the catheter further into the ET-tube will place the balloon in the left main bronchus. To verify correct placement of the balloon immediately distal to the ET-tube and to prevent too deep insertion of the catheter, the 24 cm marker has to be lined up with the 24 cm mark on the ET-tube.

The position of the A-View catheter can be checked by inflating the A-View catheter with 5 ml of saline and gently ventilating the patient manually if a swivel Y-connecter is used. If it is in the correct position, the left side of the thorax will not rise and on auscultation breath sounds are absent. Positioning of the filled A-View catheter can also be checked by TEE itself. Once the balloon is inflated, the carina and main bronchi are identified by the specific shape of the carina (horizontal eight) (Figure 3). When the catheter is in the right position saline (20 - 50 ml) is injected until the outline of trachea and the distal ascending aorta becomes visible (Figure 4). A sudden increase in filling resistance in the syringe indicates adequate filling of the balloon. Finally bronchoscopy can be used to check the correct position of the catheter, but only before filling of the balloon.

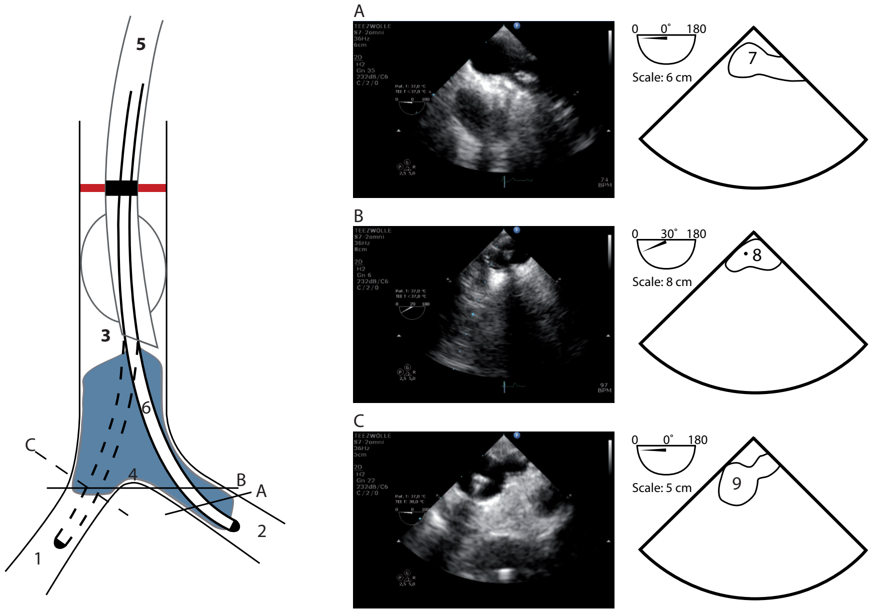

Figure 3: Image showing the correct position of the A-View catheter in the trachea and the left main bronchus. A. Placement into left main bronchus; B. TEE view of carina; C. Placement into right main bronchus. (1= right main bronchus, 2= left main bronchus, 3= trachea, 4=carina, 5= ET tube, 6= A-View catheter, 7= A-View catheter into left main bronchus, 8= A-View catheter at carina, 9= A-View catheter into right main bronchus).

Potential views of the A-View method

A-View Distal Ascending Aorta View

From the conventional TEE mid esophageal ascending aorta short axis view the A-View distal ascending aorta short axis view is developed by retraction of the probe until a depth of approximately 25-30 cm from the incisors with the multiplane angle adjusted to 30 degrees. Rotating the multiplane angle to between 70 and 120 degrees will develop the mid esophageal A-View ascending aorta long axis view (Figure 4). The anterior and posterior walls of the distal ascending aorta appear parallel to one another. The proximal part of the distal ascending aorta will appear on the left lower part of the monitor and the distal end will appear on the upper left part. The posterior wall is in close contact with the trachea that contains the A-View catheter.

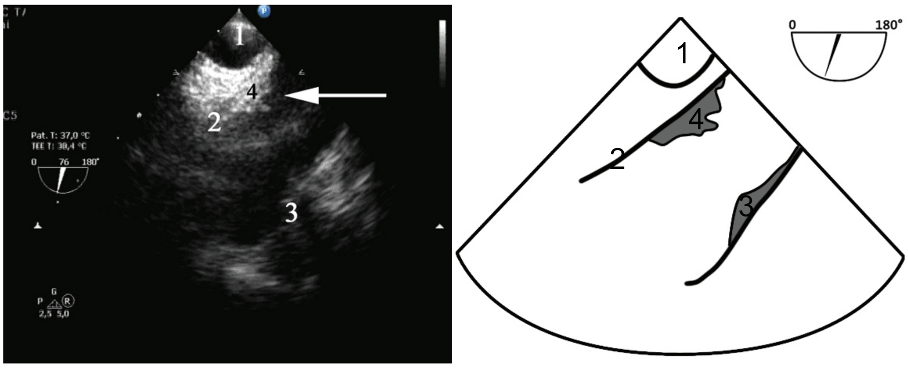

Figure 4: A-View distal ascending aorta long axis view. Image of trachea and the ascending aorta as imaged with the A-View method with plaque formation on the posterior and anterior wall (1= A-View catheter in trachea, 2= Posterior wall of distal ascending aorta, 3= Anterior wall of distal ascending aorta, 4= Mobile protruding atheroma indicated by the arrow).

A-View Aortic Arch View

By further retraction of the probe (2-5 cm) with the multiplane angle still at 70 degrees the aortic arch will become visible (Figure 5), and can be followed by adjusting the multiplane angel to 0 degrees, until the position is similar to that of the upper esophageal aortic arch long axis view with conventional TEE. In this position, the arch will appear horizontal.

Figure 5: A-View aortic arch short axis view. Image of the ascending aorta and the innominate artery as imaged with the A-View method (1 = A-View catheter in trachea, 2 = Innominate artery, 3 = Upper part of aortic arch, 4 = left carotid artery).

A-View Aortic Branch Vessels View

By slightly (2-5 cm) retracting the TEE probe further from the A-View Aortic Arch View with the multiplane angle in 0 degrees angle, the innominate (brachiocephalic) artery will become visible together with the left carotid artery with the trachea in the middle of the screen (Figure 5, 6). Rotating the TEE probe to the left and right will allow complete visualization of the entire aortic arch with the right innominate artery, left carotid artery and left subclavian artery. In relative small patients i.e. 150-160 cm of length, this image is sometimes impossible to obtain because the distance between the distal end of the ET-tube and the carina is too short. The (air-filled) cuff of the ET-tube will overlap the ultrasound-conducting window and ultrasound conduction is hampered. This can be resolved by retracting the ET-tube 3 cm together with the empty A-View catheter. This will now allow imaging of the aortic arch. If the ET tube was retracted it must be repositioned after completion of the investigation. For repositioning of the ET-tube the A-View catheter can serve as an 'intubation stylette'.

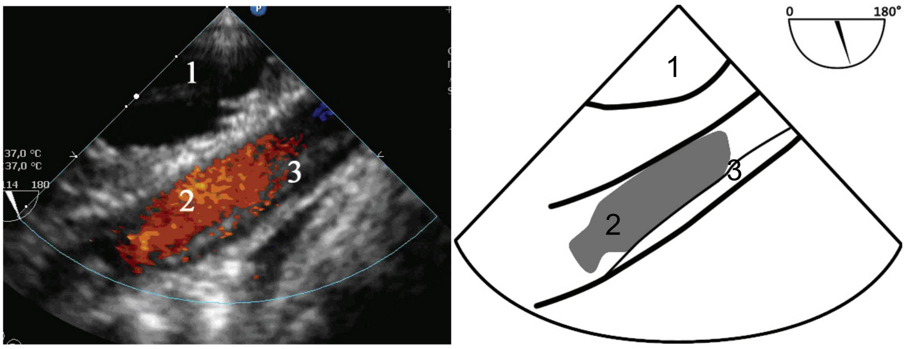

Figure 6: A-View aortic branch vessels long axis view. Image of the left carotid artery with a residual dissection as imaged with the saline filled balloon (1 = A-View catheter in trachea, 2 = Left carotid artery, 3 = Intimal flap).

When finished, all saline should be aspirated from the balloon, the catheter can then be removed, and ventilation resumed. If a swivel-Y connector is used, the catheter can be left in the trachea during ventilation. The balloon should be inspected on rupture or strains of blood on the outside. In case of blood, additional inspection of the trachea by bronchoscopy is indicated to exclude tracheal or bronchial damage that require intervention.

Learning curve

When introducing a new observer dependent diagnostic it takes time to develop the skills needed to acquire and interpret the result properly, before it can be used in daily practice. All users have to gain experience with the A-View method. The associated learning curve will likely be steep and short because the A-View method is a simple extension of conventional TEE. The skills needed to perform the A-View method are more or less the same as for conventional TEE. We are confident that those who use conventional TEE on a regular basis (i.e. cardiothoracic anaesthesiologist and cardiologist) are capable of acquiring the needed skills, i.e. catheter deployment, image acquisition and image interpretation after performing 5 to 10 A-View method procedures. In case of the cardiologist performing the TEE investigation, the anesthesiologist must take care of patient management and A-View placement. Moreover, during extra-corporeal circulation one can use the method without time limit, making this a rather ideal situation to gain experience with the method without having the risk of cardio-pulmonary side-effects.

Possible uses for the A-View Method

Screening of the distal ascending aorta for atherosclerosis (Case A)

A 71-year-old female was scheduled for elective coronary artery bypass grafting. There were no preoperative risk factors beside hypertension. When using the A-View method, a moving mass on the posterior wall of the distal ascending aorta of 22 mm length and 5 mm thick, just opposite of the location of the planned aortic cannulation in the anterior wall of the distal ascending aorta was visible (Figure 4).

The surgeon changed the initially planned site of cannulation to the aortic arch and clamped the aorta below this soft plaque. Control with the A-View method after the surgical procedure confirmed that there was no detachment from the aortic wall. Postoperatively, the patient awakened without embolic events.

Screening for distal ascending aorta dissection (Case B)

A 50-year-old man underwent emergency operation for a Stanford type A aortic dissection. During this emergency operation, aortic root, ascending aorta and proximal aortic arch replacement took place with a total circulatory arrest time of 32 minutes at 16°C. Postoperative recovery was uneventful, but questions remained about aortic insufficiency, pericardial effusion and the possible remaining dissection in the distal arch and main side branches. Therefore, 3 weeks after the operation, on request by the cardiologist conventional TEE and the A-View method were performed. Conventional TEE investigation revealed no clinical relevant pericardial effusion, aortic insufficiency grade I, a hematoma around the proximal ascending aorta and an intimal flap in the distal descending aorta with pendulous flow. Using the A-View method, the distal part of the ascending aorta and proximal aortic arch were visualized and a residual dissection of the left carotid artery and left subclavian artery were visible (Figure 6). The innominate artery showed no dissection. Based on the acquired information from both the TEE and the A-View method it was decided that no additional treatment was necessary.

Screening for distal ascending aorta intramural hematoma (Case C)

A 58-year-old woman was transferred to our hospital with an acute Stanford type B aortic dissection for further medical treatment. The CT scan confirmed the diagnosis, however doubt remained whether there was a hematoma or a dissection in the distal ascending aorta or in the aortic arch. The cardiologist requested for a conventional TEE under general anesthesia. This showed intimal rupture of the descending aorta just below the left subclavian artery with flow into both true and false lumen and no pericardial effusion. It was not possible to image the distal ascending aorta or aortic arch. Subsequently, using the A-View method, the distal ascending aorta, aortic arch and carotid arteries were visualized. An intimal tear just between the innominate artery and left carotid artery was diagnosed (Figure 7). The innominate artery still had a normal flow pattern. The initial plan of medical treatment changed into surgical treatment due to this additional information. The patient was further treated as a Stanford type A dissection and scheduled for distal ascending aorta surgery.

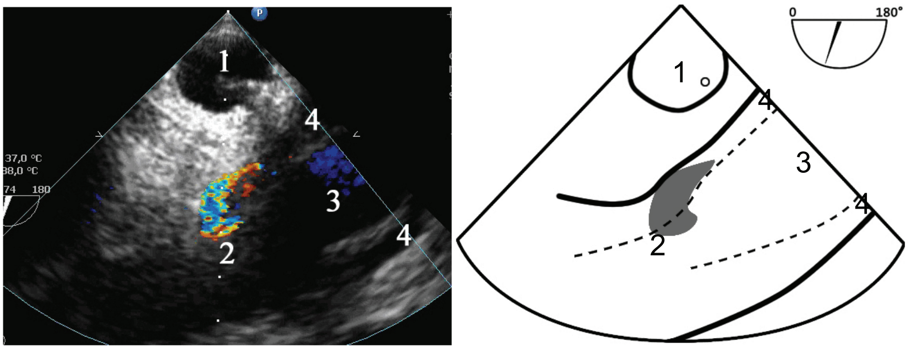

Figure 7: A-View aortic arch long axis view. A dissection just next to the innominate artery is visible with a further dissection into the descending aortic arch (1 = A-View catheter in trachea, 2 =Intimal tear next to the innominate artery, 3 = True lumen aortic arch, 4: False lumen aortic arch).

Monitoring cerebral blood flow (Case D)

A 40-year old male patient was transferred for surgical treatment of an acute Stanford type A-dissection. During the one-hour transport from the referral hospital, the clinical condition of the patient deteriorated rapidly. On arrival in the operating theatre, the patient was resuscitated and emergency groin cannulation was performed to initiate extra corporeal circulation (ECC). There was no information available whether the dissection had interrupted cerebral blood flow. The patient showed a bispectral index level of zero and dilated fixed pupils. During ECC, the carotid arteries were checked by the A-View method and they showed normal flow without dissections. This additional information was the main reason to proceed with the operation. During aortic arch replacement the A-View method was used to monitor selective antegrade cerebral perfusion through the innominate artery and the left carotid artery (Figure 8). Despite this, the patient died in the OR due to massive bleeding from ruptured intercostal arteries.

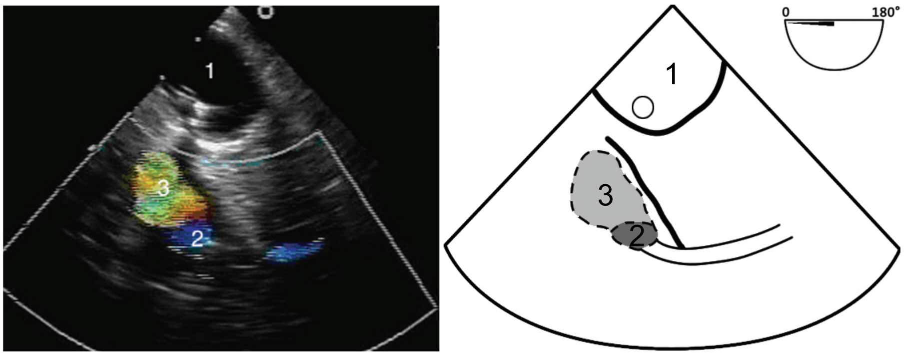

Figure 8: A-View aortic branch vessels short axis view.
Image of the innominate artery with a retrograde perfusion canula during selective antegrade cerebral perfusion during ECC. (1= A-View catheter in trachea, 2= cerebral perfusion catheter with balloon, 3= innominate artery)

Discussion

With the introduction of the A-View method, it is possible to image the distal ascending aorta and the proximal aortic arch before sternotomy. Since the introduction of the A-View method, it is used for the clinical indications as described.

Screening of distal ascending aorta Atherosclerosis

Postoperative neurological complications occur in 3% of all cardiac operations and account for 20% of all deaths after cardiac surgery(10). The incidence of post-cardiac-surgery stroke rates increase from 1% in patients under 50 years of age to 7% in patients over 75 years of age (11-13). Stroke after cardiac surgery is (often) caused by emboli merging from atherosclerotic plaques in the distal ascending aorta to the brain, due to manipulations during conventional on-pump cardiac surgery.

Early detection of the cardiac surgery patient at risk for embolic complications is necessary in order to prevent devastating complications such as stroke. In the presence of severe atherosclerosis, the uses of alternative surgical strategies that avoid or reduce manipulation of the ascending aorta are desired. Such strategies are for example femoral artery cannulation, off-pump CABG without proximal anastomoses, no-touch technique of the ascending aorta or even ascending aorta replacement. Initial results have shown that the A-View method enables the detection of the presence and severity of ascending aorta atherosclerosis before sternotomy and therefore may give valuable diagnostic information about the degree of atherosclerosis so surgical strategy can be adapted (3).

Screening for distal ascending aorta dissection or hematoma

Aortic dissection is an acute illness with an extremely high mortality rate during the first 48 hours after occurrence. Survival can be improved by early diagnosis and prompt initiation of adequate medical and/or surgical therapy (14). Treatment of aortic dissection depends on the location of the intimal tear and the extension of the dissection. In general, a dissection of the ascending aorta with or without involvement of the descending aorta (Stanford type A) is treated by surgery, and a dissection of the descending aorta without any dissection in the ascending aorta or arch (Stanford type B) is treated by medication or endovascular stenting. In addition, the extension of a dissection in the main branches of the aortic arch should be evaluated.

At present MRI is the gold standard in diagnosing aortic dissection but its use is limited(15). Therefore, CT scanning is the most used imaging modality in the assessment of acute aortic dissection(16). Fast spiral CT-scan (MSCT), particular with multidetector arrays, enables accurate imaging of the thoracic aorta in considerable short time. However, disadvantages of these CT scan devices are the need for potential nephrotoxic contrast, the exposure to ionizing radiation and the need for time consuming transportation. Both, MRI and CT are difficult to perform in hemodynamically unstable patients, and sometimes are not capable of distinguishing between type A and B dissection. Conventional TEE is easy to perform in the hemodynamic unstable patient and does have a high sensitivity in detecting thoracic aortic dissection. Combined with the A-View method, TEE will provide the complete view of the thoracic aorta and its main cerebral side branches. Time gained in the diagnostic phase before surgery may have an impact on improved clinical outcome after surgery or stenting.

Monitoring cerebral blood flow

During ECC, cerebral blood flow monitoring by conventional TEE is mostly impossible since the innominate artery runs just in front of the trachea. Identification of cerebral malperfusion requires monitoring by direct visualization of the innominate and left carotid artery in order to detect dissections into these vessels. Quantification of blood flow by using Doppler monitoring will identify cerebral malperfusion. The A-View method may provide adequate imaging of flow in anesthetized and intubated patients during cardiac surgery. Emboli detection, flow velocity and control of antegrade or retrograde cerebral perfusion during aortic arch repair may help to enhance clinical outcome after extensive aortic surgery. Information regarding perfusion to the brain can be obtained with surface echocardiography, but if a patient is undergoing cardiac surgery and thus is anesthetized and intubated the A-View method provides an additional means of obtaining this information. In addition to surface echocardiography imaging of the origin of the carotid arteries in the aortic arch is possible using the A-View method.

Alternative Imaging Techniques

Epiaortic ultrasound scanning has not gained widespread use despite that is considered to be the 'gold' standard for detecting atherosclerosis in the ascending aorta. It has not gained widespread use, since there is a lack of optimized ultrasound devices, it would lengthen the surgical procedure, it may endanger the sterility of the surgical field, and there is a false belief by many surgeons that palpation is as sensitive as epiaortic ultrasound scanning(17,18). Moreover, as it is applied during the operation decisions regarding surgical strategy are to be made at a late stage. Preferably, such decisions are to be made pre-operatively(19).

When using the supra-sternal ultrasonic window or surface echocardiography the aortic arch with its side branches can be imaged in awake patients. But still the distal ascending aorta, i.e. the section between the right pulmonary artery and the innominate artery, cannot be entirely imaged(20). During cardiac surgery the sterile draping hampers this method. In contrast, the A-View method is capable of imaging the aortic arch, the distal ascending aorta and its side branches during cardiac surgery when the patient is already anesthetized and intubated.

Finally transpharyngeal imaging can be used to image the carotid arteries to monitor for cerebral blood flow, but this technique is not capable of imaging the aortic arch, the distal ascending aorta or the origin of its side branches(21).

To conclude, The A-View method offers an approach to (preoperatively) resolve the blind spot of TEE. The method already has shown its use for numerous indications, i.e. assessment of ascending aorta atherosclerosis, monitoring cerebral blood and diagnosing aortic dissection. The A-View method seems a promising tool for patients undergoing cardiac surgery or those suffering from aortic disease to direct (surgical) management and may eventually improve patient outcome.

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5

COMPARISON OF METHODS TO ESTIMATE CONFIDENCE INTERVALS OF PREDICTIVE VALUES OF DIAGNOSTIC TEST RESULTS IN A NESTED CASE-CONTROL DESIGN

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Comparison of methods to estimate confidence intervals of predictive
values of diagnostic test results in a nested case-control design.
Submitted

An essential step in the evaluation process of a (new) diagnostic test is to assess the diagnostic accuracy measures. An important measure is the predictive value, i.e. the absolute probability that the disease is present or absent given the test result (figure 1) (1-4). Typically, diagnostic accuracy studies use a cross-sectional design in a cohort of patients suspected of the disease under study, who undergo the new test (index test) and subsequently the prevailing reference standard (5, 6) .

An alternative for this full cohort design is the nested case-control design, in which the controls and cases are sampled from a pre-defined cohort (5-7). This design is particularly advantageous for diagnostic research purposes, when the prevalence of the disease is rare, when the index test is costly or difficult to assess, and when using stored (e.g. biological) material from existing cohorts to perform the index test (5, 6). Limitations, strengths and rationale of the nested case-control design are extensively discussed in the literature, mostly for etiologic research(7-9), but also recently for the evaluation of diagnostic tests (5, 6).

As an important aim in diagnostic research is to estimate the absolute probability of having the disease given test results (predictive values), the nested character of the design in a cohort with known size is essential. In non-nested or regular case-control studies, controls are sampled from a source population with unknown size. The prevalence of disease and hence the predictive values cannot simply be estimated. Only relative probabilities can be estimated. Absolute disease probabilities can be estimated from a nested design, where cases and controls are sampled from a pre-defined cohort with known prevalence of disease, by weighing with the inverse sampling fraction (figure 1) (6). The sampling fraction can be simply calculated as the prevalence of the cohort divided by the prevalence of the nested case-control sample.

However, the estimation of the standard error (SE) of the predictive values derived from a nested case-control diagnostic accuracy study is not straightforward. When simply using the standard formula for the SE of a proportion ($\sqrt{\frac{\pi(1-\pi)}{n}}$, with π is the proportion, here predictive value, and n the number of patients), the question is which value for n to use. The actual observed (measured) number of cases and controls does not correspond to the estimated proportion (too low). But simply using the upwardly corrected number of controls and (if also sampled) cases falsely increases the number as if they were all observed, yielding too small SE's.

Therefore, modifications have to be made to the standard formulas, to estimate the correct SE of the predicted values of a diagnostic index test from a nested case-control study.

A) Full study population, in general

		Disease +	Disease -	
Test Result	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	N

B) Full study population, example

		Disease +	Disease -	
Test Result	+	a	b_1	$a+b_1$
	-	c	d_1	$c+d_1$
		a+c	b_1+d_1	N_1

C) Nested case-control sample, in general

		Disease +	Disease -	
Test Result	+	30	100	130
	-	10	300	310
		40	400	440

D) Nested case-control sample , example

		Disease +	Disease -	
Test Result	+	30	10	40
	-	10	30	40
		40	40	80

Figure 1: Theoretical example of case-control sample, nested in a cohort with known size and prevalence of the disease. In a full-cohort approach, index and reference test results are assessed for all patients. The positive predictive value (PPV) is a/(a+b); the negative predictive value (NPV) d/(c+d) (table A). In a nested case-control design, one samples from the full cohort (commonly) all subjects with a positive reference test (cases) and a fraction (see cell b_1 and d_1, Table C) of those with a negative reference test (controls). The results of the index test are only retrieved or measured (e.g. in stored biological material) in the sampled cases and controls. The absolute disease probabilities can simply be calculated by weighing the denominator with the inverse sampling fraction: the PPV = a/(a+(1/sampling fraction*b_1), and the NPV = (d_1*1/sampling fraction)/(c+(d_1*1/sampling fraction)), with sampling fraction (b_1+d_1)/(b+d) (table C). For example, the PPV and NPV from the full study are 30/(30+100)=0.23 and 300/(10+300)=0.97 (table B). Applying the methods for the nested case-control sample with only 10% of all non-diseased patients yields the same results. Sampling fraction = (10+30)/(100+300)=0.1, PPV=30/(30+(10 * 10)) = 0.23, NPV = (30 * 10)/(10+(30 * 10))=0.97 (Table D).

Recently Mercaldo and colleagues published a method to estimate the SE of predictive values for a case-control approach(10). Besides the method by Mercaldo and colleagues we believe that several other methods can theoretically be used. We compared the method proposed by Mercaldo with five other methods. We studied several combinations of cohort prevalence and case-control ratios using empirical data of a large diagnostic study including a cohort of patients who were suspected of deep venous thrombosis.

Methods

Patient data

We used data from a published cross-sectional diagnostic study that collected a cohort of 2086 adult patients suspected of deep vein thrombosis (DVT) in primary care(11, 12). In brief, the general practitioners systematically documented information on patient history and physical examination. Physical examination included swelling of the affected limb and difference in circumference of the calves calculated as the circumference (in centimeters) of affected limb minus circumference of unaffected limb, further referred to as calf difference test. The calf-difference was considered to be abnormal if the difference in circumference between the legs was more then 3 cm. Subsequently, all patients underwent D-dimer testing. Repeated compression ultrasonography of the symptomatic leg was assessed in all patients to determine the 'true' presence (yes/no) of DVT (reference test).

In the present methodological study, we focus on the calf difference and D-dimer test as index tests. D-dimer level was measured either with the ELISA method (VIDAS, Biomerieux, France) or the latex assay method (Tinaquant, Roche, Germany) depending on the hospital to which the patient was referred. Based on previous research, D-dimer test was considered abnormal if the latex assay yielded a D-dimer level ≥400 ng/mL or ≥500 ng/mL for the ELISA assay(13).

Nested case-control samples

We first created a source population with patients from the original data set of N=2086 such that the prevalence of DVT was 0.1, to mimic a rare disease situation that commonly directs case-control studies (figure 2, line 1 and 2). Patients in the source population (n=1400) were drawn without replacement. Values estimated from this source population will later serve as the commonly unknown true parameter values (see below and Table 1). Subsequently, we created a cross-sectional cohort of 1400 patients that were drawn with replacement from our source population (cohort, figure 2, line 3). A nested case-control sample was then created from the cohort (figure 2, line 4). We included all patients with DVT (cases) from the corresponding cohort in the nested case-control sample, and an equally sized random sample from the subjects without DVT (controls): case-control ratio = 1:1. We repeated this 1000 times, by creating 1000 cohorts from the source population and hence 1000 nested case-control samples. In these 1000 samples we estimated the uncertainty of the predictive values of both index tests, using the six methods described below.

All this was also done for three other case-control ratios: 2 controls per case (ratio 1:2), 3 controls per case (1:3), and 4 controls per case (1:4).

Finally, the entire process of sampling of the source population and subsequent sampling of 1000 cohorts and 1000 nested-case control samples (with four different case-control ratios) was repeated for a source population with a DVT prevalence of 0.05 and 0.2.

Methods to estimate the uncertainty of predictive values of a diagnostic test from a nested case-control study

We compared six methods to estimate the 95% CI of the predictive values of the two index tests (D-dimer test and calf circumference difference) using the ultrasound as reference. We explain the methods for the predictive value of a positive result (positive predictive value = PPV), but they can similarly be applied to the negative predictive value (NPV). Notations used below, refer to those in figure 1.

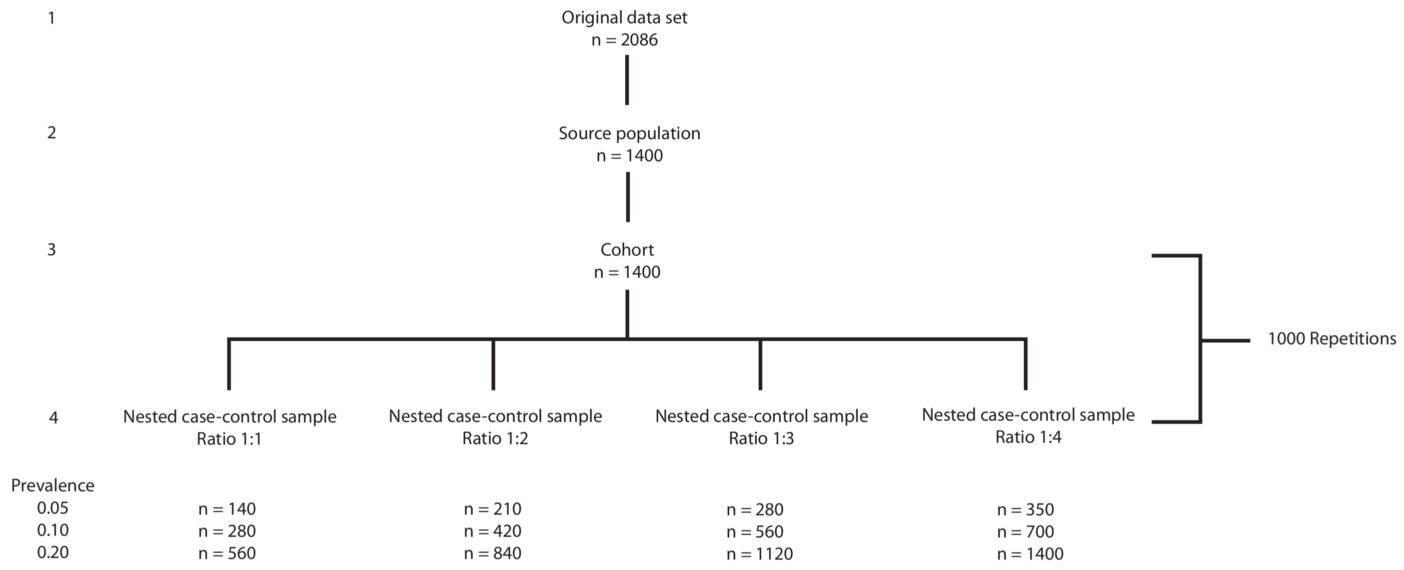


Figure 2: Flow-chart of the sampling process of the nested case-control samples. This process was repeated for a deep venous thrombosis prevalence in the source population of 0.05, 0.1 and 0.2. "n" in the nested case-control sample represents the average sample (cases plus controls) size across 1000 samples.

1. Estimate the standard error of the PPV (SE(PPV)) using the standard formula for the SE of a proportion with the actually observed number of patients in the nested case-control sample:

$$\mathrm{SE(PPV)} = \sqrt{\frac{\frac{a}{a+b_1} \bullet \frac{b_1}{a+b_1}}{a+b_1}} \qquad (1).$$

The 95% confidence interval can simply be calculated as PPV ± 1.96*SE(PPV). Calculating the SE with the actually observed numbers in the nested case-control samples (i.e. without correction for the sampling fraction that is used to estimate obtain the correct PPV, see figure 1), agrees to the number of patients actually measured. However, the proportions in the formula do not correspond to the estimated PPV.

2. Estimate the SE(PPV) using the standard formula for SE of a proportion with correction for the sampling fraction in the numerator of formula 1 above, but not in the denominator:

$$\mathrm{SE(PPV)} = \sqrt{\frac{\frac{a}{a+\frac{1}{Sampling\ \ fraction} \bullet b_1} \bullet \frac{\frac{1}{Sampling\ \ fraction} \bullet b_1}{a+\frac{1}{Sampling\ \ fraction} \bullet b_1}}{a+b_1}} \qquad (2).$$

The correction is only applied to the numerator as these reflect the (corrected) PPV estimates. Applying the correction also to the denominator, will make the SE too small: a larger number of patients than actually observed would then be used in the SE estimation.

3. Estimate the empirical confidence interval of the PPV using a bootstrap procedure. We drew 1000 bootstrap samples from the observed nested case-control sample and calculated the PPV for each bootstrap sample. The values corresponding to the 2.5 and 97.5 deciles equal the confidence interval limits.

4. The method recently described by Mercaldo and colleagues(10). This method uses the prevalence from the underlying cohort (not to be confused with our source population) and the sensitivity and specificity estimated from the case-control sample to calculate the correct PPV. Not only the PPV can be estimated using the sensitivity, specificity and prevalence, but also the SE(PPV):

$$\mathrm{SE(PPV)}^2 = \frac{[p \bullet (1-\mathrm{Spec}) \bullet (1-p)]^2 \bullet \frac{\mathrm{Sens} \bullet (1-\mathrm{Sens})}{a+c} + [p \bullet \mathrm{Sens} \bullet (1-p)]^2 \bullet \frac{\mathrm{Spec} \bullet (1-\mathrm{Spec})}{b_1 + d_1}}{[\mathrm{Sens} \bullet p + (1-\mathrm{Spec}) \bullet (1-p)]^4} \qquad (3)$$

The last two methods use a logarithmic scale.

5. Weighted logistic regression. This is an ordinary logistic regression model with outcome disease present (y/n) and one covariable (index test result, positive or negative), with weights for cases and controls. The model can be written as log odds(PPV) = $\log\left(\frac{ppv}{1-ppv}\right) = \alpha + \beta x$. With x =1 for a positive index test result.
Each case receives a weight w(cases) = N_1/N (rather than simply weight 1) and each non-case receives weight w(non-cases) = N_1/N*(1/sampling fraction). Hence, the sum of the weights over all sampled subjects equals the total number of subjects in the nested case-control sample (N_1). This sum equals the effective sample size in the estimations of the PPV and SE(PPV). Results of the weighted regression analysis are the intercept (α) and the regression coefficient for the index test (β). The standard error of the logit(PPV) can be calculated from the covariance matrix SE(logit[PPV]) = square root (variance(α)+variance(β)+ 2*covariance(α,β). The covariance matrix is estimated with the correct number of observed (N_1) patients, since case and controls were weighted in the analysis.

6. Use the method by Mercaldo and colleagues (method 4) (10) on the log odds scale. One uses the sensitivity, specificity and prevalence in the known cohort, to estimate the SE of the logit(PPV) by:

$$\mathrm{SE(logit(ppv)2} = \left(\frac{1-sens}{sens}\right) \bullet \frac{1}{a+c} + \left(\frac{spec}{1-spec}\right) \bullet \frac{1}{b_1+d_1} \qquad (4).$$

Statistical analysis

We estimated for each estimation method the 95% confidence intervals of the predictive values. The six methods were applied for both index tests and all four case-control ratios. The average 95% confidence interval width and the coverage probability were estimated from the 1000 nested case-control samples. The narrower the average confidence interval width, the more precise the estimated predictive value(14). The coverage probability is the proportion of the 1000 confidence intervals that included the true PPV estimated from of the source population. The coverage should not fall outside two SE's of the nominal probability (p) (14). Nominal p is 0.05 for a 95% confidence interval, with SE(nominal p) = 0.0069 for a simulation study with 1000 repetitions (Se(p) = $\sqrt{\frac{p(1-p)}{B}}$, with B the number of repetitions). The corresponding coverage ranges from 0.936 – 0.964.

If the coverage probability of the PV's falls outside this interval we speak of "substantial undercoverage" for lower coverage probability (<0.936), or overcoverage for higher (>0.964) coverage probability.

The ideal estimation method has a coverage probability close to 95% and a small 95% confidence interval of the estimated predictive values. Analyses were performed with R version 2.6.0 (15).

Results

Table 1 shows accuracy estimates of both index tests as estimated from the source population. The PPV of both tests was low and the NPV of both tests was high as a result of the low prevalence of DVT. For both tests PPV increased and NPV decreased with increasing prevalence of DVT. The D-dimer test was very sensitive with limited specificity. The calf difference test was moderately sensitive and specific. The D-dimer test was positive in 978 (70%) patients for a DVT prevalence of 0.1. The calf-difference test was positive in 568 (41%) patients. Changing the prevalence of diseases did not change the percentage of positive tests. As expected, for both tests, the sensitivity, specificity and diagnostic odds ratio were similar for each prevalence.

Prevalence of DVT	PPV	NPV	Sensitivity	Specificity	DOR	Positive test result (%)
D-dimer test (dichotomous)						
0.05	0.07	0.99	0.96	0.32	10.7	69
0.1	0.14	0.99	0.97	0.33	9.2	70
0.2	0.26	0.97	0.96	0.33	11.9	73
Calf-difference test (dichotomous)						
0.05	0.09	0.98	0.69	0.65	4.0	37
0.1	0.17	0.95	0.68	0.64	3.1	39
0.2	0.32	0.89	0.67	0.65	3.8	41

Table 1. Estimates of diagnostic accuracy of the D-dimer test and the calf-difference test in the source population for different values of the prevalence of deep venous thrombosis (DVT). PPV = positive predictive value; NPV = negative predictive value, DOR=Diagnostic Odds Ratio).

Method one, two and five showed clear overcoverage at low prevalences of 0.05 and 0.1 in the cohorts for all case-control ratios. They showed less overcoverage at a prevalence of 0.20 and even undercoverage (figure 4, method 5). Method three yielded slight overcoverage for lower case-control ratios (1:1, 1:2) and for low prevalence's (0.05 and 0.01). Method four and six showed undercoverage for higher case-control ratios (1:3, 1:4). Extreme undercoverage was seen at a prevalence of 0.20 (Figure 3 and 4, left panels) for both method four and six.

In general, method one showed the largest confidence interval width corresponding to the overcoverage, whereas method four and six showed very similar and small widths. Method three showed slightly larger widths then method four and six (Figure 3 and 4, right panels).

Discussion

We compared six methods for estimating the confidence intervals of predictive values of a diagnostic test when using a nested case-control design. The six methods were compared in terms of coverage and the width of the 95% confidence intervals, using simulations in an empirical study of patients suspected of DVT. Our data show that a bootstrap procedure (method 3) is slightly better then previously proposed methods (method 4 and 6). Methods 4 and 6 showed some undercoverage, particularly for the D-dimer test with frequent positive results (positive results around 70%). These two methods seem therefore less optimal for estimation of the standard error and thus confidence intervals of predictive values. For a prevalence of 0.2 in the underlying cohort and a case-control ratio of 1:4 all methods showed substantial undercoverage. In fact a case-control ratio of 1:4 implies a prevalence of 0.2 in the nested case-control sample. Hence, one may argue that a full cohort study is to be preferred, when the disease prevalence in the cohort is 0.2 or higher. Case-control studies are particularly advantageous when the prevalence of a disease in the cohort is rare (i.e. below 0.1).

By applying a nested case-control design in diagnostic accuracy studies the number of patients undergoing the index test can be substantially reduced, hereby increasing the efficiency of the particular study (5, 7, 8, 16). This becomes more important if the index test comes with large patient burden, is costly, the disease is rare, and when stored biological material is used for the index tests. Previously it has been shown that by applying a correction for the sampling fraction precise point estimates of the predictive values can be obtained (6). Applying a bootstrap procedure to estimate the confidence intervals yields adequate results for the uncertainty in the estimated predictive values. Limitation of this method can be that, due to the low numbers, in some of the bootstrap samples one of the cells of the 2x2 table remains empty. If this happens PPV may be estimated with a continuity correction for low numbers.

The predictive values obtained with Mercaldo and colleagues method were equal to those derived with the traditionally used method. The overall coverage of methods 4 and 6 was between 0.90 and 0.95 which were similar to those found by Mercaldo and colleagues themselves (10). The latter could be due to the fact that in our study the PPV was relatively low. With increasing case-control ratio, Mercaldo and colleagues method yielded more undercoverage. This could be due to the fact that in their original paper the case-control ratio was not explicitly varied, although in their equation the case-control ratio implicitly has influence on the SE and hence the confidence interval. Besides the study by Mercaldo and colleagues we are not aware of any other studies coping with this issue of uncertainty of predictive values estimated from nested case control studies.

A limitation of our study could be that we looked at only one original cohort in our simulations and studied only two index tests. Although the results for the different combinations simulated are alike, it is thinkable that for other combinations of cohort, prevalence and diagnostic accuracy the result could slightly differ.
By using a fixed cohort size (n=1400) for the different prevalence's the size of the nested case-control sample varied (Figure 2). This could have influenced our results since the SE and the confidence interval depends on the number of observations. Alternatively one could use a fixed number of cases in with varying cohort sizes for different prevalence's.

In conclusion, in diagnostic accuracy studies using a nested case-control design, one can apply a simple bootstrap procedure to obtain an adequate confidence interval for the absolute disease probabilities or predictive values of test results. The bootstrap procedure showed the best combination of coverage and 95% confidence interval width, compared with the other methods. Our findings and inferences similarly apply to studies investigating the predictive values of results from prognostic tests or biomarkers, in a nested case control setting.

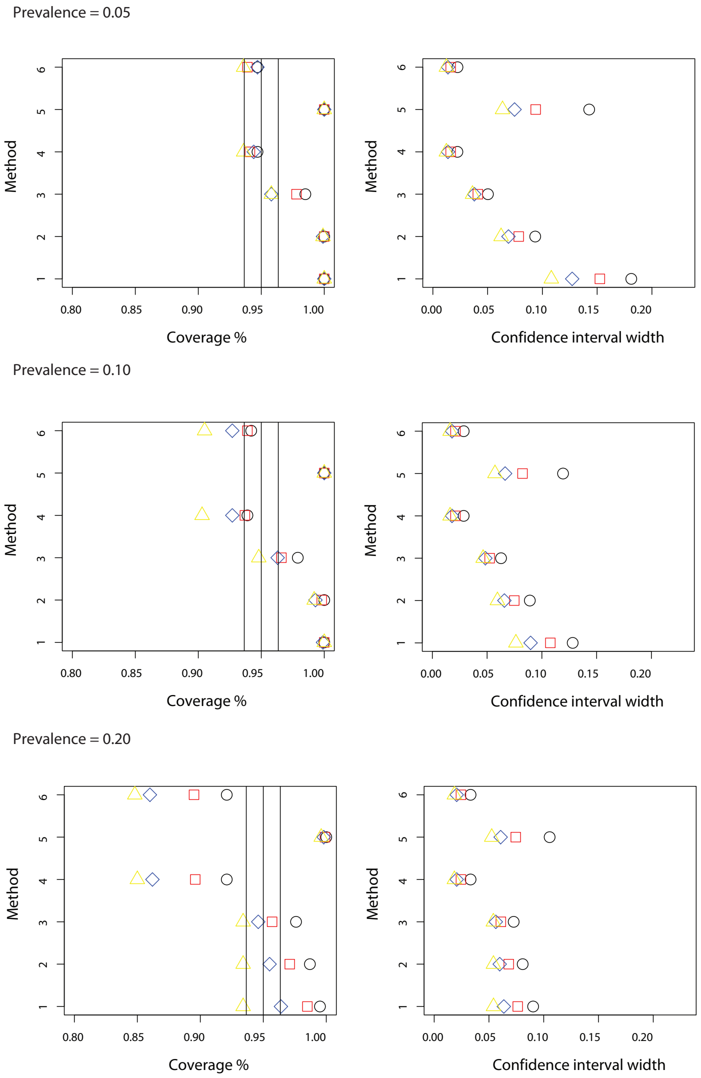
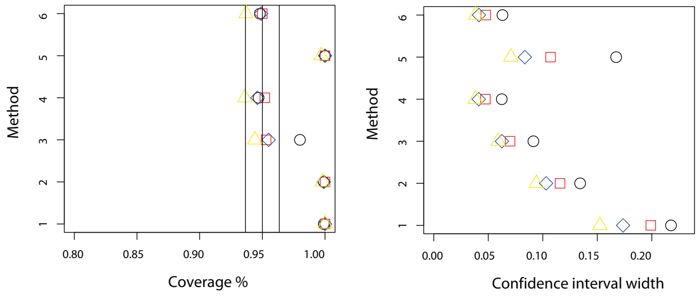
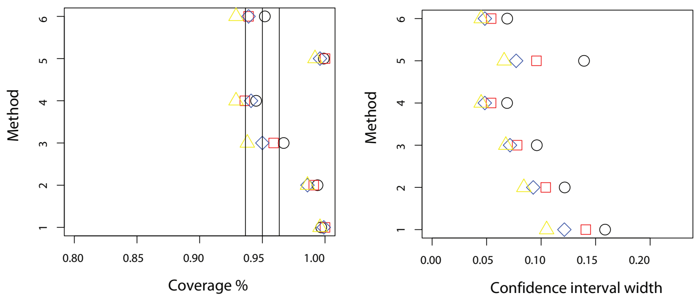


Figure 3: For each estimation method (for details see text) and per deep venous thrombosis prevalence, the plot of the positive predictive value coverage probabilities and the 95% confidence interval width, for the D-dimer test. 1 = Standard formula for obtaining a standard error of a proportion, 2 = as 1st method but with correction for sampling fraction, 3 = Bootstrap procedure, 4 = Mercaldo and colleagues method, 5 = Weighted logistic regression, 6 = Logit transformation of Mercaldo and colleagues method). Colors/figures represent the different sampling fractions (Circle = 1 case: 1 control, Square = 1:2, Diamond = 1:3, Triangle = 1:4). The vertical lines represent the ideal 95% coverage with its confidence interval, i.e. the levels of acceptability.

Prevalence = 0.05



Prevalence = 0.10



Prevalence = 0.20

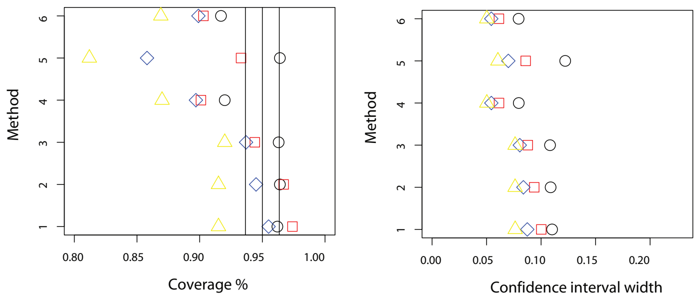


Figure 4: For each estimation method (for details see text) and per deep venous thrombosis prevalence, the plot of positive predictive value coverage probabilities and 95% confidence interval width per method for different prevalence's for the calf difference test (1 = Standard formula for obtaining a standard error of a proportion, 2 = as 1st method but with correction for sampling fraction, 3 = Bootstrap procedure, 4 = Mercaldo and colleagues method, 5 = Weighted logistic regression, 6 = Logit transformation of Mercaldo and colleagues method). Colors/figures represent the different sampling fractions (Circle = 1 case: 1 control, Square = 1:2, Diamond = 1:3, Triangle = 1:4). The vertical lines represent the ideal 95% coverage with its confidence interval, i.e. the levels of acceptability.

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6

DIAGNOSTIC ACCURACY OF MODIFIED TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR PRE-INCISION ASSESSMENT OF AORTIC ATHEROSCLEROSIS IN CARDIAC SURGERY PATIENTS

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Diagnostic accuracy of modified transesophageal echocardiography for pre-incision assessment of aortic atherosclerosis in cardiac surgery patients.
Submitted

Epiaortic ultrasound scanning of the ascending aorta is a safe and useful device to detect atherosclerosis in patients undergoing cardiac surgery. Combined with appropriate modifications of the operative technique based on epiaortic ultrasound scanning findings, notably less manipulations of the atherosclerotic aorta, the use of epiaortic ultrasound scanning can effectively reduce post-operative incidence of stroke when severe ascending aorta atherosclerosis is present(1-5). Although it is not widely used, epiaortic ultrasound scanning is considered the 'gold' standard for detecting atherosclerosis in the ascending aorta. However, epiaortic ultrasound scanning can only be applied during surgery, i.e. after sternotomy(6-12). If then the atherosclerosis appears more severe than anticipated, decisions regarding possible changes in surgical strategy have to be made at a relatively late stage. Preferably, such decisions are made pre-operatively, i.e. pre-sternotomy(13).

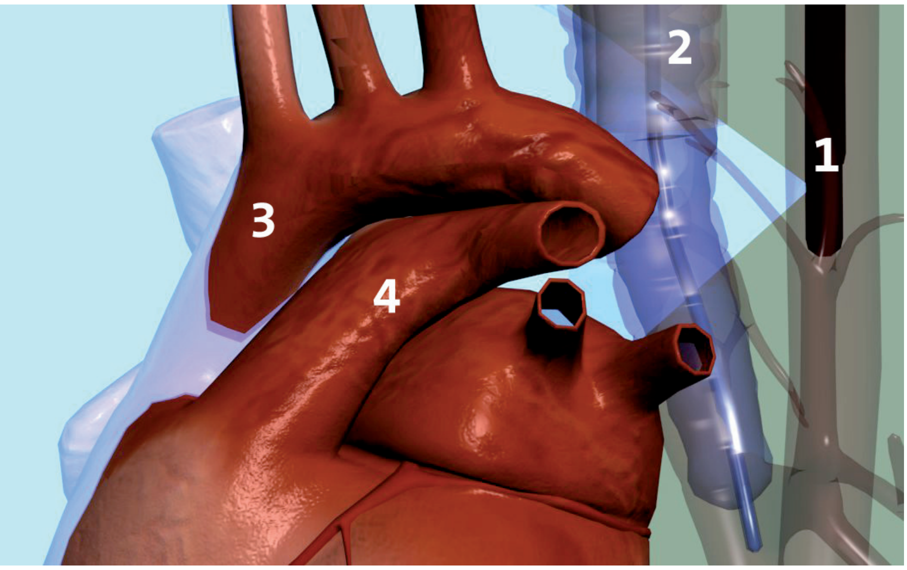

Figure 1: Overview of the mediastinum illustrating the anatomic interrelation of structures, the A-View balloon catheter and the transesophageal echocardiography (TEE) probe. 1. Esophagus with TEE probe and new ultrasound conducting window through blind spot; 2. Trachea and left main bronchus with A-View catheter; 3. Distal ascending aorta; 4. Pulmonary trunk.

Transesophageal echocardiography (TEE) is a widely used imaging modality permitting evaluation of the extent of atherosclerosis in the thoracic aorta before sternotomy. However, assessment of the distal ascending aorta using TEE is disturbed by the interposition of the air-filled trachea between the oesophagus and the ascending aorta: the so-called 'blind spot' (Figure 1)(9). Recently the A-View (Aortic-view) method was introduced as a modification of conventional TEE to overcome this limitation(14-16). The A-View method uses an intra-tracheal balloon (the A-View catheter, Cordatec Inc, Zoersel, Belgium) filled with saline to replace the air in the distal trachea and left main bronchus. Hence, it becomes possible to assess the distal ascending aorta and aortic arch for the presence and severity of atherosclerosis before cardiac surgery (Figure 1)(14,15).

The question arises whether pre-sternotomy use of the A-view method followed by the indicated (changes in) surgical strategy yields better patient outcome compared to surgery using epiaortic ultrasound scanning. Obviously, this requires a direct comparison of both strategies in a randomized follow-up study. This would include a large number of subjects given the relatively low incidence of post-operative stroke. Presently, it is too early for such trial. Alike therapies, also diagnostic devices should undergo a rigorous and phased evaluation before their introduction in practice(17-21). The first technical and safety evaluations, showed that the A-View method is indeed capable of visualizing the distal ascending aorta, and does not lead to unexpected complications due to the device (14). Subsequently, a diagnostic (cross sectional) accuracy study – here directly comparing the results of the A-view method with that of the epiaortic ultrasound scanning both applied in the same patients - is commonly executed. This was the purpose of the present study, to determine to what extent the A-View method can discriminate between cardiac surgery patients with and without aortic atherosclerosis, using the epiaortic ultrasound scanning as reference standard.

Methods

Study population

After approval by the institutional medical ethical committee and obtaining written informed consent, 465 consecutive patients above 65 years old, scheduled for elective cardiac surgery with a median sternotomy were included. Patients were included between May 2006 and December 2008. Excluded were patients with contra-indications to TEE (esophageal pathology and hiatus hernia), or contra-indications for the A-View method (i.e. severe COPD and tracheal stenosis)(14,15). This multicenter study was performed in one academic center (University Medical Center Utrecht, Utrecht, the Netherlands) and two general university affiliated teaching hospitals (Isala Clinics, Zwolle, the Netherlands, and Amphia Hospitals, Breda, the Netherlands). The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (1989) and Good Clinical Practice.

Design and Measurements

The study followed a cross-sectional diagnostic design. All consecutive patients underwent the same systematic work-up including the A-View method followed by epiaortic ultrasound scanning as reference standard (no partial or differential outcome verification) (22-24). Heart rate, mean arterial pressure, oxygen saturation, and end tidal CO_2, were continuously recorded. The study was designed as a pure diagnostic study, and no interventions were performed based on the results of the test under study (the A-View method). All treatment decisions were based upon current guidelines and routine clinical care practice.

The A-View method

The A-View method has been described extensively(14,15). In brief, after induction of anesthesia and intubation of the trachea, but before surgical incision, the A-View catheter was introduced through the endotracheal tube into the left main bronchus. After checking the correct position of the catheter by auscultation, and interrupting ventilation, the balloon was filled with 20-50 ml of sterile saline. During a short period of apnea (1-2 minutes) the A-View method was performed by retracting the TEE-probe (S7-2 omniplane TEE transducer, Philips, Eindhoven, the Netherlands, a transesophageal phased array transducer with 64 elements, with 7 to 2 MHz extended operating frequency range and with a field of view of 90 degrees.) from the mid esophageal aortic short axis view (15,25) until the distal ascending aorta and aortic arch with its side-branches was visualized (20-30 cm from the incisors) (Figure 2). To obtain optimal view the depth for imaging the ascending aorta was adjusted between 8 and 10 cm. When necessary, lateral flexion of the tip of the echo-probe was used to improve imaging quality. After completion of the investigation, saline was aspirated from the A-View catheter, the catheter was removed, and ventilation resumed. After removal of the A-View catheter the tip was inspected for the presence of blood. If blood was present on the catheter, bronchoscopy was performed to detect possible side effects caused by the A-View catheter. The A-View method was performed and interpreted online, by the attending anesthesiologist (observer), and thus the A-View method result was blinded for the results of the reference test (epiaortic ultrasound scanning) since the epiaortic ultrasound scanning result was not yet known.

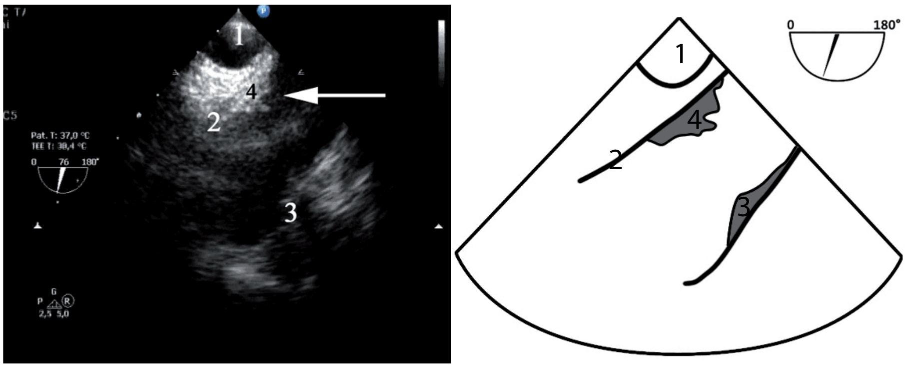

Figure 2: Distal, long axis view of the ascending aorta as imaged with the A-View method with plaque formation on the posterior and anterior wall (1= Trachea, 2= Posterior wall of distal ascending aorta, 3= Anterior wall of distal ascending aorta, 4= Mobile protruding atheroma indicated by the arrow).

The presence and severity of atherosclerosis of the distal ascending aorta were real-time documented by the observer (the attending anesthesiologist) using a five-point scale (grade I: normal aorta, grade II: extensive intimal thickening, grade III: protruding atheroma < 5 mm, grade IV: protruding atheroma > 5mm and grade V: mobile plaques (26)). Presence of evident ascending aorta atherosclerosis was defined as presence of grade III, IV and V and absence as grade I and II. For location of ascending aorta atherosclerosis the ascending aorta was divided in two segments, proximal (from the aortic valve until the right pulmonary artery) and distal (from the right pulmonary artery until the innominate artery).

Epiaortic ultrasound scanning (reference test)

Epiaortic ultrasound scanning was performed after sternotomy and opening of the pericardium before aortic cannulation by the cardiac surgeon. An epiaortic probe (L15-7io epiaortic probe, Philips, Eindhoven, the Netherlands, a broadband compact linear array transducer, with 15 to 7 MHz extended frequency range and with a field of view of 8 degrees of trapezoidal imaging) was placed on the ascending aorta, and short and long axis views of the proximal and distal ascending aorta were obtained. The epiaortic ultrasound scanning probe used contained a build in standoff that allows high-resolution imaging of both the anterior and posterior wall of the ascending aorta. epiaortic ultrasound scanning was performed by the attending cardiac surgeon, without knowledge of the results of the A-view method and interpreted afterwards by the anesthesiologist. To enhance direct comparison required for a diagnostic accuracy study, the epiaortic ultrasound scanning result for aortic atherosclerosis was coded following the same scoring categories as used for the A-View method.

Outcome

The primary outcome of our study was the presence or absence of clinically significant atherosclerosis (grade III to V) in the distal ascending aorta as determined by epiaortic ultrasound scanning. Secondary endpoints included the degree of aortic atherosclerosis according to above defined 5 point scale, and complications due to the use of the A-View catheter, notably cardiopulmonary side effects (such as tachycardia, hypoxemia and hypercarbia). Damage due to the placement of the A-View catheter into the trachea, and main left bronchus were actively sought and recorded.

Statistics

We, a priori, estimated that to find a sensitivity of the A-View method (for the primary endpoint) of 90% and to be able to exclude a sensitivity of 80% (standard error of 5%), 120 patients with clinically relevant atherosclerosis would be needed; using an alpha of 0.05 and a beta of 0.1. The same applies to the specificity. The frequency of clinically significant ascending aorta atherosclerosis (grade III to V) among patients undergoing cardiac surgery is estimated at about 30%. Therefore, inclusion of 465 patients would suffice for estimation of the hypothesized diagnostic accuracy parameters. We constructed contingency tables comparing the presence (and severity) of ascending aorta atherosclerosis based on the A-View method with the results from epiaortic ultrasound scanning (reference test). We estimated the positive and negative predictive value, sensitivity and specificity and both likelihood ratios with their 95% confidence intervals. This was done for each possible threshold along the 5 grades of aortic atherosclerosis. The degree of agreement between the A-View method and epiaortic ultrasound scanning for the 5 grades of atherosclerosis was also estimated, using the weighted Kappa-statistic. A total of 136 patients had values missing for one or more of the variables, 120 patients had missing data because one or both imaging modalities was not performed (for further explanation see results section and figure 3). The missing data per study variable ranged from 0.2% for hypertension to 29.2% for the end-tidal CO_2 and mean arterial blood pressure after use of the A-View method. Since data omission rarely occurs at random, it is widely acknowledged that simple complete case analyses not only leads to loss of statistical power, but more importantly also causes biased results (27-30). Hence, to obtain more valid results it is recommended rather to multiply impute missing values than to perform complete case analyses. Accordingly we imputed the missing values of all study variables by using multiple imputation in R version 2.6.0 (31) before executing the above analysis. The results of the complete case analysis are shown in appendix A for comparison purposes.

Results

The A-View method and epiaortic ultrasound scanning were performed in 345 out of the 465 patients (Figure 3). Imaging was not obtained because of unavailability of a trained observer (anesthesiologist) or due to logistical reasons of the planned surgical procedure. Table 1 shows the comparison of the subjects with data on one or both of the two methods missing versus the complete cases. As there were some differences between both groups, we thus multiply imputed the missing A-View and epiaortic ultrasound scanning results (see methods).

The mean age of the 465 patients was 74 (Standard Deviation 5.2) years. The study population consisted of 289 (62%) males and 176 females (38%). One hundred and twelve patients underwent isolated coronary bypass surgery, 107 had only valve surgery, 239 patients had combined bypass and valve surgery, and 7 had other surgical procedures performed.

The positive predictive value of the A-View method to detect clinically relevant atherosclerosis was 67%, and negative predictive value was 97%. The sensitivity was 95% and the specificity was 79% (Table 2).

The A-View method result overestimated the severity of atherosclerosis in 122 patients, and underestimated the severity of atherosclerosis in 17 patients (Table 3). For true grade I atherosclerosis, the A-View method result was in 20% (37/187) grade II and in 17% (32/187) above the threshold for our primary end-point, i.e.

grade III-V). Hence for our primary outcome it can be considered as 17% false-positive results. If the true grade of atherosclerosis was grade II, the A-View method had 26% (35/136) false-positive results. For grade III the overestimation was 13% (16/122).

Underestimation that changed the result, i.e. false-negative results, for grade III was there in 6% (7/122). There were no misclassifications for grade IV and V atherosclerosis (Table 3). The weighted Kappa statistic was 0.64 (95% CI 0.54-0.74).

Figure 4 shows the receiver operator characteristic (ROC) curve of the A-view method for the detection of atherosclerosis for each possible threshold in table 3. The area under the ROC curve was 0.89. By increasing the threshold for clinically relevant aortic atherosclerosis from grade I to III, the positive predictive value increased from 67 to 92% but at the cost of a reduction of the negative predictive value from 97% to 75% (Table 4).

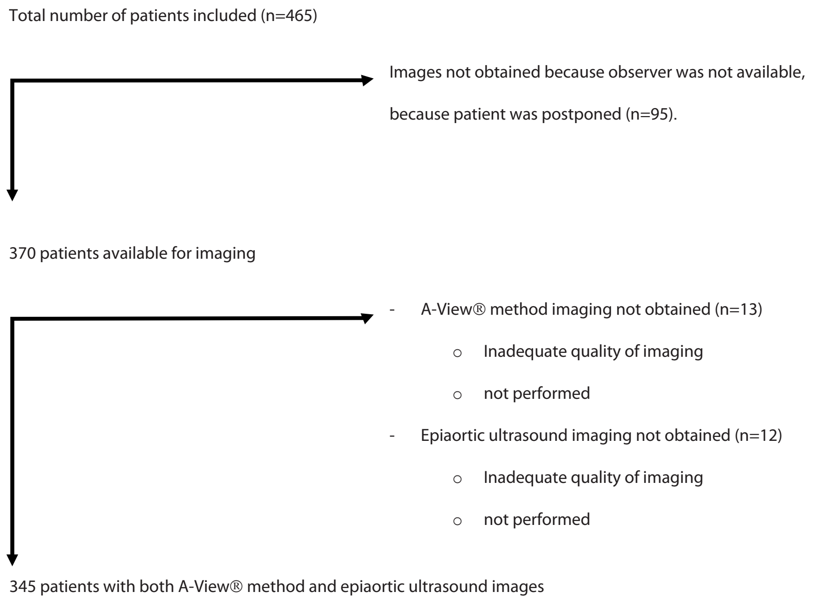

Figure 3: Flow chart of patient inclusion and obtaining images.

Safety

During the intraoperative use of the A-View method no clinical significant hemodynamic and ventilatory effects were observed (Table 4). In ten patients (2.9%) there was blood on the catheter. Bronchoscopy revealed insignificant mucosal bleeding without any additional interventions needed in all of these patients. We observed one unexpected severe complication. In one patient massive pulmonary hemorrhage was observed after weaning of cardiopulmonary bypass. This patient was admitted to intensive care and ventilated for several days. The patient was discharged from the intensive care and recovered without further sequelae.

	A-View method and epiaortic ultrasound scanning Images obtained (n=345)	A-View method or epiaortic ultrasound scanning Images not obtained (n=120)	p-value
Male (%)	209 (60)	80 (67)	0.13
Age in years (SD)	74 (5.4)	74 (4.7)	0.96
Height in centimeters (SD)	171 (10.0)	170 (9.3)	0.39
Weight in kg's (SD)	79 (14)	80 (13)	0.45
Creatinine (mmol/l) (SD)	98 (52)	106 (59)	0.15
Chronic pulmonary disease (%)	46 (13)	21 (18)	0.16
Peripheral vascular disease (%)	44 (13)	13 (13)	0.55
Neurological dysfunction (%)	43 (13)	15 (13)	0.54
Hypertension (%)	171 (50)	53 (45)	0.20
Left ventricular function (%)			
>50%	195 (57)	61 (54)	0.68
30-50%	122 (36)	43 (38)	
< 30%	23 (7)	10 (9)	
Recent myocardial infarction (%)	23 (7)	14 (12)	0.06
Diabetes mellitus (%)	79 (23)	23 (19)	0.65
Type of operation (%)			
CABG	91 (26)	21 (18)	0.007
Valve	85 (25)	22 (18)	
Combined	162 (47)	77 (64)	

Table 1: Patient demographics (SD = Standard deviation)

		Epiaortic ultrasound scanning		
		Presence	Absence	Total
A-View Method	Presence	135	67	202
	Absence	7	256	263
	Total	142	323	465

Table 2: Presence (Grade III, IV or V) versus absence (Grade I or II) of distal ascending aorta atherosclerosis visualized with the A-View method compared to the epiaortic ultrasound scanning result. Positive predictive value 67% (95% Confidence interval = 60% - 73%), Negative predictive value 97% (95% - 99%), Sensitivity = 95% (92% – 98%), Specificity 79% (75% - 84%), likelihood ratio of a positive test result = 4.6 (3.7 – 5.7), likelihood ratio of a negative test result = 0.06 (0.03 – 0.13).

		Epiaortic ultrasound scanning				
		I	II	III	IV	V
A-View method	I	118	10	3	0	0
	II	37	91	4	0	0
	III	31	33	99	3	0
	IV	1	1	15	9	0
	V	0	1	1	2	6

Table 3: Severity of distal ascending aorta atherosclerosis visualized with the A-View method compared to the epiaortic ultrasound scanning result (grade I: normal aorta, grade II: extensive intimal thickening, grade III: protruding atheroma < 5 mm, grade IV: protruding atheroma > 5mm and grade V: mobile plaques (26)). Weighted kappa statistic = 0.64 (95% Confidence interval = 0.54 -0.74).

	Before use of the A-View method	After use of the A-View method
Saturation, %	99 (1)	98 (3)
End-tidal CO_2, KPa	4.2 (0.5)	4.8 (0.6)
Heart rate, beats/min	66 (11)	68 (12)
Mean arterial pressure, mmHg	75 (13)	76 (12)

Table 4: Hemodynamic and ventilatory variables before and after the A-View method expressed as mean (Standard deviation).

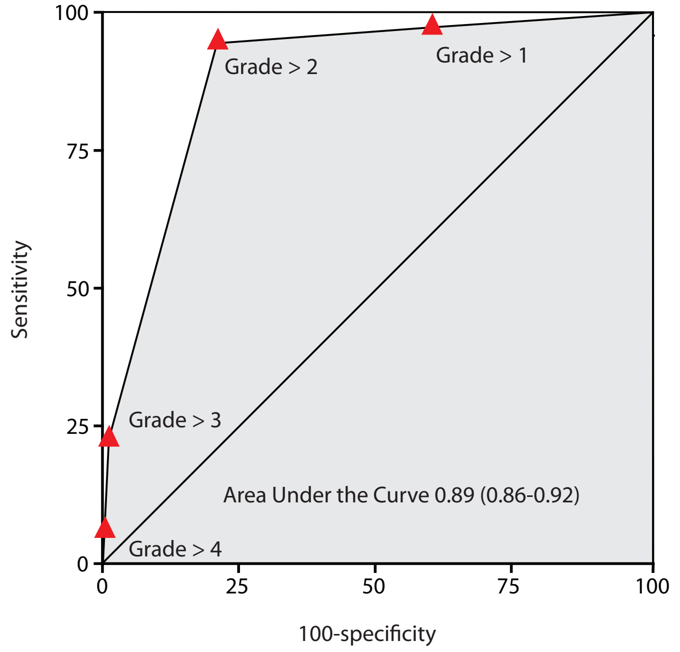

Figure 4: Receiver operating characteristic (ROC) curve of the A-View method result for the detection of atherosclerosis in the distal ascending aorta in patients undergoing cardiac surgery. Red triangles represent the different threshold values (see table 5 for the diagnostic accuracy parameters of each threshold).

Threshold	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Likelihood Ratio of a Positive Test	Likelihood Ratio of a Negative Test
Grade > 1	42 (36-47)	98 (95-100)	98 (96-100)	40 (34-45)	1.62 (1.48-1.78)	0.05 (0.02-0.16)
Grade > 2	67 (60-73)	97 (95-99)	95 (92-99)	79 (75-84)	4.58 (3.69-5.69)	0.06 (0.03-0.13)
Grade > 3	92 (83-100)	75 (70-79)	23 (16-30)	99 (98-100)	25.2 (7.8-80.2)	0.77 (0.71-0.85)
Grade >4	90 (71-100)	71 (67-75)	6 (2-10)	100 (99-100)	20.5 (2.6-160.1)	0.94 (0.90-0.98)

Table 5: Diagnostic accuracy parameters of the A-view method as compared to epiaortic ultrasound scanning for various thresholds expressed as percentage (95% Confidence interval) (see also figure 4).

Discussion

The A-View method showed good accuracy for determining the presence and absence of distal ascending aorta atherosclerosis. Depending on the threshold for presence of clinically relevant atherosclerosis, it seems notably suitable to exclude aortic atherosclerosis, given the high negative predictive value (97%) and sensitivity (95%). As diagnostic tests by themselves do not improve patient outcome, only via the treatment strategies indicated or chosen based on its results(32), it seems that one can safely proceed with surgery as planned in case of a negative result. If the result is positive for ascending aorta atherosclerosis, we recommend one should anticipate that changes to the surgical plan might have to be made to reduce manipulation of the ascending aorta.

Several issues require attention. First, not all included subjects underwent all measurements or images. The main reason was a change in the operation-schedule leading to unavailability of a trained observer of the A-View method and epiaortic ultrasound scanning. Although the characteristics between patients with and without missing A-View method or epiaortic ultrasound scanning results were only slightly different, we still aimed to reduce any potential for selectively missing values by multiply imputing the missing data. Furthermore, the results of the complete case analysis (on N=345) and the imputed analysis were very similar (appendix A). Since the prevalence of clinically relevant atherosclerosis was higher than anticipated, the complete case analysis still yielded the anticipated statistical power requiring at least 120 with (in fact 128 out 345) and 120 subjects without atherosclerosis.

Second, the epiaortic ultrasound scanning result was interpreted by the attending anesthesiologist, the same that interpreted the A-View method result. Not blinding the epiaortic ultrasound scanning result for the A-view method result could have influenced the interpretation of the epiaortic ultrasound scanning images: incorporation bias. To minimize the potential for incorporation bias, however, the results of the A-View method were not communicated to the surgeon that actually performed the epiaortic ultrasound scanning(18). Therefore, the surgeon did not actively search for an atherosclerotic plaque that was seen with the A-View method. Moreover, we found that the A-View method detected a higher degree of atherosclerosis in 122 patients. This also indicates that there was likely no incorporation bias. If the effect of incorporating the knowledge of the A-View result into the epiaortic ultrasound scanning reading would be large, one would expect that the result of the epiaortic ultrasound scanning was more often alike the A-View result. Hence we feel that the effect of not blinding the epiaortic ultrasound scanning image for the A-View method result was small.

Third, we used epiaortic ultrasound scanning as a reference standard rather than modern magnetic resonance imaging (MRI) and computer aided tomography (CT) scanners because epiaortic ultrasound scanning is at present the most widely used reference standard for this disorder. MRI and CT have limited application and availability in routine care of cardiac surgery patients. Even more importantly, they are not capable of providing real-time images of the ascending aorta to direct immediate changes in surgical strategy.

Finally, when introducing a new observer dependent diagnostic test, it always takes time to develop the skills needed to acquire and interpret its results. Before patient inclusion started, the participating observers received additional training on the A-View method. We found a short and steep learning curve probably because the A-View method is just an extension of conventional TEE known to anesthesiologists for years. To test the influence of learning effects further, we repeated the entire analysis without the first 5 patients per center. It yielded the same results for the accuracy of the A-View method.

Strengths of our study is that we performed a prospective study in which patients were consecutively selected based on their indication to undergo the index test (intention to test in practice), and all underwent the reference test irrespective (unselected) of the A-View method result(33). Retrospectively selecting study patients based on their "true" presence or absence of the disease or only those who completed the reference test commonly leads to the problematic and well-known partial and differential verification biases(22-24).

In 67 patients the A-View method showed clinical relevant atherosclerosis, which was not detected with epiaortic ultrasound scanning. This could be because the linear ultrasound beam of the epiaortic probe is smaller then the V-shaped TEE-probe ultrasound beam. Therefore, the A-View method allows imaging of a larger part of the ascending aorta, such that the chance to detect atherosclerotic plaques is higher. Furthermore, as the epiaortic ultrasound scanning probe is placed directly to the ascending aorta there may be limited visualization of the anterior wall of the ascending aorta, despite the build in standoff. Finally, due to the epicardial fold imaging of the innominate artery and its surroundings with epiaortic ultrasound scanning is limited, whereas the A-View method is capable of imaging this region without difficulty. Since this region is one of the preferential places for atherosclerotic plaques epiaortic ultrasound scanning may underestimate the presence and severity of atherosclerosis. The A-View method overestimated the presence of atherosclerosis depending on the severity (grade) of atherosclerosis in 13-26%. For those patients with a false-positive result this would lead to a more careful surgical strategy then planned, which can hardly be considered harmful after all. Most changes in surgical strategy are small, for example changing cross-clamping site or cannulation site.

In contrast to previous studies showing no unintended effects whatsoever(14,15), this study showed one patient who suffered from massive pulmonary hemorrhage. During introduction of the catheter a higher then normal resistance was felt. After finishing imaging the catheter was removed and a small spot of blood was seen on the catheter. Contrary to study protocol prescriptions, bronchoscopy was not considered necessary at that time. After weaning from cardiopulmonary bypass massive pulmonary bleeding was noted. The bronchoscopy performed at that time revealed a small mucosal tear without active bleeding. The patient was admitted to the intensive care and remained there for several days with severe respiratory failure due to extensive clot formation in the lungs. He fortunately recovered completely without further interventions and without further sequelae. The most likely explanation for this pulmonary hemorrhage is the (traumatic) introduction of the A-View catheter into the left bronchus, which made a small bleeding tear during complete heparinization. In the patients in whom bronchoscopy was performed because of blood on the A-View catheter, there were only small mucosal bleedings. These did not need additional interventions. Use of bronchoscopy and subsequent therapy guided by its findings is advised for all patients who undergo the A-View method, and certainly in those patients who show signs of (mucosal) tracheal or bronchial bleeding, i.e. blood on the A-View catheter after removal from the trachea.

Viewing all the above, the question remains whether the use of the A-View method with so-directed surgery is indeed more cost-effective than the use of epiaortic scanning. Otherwise, whether the beneficial effects outweighs the risks of its use. This requires a randomized comparison between a strategy where patients are managed by the A-View method with subsequent surgical choices and a strategy with epiaortic ultrasound scanning and subsequent surgical choices, using a clinical relevant outcome (for example a reduction of embolic load or stroke)(32,34). The present study was not designed to study effects on patient outcome but solely to quantify the diagnostic performance of the A-View method with the epiaortic ultrasound scanning as reference.

To conclude, the A-View method yields adequate diagnostic accuracy in the detection of distal ascending aorta atherosclerosis without significant cardiopulmonary side effects provided that the A-View catheter is introduced carefully. The method seems capable to exclude atheroclerosis of the distal ascending aorta. A randomized study is needed to quantify whether its use is indeed more cost-effective compared to current care.

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Appendix A: Results of complete case analysis.

		Epiaortic ultrasound scanning		
		Presence	Absence	Total
A-View method	Presence	124	44	168
	Absence	4	173	177
	Total	128	217	345

Presence (Grade III, IV or V) versus absence (Grade I or II) of distal ascending aorta atherosclerosis visualized with the A-View method compared to the epiaortic ultrasound scanning result. Positive predictive value 74% (95% Confidence interval = 67% - 80%), Negative predictive value 98% (96% - 100%), Sensitivity = 97% (94% – 100%), Specificity 80% (74% - 85%), likelihood ratio of a positive test result 4.8 (3.7 – 56.2), likelihood ratio of a negative test result 0.04 (0.01 – 0.10).

		Epiaortic ultrasound scanning				
		I	II	III	IV	V
A-View method	I	111	9	3	0	0
	II	25	28	1	0	0
	III	31	10	92	2	0
	IV	1	1	14	8	0
	V	0	1	1	1	6

Severity of distal ascending aorta atherosclerosis visualized with the A-View method compared to the epiaortic ultrasound scanning result (grade I: normal aorta, grade II: extensive intimal thickening, grade III: protruding atheroma < 5 mm, grade IV: protruding atheroma > 5mm and grade V: mobile plaques (26)). Weighted kappa statistic (95% confidence interval) = 0.65 (0.53 -0.73).

	Before use of the A-View method	After use of the A-View method
Saturation, %	99 (1)	98 (3)
End-tidal CO_2, KPa	4.2 (0.5)	4.8 (0.6)
Heart rate, beats/min	65 (12)	68 (13)
Mean arterial pressure, mmHg	75 (13)	76 (12)

Hemodynamic and ventilatory variables before and after the A-View method expressed as mean (SD).

Threshold	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Likelihood Ratio of a Positive Test	Likelihood Ratio of a Negative Test
Grade > 1	56 (50-63)	98 (95-100)	98 (95-100)	55 (49-62)	2.2 (1.9-2.5)	0.04 (0.01-0.03)
Grade > 2	74 (67-80)	98 (96-100)	97 (94-100)	80 (74-85)	4.8 (3.7-6.2)	0.04 (0.01-0.10)
Grade > 3	91 (81-100)	69 (63-74)	23 (16-31)	99 (97-100)	17.0 (5.3-54.4)	0.78 (0.70-0.86)
Grade >4	89 (68-100)	64 (59-69)	6 (2-10)	100 (99-100)	13.6 (1.7-107.2)	0.94 (0.90-0.99)

Diagnostic accuracy parameters of the A-view method as compared to Epiaortic ultrasound scanning for various thresholds expressed as percentage (95% Confidence interval).

7

INTER- AND INTRA-OBSERVER VARIABILITY OF MODIFIED TRANSESOPHAGEAL ECHOCARDIOGRAPHY FOR PRE-INCISION DETECTION OF DISTAL ASCENDING AORTA ATHEROSCLEROSIS IN CARDIAC SURGERY PATIENTS

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Epiaortic ultrasound scanning combined with appropriate modification of surgical procedure can effectively reduce the incidence of post-operative stroke(1-5). Epiaortic ultrasound scanning is considered the "gold" standard for detection of atherosclerosis in the ascending aorta, but it can only be performed after sternotomy(6-12). Therefore, changes in surgical strategy, in case of unexpected severe atherosclerosis, have to be made during surgery, this limits the available options (13).

Indeed the most widely used imaging modality, transesophageal echocardiography (TEE), is capable of assessing the ascending aorta for atherosclerosis before and during cardiac surgery. However, assessment of the distal ascending aorta is hampered by the interposition of the air-filled trachea and left main bronchus between the oesophagus and the distal ascending aorta; to the so-called "blind spot"(9). The distal ascending aorta is the part where cannulation and cross-clamping takes place and where often atherosclerotic plaques are most often present. To overcome this limitation the A-view (Aortic-view) method (Cordatec Inc., Zoersel, Belgium), a modification of conventional TEE, was recently introduced(14,15). This new diagnostic method uses a saline filled balloon catheter to replace the air in the trachea hereby creating an ultrasound conducting window and the possibility of imaging the distal part of the ascending aorta.

Similarly to drug therapies or surgical procedures, diagnostic devices should undergo a rigorous and phased evaluation before their introduction into clinical practice(16-20). The technical and safety evaluations, showed that the A-View method is indeed capable of visualizing the distal ascending aorta, and does not lead to unexpected complications due to the device (15). Subsequently, a diagnostic (cross sectional) accuracy study, directly comparing the results of the A-view method with that of epiaortic ultrasound scanning both applied in the same patients was executed. This study showed good diagnostic accuracy, notably for exclusion of ascending aorta atherosclerosis with a negative predictive value of 97%, sensitivity of 95%, the positive predictive value of 67%, and specificity of 79%. This study addresses the test's reproducibility across (inter-observer variability) and within (intra-observer variability) of the A-view method.

Methods

Study population

This study was a sub-study of a larger multicenter study on the diagnostic accuracy of the A-View method. The study population, design and main (accuracy) results have been described. In brief, after approval by the institutional medical ethical committee and obtaining written informed consent, 465 consecutive patients above 65 years old, scheduled for elective cardiac surgery with a median sternotomy were included. Patients were included between May 2006 and December 2008. Excluded were patients with contra-indications to TEE (esophageal pathology and hiatus hernia), or contra-indications for the A-View method (i.e. severe COPD and tracheal dysfunction)(14,15).

The study was performed in one academic center (University Medical Center Utrecht, Utrecht, the Netherlands) and two general university affiliated teaching hospitals (Isala Clinics, Zwolle, the Netherlands, and Amphia Hospitals, Breda, the Netherlands). Per center there were one (Amphia Hospitals) or two observers (other centers).

The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (1989) and Good Clinical Practice.

Design and Measurements

The study followed a cross-sectional diagnostic design. All consecutive patients underwent the same systematic work-up including the A-View method followed by epiaortic ultrasound scanning as reference standard. The study was designed as a pure diagnostic study. The grading of atherosclerosis obtained with the A-view method was thus not directly used to guide surgical management. Before patient inclusion started, the participating observers received additional training on acquiring images with the A-View method. For the present study aims, all A-View method images were eventually stored on an external hard disk drive to allow for re-reading of the same patient images by the same observer (later in time) as well by different observers.

The A-View method

The technical details of the A-View method have been described in detail previously(14,15). In brief, after induction of anesthesia and intubation of the trachea, but before surgical incision, the A-View catheter was introduced by the attending anesthesiologist, through the endotracheal tube into the left main bronchus. After checking the correct position of the catheter by auscultation, and interrupting ventilation, the balloon was filled with 20-50 ml of sterile saline. During a short period of apnea (1-2 minutes) the A-View method was performed by retracting the TEE-probe (S7-2 omniplane TEE transducer, Philips, Eindhoven, the Netherlands) from the mid esophageal aortic short axis view (14,21) until the distal ascending aorta and aortic arch with its side-branches were visualized (20-30 cm from the incisors). To obtain an optimal view the depth for imaging the ascending aorta was adjusted between 8 and 10 cm. When necessary, lateral flexion of the tip of the echo-probe was used to improve imaging quality. After completion of the investigation, saline was aspirated from the A-View catheter, the catheter was removed, and ventilation resumed.

Epiaortic ultrasound scanning (reference test)

Epiaortic ultrasound scanning was performed after sternotomy and opening of the pericardium before aortic cannulation by the cardiac surgeon. An epiaortic probe (L15-7io epi-aortic probe, Philips, Eindhoven, the Netherlands) was placed on the ascending aorta, and short and long axis views of the proximal and distal ascending aorta were obtained. The epiaortic ultrasound-scanning probe used contained a built-in standoff that allows high-resolution imaging of both the anterior and posterior wall of the ascending aorta. Epiaortic ultrasound scanning was performed by the attending cardiac surgeon, without knowledge of the results of the A-view method. The presence and severity of aortic atherosclerosis were real-time documented by the observer (the attending anesthesiologist) using a five-point scale (grade I: normal aorta, grade II: extensive intimal thickening, grade III: protruding atheroma < 5 mm, grade IV: protruding atheroma > 5mm and grade V: mobile plaques (22)). Presence of clinically evident ascending aorta atherosclerosis was defined as presence of grade III, IV and V and its absence as grade I and II. For location of ascending aorta atherosclerosis the ascending aorta was divided in two segments, proximal (from the aortic valve until the right pulmonary artery) and distal (from the right pulmonary artery until the innominate artery).

Off-line Reading of the A-View method images

For the aims of this study we retrospectively selected 60 patients with clinically relevant atherosclerosis (cases) and 60 without, each as proven with the reference standard (epiaortic ultrasound scanning). Since severe atheromatous disease occurs infrequently, a sampling strategy was used to ensure an adequate spectrum of the disease at interest in the study population. Hence, we included all patients with grade IV and V, and a random sample of grade III patients (total 60 cases with clinically relevant atherosclerosis) in the subset. Furthermore, we sampled 30 patients with grade I and 30 patients with grade II atheromatous disease (total 60 subjects without clinically relevant atherosclerosis). Sampling was done randomly using R version 2.6.0 (23).

From these 120 subjects, each stored loop of the A-view method was reviewed by 4 different observers: 1 cardiologist and 3 anesthesiologists. Each observer scored the loops on the presence or absence of the primary and secondary outcomes (see below). All loops were provided in random order, and the observers were blinded for other patient information. The observers were all well experienced in TEE interpretation. If the loops were of insufficient quality to be judged interpretable, a score of "uninterpretable" was recorded. If one of the observers judged the quality of the loops insufficient this patient was excluded from further analysis. Per observer pair we used all patients of which the observer pair both graded the severity of atherosclerosis. To enhance comparison across and within observers as well as with the reference standard result, the A-View method result was coded following the same scoring systems for atherosclerosis as used for the reference standard described above. To study the intra-observer variability scoring of the loops was repeated after a washout period of 1 month.

Apart from the scoring scheme, for atherosclerosis we explicitly conducted no further discussion or consensus meeting among the observers prior to or during the reading session. This allowed us to study the inter- and intra-observer variability of the test, if it was introduced and used in practice as such, under the present conditions.

Statistical analyses

For studies on the inter- and intra-observer variability there are no formal sample size calculations. Comparable studies included 40 to 80 patients(24,25). The 120 subjects we have chosen lay well above the number of included patients in those earlier studies.

We compared the result of the first with the second reading (intra-observer variation) and the results of the first reading across different observers (inter-observer variation). For this, we used the Kappa-statistic. Kappa is a statistic that reflects the extent of agreement between observers beyond that expected by chance alone. A Kappa below 0.2 indicates slight agreement, a kappa of 0.2-0.4 fair, a kappa between 0.4-0.6 moderate agreement, a Kappa of 0.6-0.8 represents substantial agreement and a Kappa of 0.8 or greater represents excellent agreement(26). Subsequently we also compared the agreement in scoring for the secondary outcomes, the grading of severity over the five above defined atherosclerosis categories. For this we used the weighted Kappa statistic(26). In addition we calculated the proportions of agreement using the so-called proportion of overall agreement and the proportion of specific agreement (P*s*) according to *Fleiss JL*. The latter is a conditional probability, the probability that an observer will make an assignment to a certain category conditional on the same categorization of another randomly selected observer(27).

Results

Of the selected 120 loops, there were some loops considered to have insufficient image quality or were insufficiently scored. Depending on the observer pair, 93 to 113 patients were available for the analyses. Table 1 shows the distribution of atherosclerosis determined with the reference standard (epiaortic ultrasound scanning) in the sample subset.

	Aortic Atheroma Grade					
	I	II	III	IV	V	n
Sample subset	30 (25%)	30 (24%)	44 (37%)	11 (9%)	5 (4%)	120

Table 1: Distribution of atheromatous disease within the sample subset.

The mean age of the 465 patients in the original study-cohort was 74 (Standard Deviation 5.2) years. The study population consisted of 289 (62%) males and 176 females (38%). One hundred and twelve patients underwent isolated coronary bypass surgery, 107 had only valve surgery, 239 patients had combined bypass and valve surgery, and 7 had other surgical procedures performed.

Appendix A shows per observer the absolute number of subjects scored over the five atherosclerotic severity classes, and all pair wise comparisons of these scores across and within each (first versus second reading) of the observers.

For the presence versus absence of clinically relevant atherosclerosis, the Kappa value ranged from 0.11 to 0.44 between the various observers (table 2) and from 0.38 to 0.61 within the different observers (table 3), indicating poor to moderate agreement across observers, and moderate to substantial agreement within observers.

Viewing the agreement over the 5-point scale, we found similar results. Poor to moderate agreement between observers (inter-observer variability) weighted Kappa values ranging from 0.11 to 0.37 (table 2). Fair to substantial agreement was there within each observer (intra-observer variability) with Kappa values ranging from 0.35 to 0.60 (table 3).

Observer pair	Presence vs Absence of Atherosclerosis	5 Category grading of Atherosclerosis
1 - 2	0.24 (0.05-0.43)	0.16 (-0.04-0.36)
1 - 3	0.25 (0.00-0.50)	0.26 (0.06-0.45)
1 - 4	0.44 (0.27-0.61)	0.37 (0.16-0.58)
2 - 3	0.11 (-0.09-0.31)	0.11 (-0.09-0.32)
2 - 4	0.28 (0.09-0.47)	0.18 (-0.03-0.38)
3 - 4	0.19 (0.00-0.39)	0.22 (0.02-0.42)

Table 2: Kappa values (95% confidence interval) for the primary outcome, presence versus absence of atherosclerosis (Middle column) and weighted Kappa values for the secondary outcome, grading severity of atherosclerosis across five categories (right column) for all inter-observer combinations (see appendix A for raw data).

	Presence vs Absence of Atherosclerosis	5 Category grading of Atherosclerosis
1 - 1	0.60 (0.44-0.75)	0.53 (0.32-0.75)
2 - 2	0.38 (0.19-0.56	0.35 (0.13-0.56)
3 - 3	0.39 (0.14-0.64)	0.36 (0.16-0.55)
4 - 4	0.61 (0.46-0.776	0.60 (0.38-0.81)

Table 3: Kappa values (95% confidence interval) for the primary outcome, presence versus absence of atherosclerosis (middle column) and weighted Kappa values (95% confidence interval) for the secondary outcome, grading severity of atherosclerosis across five categories (right column) for all intra-observer combinations (see appendix A for raw data).

The proportion of overall agreement was poor to moderate across the various observers with the proportion of overall agreement ranging from 28% to 48%, and moderate to substantial within observers (range 45% to 67%) (table 4). The proportions of specific agreement across observers ranged from 0.13 to 0.63, indicating poor to substantial agreement depending on the grade of atherosclerosis. The proportion of specific agreement was highest for grade 3 and 4 atherosclerosis (table 5, right panel). Within observers the proportions of specific agreement ranged from 0.15 to 0.74. Observer 4 scored overall the highest proportion of specific agreement. Similarly for the across observers proportion of agreements the highest proportions were found for grade 3 and 4 atherosclerosis (table 5, left panel).

	Within Observers				Across Observers					
Grade (A-View method)	1 -1	2 - 2	3 - 3	4 - 4	1 - 2	1 - 3	1 - 4	2 - 3	2 - 4	3 - 4
1	12	4	3	14	2	3	9	2	4	7
2	7	10	1	17	6	NA	6	NA	10	2
3	31	22	33	33	22	29	30	19	23	25
4	11	5	23	8	5	15	6	6	3	8
5	2	1	1	2	1	1	2	NA	NA	1
Total agreement	63	42	61	74	36	48	53	27	40	43
Proportion of agreement	56%	45%	56%	67%	35%	44%	48%	28%	41%	40%

Table 4: Overall agreement on grading of atherosclerosis within and across observer pairs. NA, not applicable, i.e. no patients were scored by both observers in this category.

	Within Observers				Across Observers					
Grade	1 -1	2 - 2	3 - 3	4 - 4	1 - 2	1 - 3	1 - 4	2 - 3	2 - 4	3 - 4
1	0.60	0.28	0.25	0.70	0.14	0.21	0.47	0.17	0.23	0.43
2	0.38	0.36	0.15	0.60	0.25	NA	0.29	NA	0.34	0.13
3	0.63	0.57	0.63	0.74	0.52	0.59	0.63	0.48	0.60	0.54
4	0.61	0.56	0.61	0.64	0.32	0.45	0.39	0.23	0.32	0.28
5	0.27	0.33	0.67	0.44	0.15	0.15	0.25	NA	NA	0.40

Table 5: Proportions of specific agreement (P*s*) on grading of atherosclerosis within and across observer pairs. NA, not applicable, i.e. no patients were scored by both observers in this category.

Discussion

We aimed to quantify the observer variability of the A-View method as if it would be introduced as such into daily practice, i.e. without elaborate or specific education of the observers on reading the loops. We found poor to moderate agreement across observers, and moderate to substantial agreement within observers for determining the presence versus absence of clinically relevant atherosclerosis. The Kappa value ranged from 0.11 to 0.44 between observers and from 0.38 to 0.61 within observers. Using the 5-point grading scale we found similar results.

Various studies have shown that epiaortic ultrasound scanning can prompt the surgical team to appropriate changes in surgical technique in the presence of severe ascending aorta atherosclerosis with epiaortic ultrasound scanning (1-5). Given that the A-view method is capable of acquiring images of the ascending aorta before sternotomy with good diagnostic accuracy(14,15), use of the latter might be an alternative to epiaortic ultrasound scanning to allow more timely decisions on surgical strategy. However, before introducing into clinical practice a new diagnostic test that requires observer interpretation and perhaps specific training in the interpretation of the images education one should demonstrate that the results can duplicated both within and across observers. The test must have at least moderate inter- and intra-observer agreement.

The poor to moderate inter-observer variability could be due to a number of factors. First, echocardiography is a dynamic investigation, which is strongly operator dependent for both the quality of the images and their interpretation. Each observer can acquire the desired optimal images according to his or her own standards and interpret those real-time. Hence, the ideal approach to quantify the amount of observer variation is to acquire images of the same patient by different operators while doing the investigation in the operating room (for inter-observer variation) or by the same observer but after some time (intra-observer variation). Obviously the latter is not possible, since the time interval between two readings by the same observer during the surgery can only be a few minutes. This would be much too small to rule out recall effects. For the quantification of the inter-observer variation such an ideal design is perhaps only theoretically possible. We considered it unethical to have four observers performing the investigation in the operation theatre, repeating the entire investigation four times. This would unnecessarily expose the patient for a longer period to the potential risks associated with the use of the A-View method(15). Hence, for this first observer variation study on the A-View method, we explicitly chose repeated interpretation of stored images. Instead of recording the complete examination as movie files, which would be second best, we could for technical reasons, only store loops with duration of two heartbeats (1-2 seconds) and not the complete examination. This was because the TEE machine did not have full-video recording facilities. This could also have hampered interpretation as some image information is only visible on longer loops, for example certain artifacts and whether or not mobile plaques are present.

Second, the four observers had different levels of experience and expertise with the A-view method, and this also could have introduced more variability in the scoring among and within observers leading to more disagreement.

Third, before the readings, we did not hold any consensus meeting to discuss the grading of the images and cut-off values to consider atherosclerosis as present or absent. Observers only received the written information from the researchers. As a consequence observers used their own interpretation and thresholds of grading aortic atherosclerosis. We chose for this design, as we aimed to study the interpretation of the A-View method as if it would be used as such by new users in their practice.

In retrospect, we may consider this also as a limitation of our study. A more extensive and plenary training of reading the A-View images (and notably the stored loops) seems indicated, and likely will reduce disagreement among observers. Furthermore, there were no clear definitions of the standard views of the A-View method that the operators should have obtained.

However, in previous studies on the reproducibility of TEE for detecting proximal ascending atherosclerosis there was uniformly high agreement between observers for interpretation of TEE, which indicates excellent reproducibility of TEE grading and stratification of aortic atheroma(25). As the A-view method is an extension of TEE, it is to be expected that also for the A-view method in the future higher agreement among (and within) observers will be found, using the appropriate training, images, and scoring tables.

Strengths of our study were that we excluded the possibility of incorporation bias, which can always influence diagnostic study results. We explicitly blinded the 4 different reviewers for the epiaortic ultrasound scanning results and for all other patient information. The epiaortic ultrasound scanning result and other information could thus not influence the A-View method interpretation of the off-line reading. Also the reviewers were unaware of the sampling fractions across the five different categories of atherosclerosis. Furthermore, the timeframe of one month between the two readings was sufficient to minimize incorporating the first within the second reading. If incorporation of the first within the second reading would have taken place, one would expect substantial more agreement within the observers, i.e. higher Kappa values.

To conclude, when experienced TEE echocardiographists were asked to rate the degree of atherosclerosis on loops of A-View method acquired views of the ascending aorta, there was moderate to substantial agreement within observers and poor to moderate agreement across observers. Given the promising diagnostic accuracy of the A-View method found in previous studies, further investigations to reduce observer variability is needed to enhance the applicability, and thus to improve the effectiveness of the method when used in practice. However, given the good observer agreement of the interpretation of conventional TEE images, it is likely that this will also be reached with the A-View method.

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Appendix A

The distribution of agreement in raw scores for observers grading the distal ascending aorta as imaged with the A-View method. Comparison of the observer pairs is presented separately in each table. The numbers in each cell represent the total number of observations for each grade of atherosclerosis in the distal ascending aorta.

	Grade	1	2	3	4	5
Observers 1 – 1	1	12	4	3	0	0
	2	5	7	1	0	0
	3	4	12	31	2	1
	4	0	1	7	11	0
	5	0	0	6	4	2

	Grade	1	2	3	4	5
Observers 1 - 2	1	2	7	4	2	0
	2	4	6	1	0	0
	3	7	13	22	3	1
	4	1	7	7	5	1
	5	0	4	5	0	1

	Grade	1	2	3	4	5
Observers 1 - 3	1	3	1	7	5	0
	2	4	0	6	2	0
	3	3	1	29	17	0
	4	1	0	4	15	0
	5	1	0	3	7	1

	Grade	1	2	3	4	5
Observers 1 - 4	1	9	5	2	0	0
	2	5	6	1	0	1
	3	7	10	30	2	1
	4	0	6	8	6	0
	5	1	2	4	3	2

	Grade	1	2	3	4	5
Observers 2 - 2	1	4	5	4	0	0
	2	9	10	15	0	0
	3	1	6	22	2	2
	4	2	1	2	5	0
	5	0	0	1	1	1

	Grade	1	2	3	4	5
Observers 2 - 3	1	9	5	2	0	0
	2	5	6	1	0	1
	3	7	10	30	2	1
	4	0	6	8	6	0
	5	1	2	4	3	2

	Grade	1	2	3	4	5
Observers 2 - 4	1	2	0	7	3	0
	2	6	0	15	15	0
	3	2	0	19	15	0
	4	1	0	3	6	0
	5	0	0	0	3	0

	Grade	1	2	3	4	5
Observers 3 - 3	1	3	5	3	1	0
	2	0	1	1	0	0
	3	4	5	33	6	1
	4	5	0	18	23	0
	5	0	0	0	0	1

	Grade	1	2	3	4	5
Observers 3 - 4	1	7	2	2	1	0
	2	0	2	0	0	0
	3	7	12	25	2	2
	4	6	12	18	8	1
	5	0	0	0	0	1

	Grade	1	2	3	4	5
Observers 4 - 4	1	14	5	2	0	0
	2	2	17	6	2	2
	3	3	5	33	3	1
	4	0	1	2	8	0
	5	0	0	1	1	2

8

COST-EFFECTIVENESS ANALYSIS OF MODIFIED TRANSESOPHAGEAL ECHOCARDIOGRAPHY TO ASSESS THE DISTAL ASCENDING AORTA IN CARDIAC SURGERY PATIENTS BEFORE INCISION

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van Zaane B
Nierich AP
Moons KGM

The incidence of ischemic stroke after cardiac surgery is about 3%, accounting for 20% of postoperative deaths(1-3). As the prevalence of atherosclerosis increases sharply with age from 10% in patients aged 50-60 years to at least 35% in patients older than 75 years, the post-cardiac-surgery stroke rate also increases to 7% in older patients(4,5). Post-operative stroke is often caused by emboli merging from atherosclerosis in the ascending aorta to the brain, as the ascending aorta is the place of cannulation and clamping(1,2,6-8).

Manual palpation, the most commonly used method to determine the ascending aorta atherosclerosis is not sensitive enough, may even be hazardous, i.e. it may dislodge vulnerable atherosclerotic plaques and can be used after sternotomy only(9).

Epiaortic ultrasound scanning has become the “gold” standard for detecting ascending aorta atherosclerosis. In combination with adaptation of the operative technique, epiaortic ultrasound scanning can effectively reduce the post-operative stroke rate(10,11). However epiaortic ultrasound scanning is infrequently used probably because it has to be performed during the operation, after sternotomy, and is not available in many centers. If ascending aorta atherosclerosis appears indeed more severe then anticipated, decisions regarding surgical strategy have to be made relatively late. Preferably, such decisions are made pre-operatively.

Transesophageal echocardiography (TEE) is a widely used diagnostic technique to visualize the extent of atherosclerosis before and during cardiac surgery (12). A major limitation of TEE is that it is not capable of imaging the distal part of the ascending aorta, due to interposition of the air-filled trachea between the oesophagus and the ascending aorta; the so-called blind spot(13). Recently the A-View method was introduced as a modification to conventional TEE to overcome this limitation. The A-view method uses a specially designed intra-tracheal balloon-catheter (the A-View catheter, Cordatec Inc. Zoersel, Belgium) to replace the air in the trachea with saline (14,15). Hence, it becomes possible to assess the distal ascending aorta for atherosclerosis before incision. A diagnostic (cross sectional) accuracy study, directly comparing the results of the A-view method with that of epiaortic ultrasound scanning, showed good diagnostic accuracy of the A-view method for the detection of distal ascending aorta atherosclerosis(16). However, the cost-effectiveness of the A-View method has not yet been assessed. In this study we investigated the cost-effectiveness on patient outcome of a strategy in which before incision the A-View method is used to detect to ascending aorta atherosclerosis with subsequent therapeutic decisions compared with the current strategy using post-incision manual palpation and subsequent decisions.

Methods

We used a Markov decision-analytical model and Monte Carlo sampling to assess the differences in longer term health benefits and costs of cardiac surgery which was adapted based on (a) the presence of atherosclerosis as detected with manual palpation after sternotomy (the manual palpation strategy) compared with (b) the presence of atherosclerosis as detected pre-sternotomy with the A-View method (the A-View strategy). We explicitly did not include conventional TEE in our comparison since manual palpation has a better diagnostic accuracy then TEE (9,17). Markov decision models are useful when events can occur at various points in time after being treated with the undergone strategy and with varying probabilities(18).

Model description

A Markov decision-analytical model is based on probabilities of transitions between health states. In our model the predefined health states were 'post cardiac surgery – well', 'post cardiac surgery – non-fatal stroke', and 'post cardiac surgery death'. To each health state we assigned a utility expressed in quality-adjusted-life-years (QALYs). The decision-analysis part of our model, estimated the fraction of patients that moved to each of these three health states (Figure 1A).

The Markov part of our model only served to determine the long-term costs and effects of the manual palpation strategy versus the A-View strategy (figure 1B). Individuals in the 'post cardiac surgery – well' state and the 'post cardiac surgery – non-fatal stroke' state could die from causes unrelated to the surgical procedure, and thus move to the 'death' state. Other state transitions were not incorporated into the model.

A large hypothetical cohort of cardiac surgery patients was run through the model with time cycles of one year. During each year, individuals were in a single health state. They could transit to other health states (i.e. die and move to the 'death' state) in subsequent years. Simulation stopped when all individuals had died. This model allowed us to simulate the life course of patients to assess the change in health benefits (QALYs) and costs for cardiac surgery guided by the A-View method versus manual palpation. Based on the difference in health benefits and costs we calculated the incremental cost-effectiveness ratio (ICER). The probabilities of the events in our model and the associated costs were the input parameters for the model (table 1). For these probabilities we added a distribution that represented the uncertainty around them. In the appendix, additional tables are provided that were used to model the cardiac surgery procedures (Appendix I-table 1A), the consequences of a major adaptation of the surgical procedures (Appendix I-table 1B), and the total costs of a non-fatal stroke event (Appendix I-table 2).

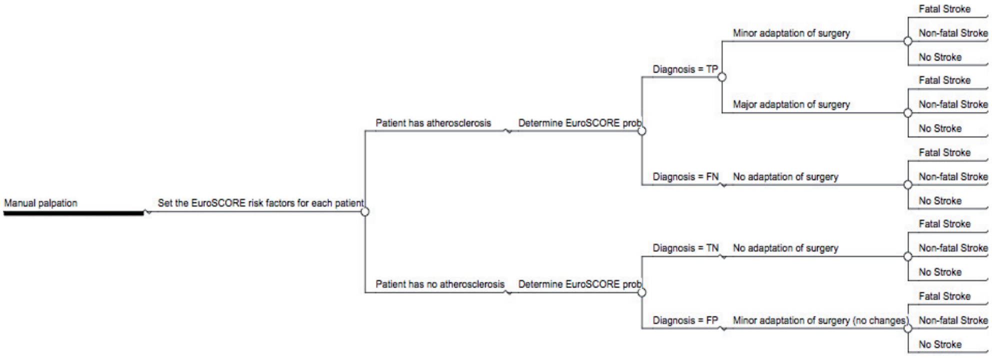


Figure 1a

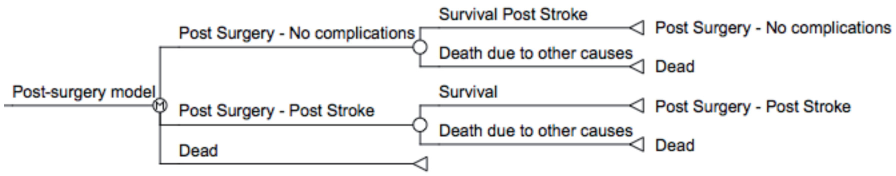


Figure 1B

Figure 1: Visualization of the decision-analytical part of the model for the manual palpation strategy [A], and the ensuing Markov part of the model [B]. The structure of the model for the A-View strategy is similar.

Input parameter	Value*	Range$	Uncertainty/ Assigned underlying distribution	Source
CostDeath	2,575	1,288 – 5,151	Uniform	Expert opinion(20)
CostDiagnosticAVIEW	200	-	-	Manufacturer
CostFatalStrokeEvent	2,575	1,288 – 5,151	Uniform	#
DiscountRateCosts	4%	-	-	Dutch guidelines
DiscountRateEffects	4%	-	-	Dutch guidelines
ProbOfMajorAdaptationOfSurgeryGivenAtherosclerosis	2.7%	2.3% - 3.1%	Beta(163/6051)	(19)
ProbThatAStrokeEventIsNotFatal	62.2%	46.3% - 76.9%	Beta(23,37)	(11)
ProbOfDeathAfterSurgery_AgeLessThan61	1.18%	0.82% - 1.42%	Uniform	(21)&
ProbOfDeathAfterSurgery_Age61to70	2.33%	1.95% - 2.71%	Uniform	(21)&
ProbOfDeathAfterSurgery_AgeGreaterThan70	4.35%	3.49% - 5.24%	Uniform	(21)&
utilPostStroke	0.439	0.186 – 0.653	Triangular	(22)^
utilWell	1	-	-	Default

*	All costs were recalculated to 2008 euros.
$	Range concerns the full range for uniform distributions and 95% confidence intervals for other distribution types.
#	The cost of a fatal stroke was assumed equal to the cost of death.
&	Values were recalculated from the actuarial survival curves by age in the source material.
^	Estimates of the utility of patients after major stroke vary widely; therefore a large range was used.

Table 1: The baseline values that were used as input parameters for the cost-effectiveness model, along with their range and distribution (if applicable).

In our model, major surgical adaptations were performed in 2.7% of all surgical procedures (19). Half of these were in patients undergoing CABG or single valve surgery procedure, and half complex CABG (> 2 arterial grafts), CABG + single valve or double valve procedure. The adaptations all consisted of ascending aorta replacement with CABG. The mean overall cost of surgery without adaptation equals € 23,475, and of surgery with major adaptation € 23,586

Accuracy of the two diagnostic strategies

For manual palpation we found a sensitivity of 31 % ([95% CI] 22% – 40%) and a specificity of 98% ([95% CI] 96% – 100%) when compared with epiaortic ultrasound scanning, in agreement with the literature (9). For the A-View strategy we previously reported a sensitivity of 97% ([95% CI] 94% – 100%) and specificity of 80% ([95% CI] 74% – 85%)(16). These estimates were thus used in our cost-effectiveness model.

Expected early mortality in cardiac surgical patients

Within the model we used the logistic version of the well-known and validated EuroSCORE risk equation to predict early (within 30 days) mortality in our patients(23-25) The prevalence of the risk factors included in the EuroSCORE was also derived from the literature(25) As the risks predicted by the standard EuroSCORE equation is substantially higher than observed in clinical practice in the Netherlands, we choose to modify the predicted risks for our cohort of patients(26). This was achieved by multiplying all predicted risks by a reduction factor of 0.29, a risk reduction of 71%. The relation between the predicted and the observed mortality was derived from a study by Svircevic et al(26).

Model assumptions

The following assumptions were made with respect to our cost-effectiveness model:

1. The prevalence of atherosclerosis depended only on age, not on gender.
2. All patients who die per- or post-operatively had a fatal stroke. Hence, the

predicted risk of death from the EuroSCORE equation was taken as the risk of a fatal stroke.

3. The beneficial effect from adapting the surgical procedure was similar for minor and for major adaptations and that only the costs differed with the degree of adaptation.
4. All patients with atherosclerosis in the ascending aorta that required adaptation (if detected) also had the risk factor extra-cardiac arteriopathy as defined in the EuroSCORE risk equation. Consequently, patients with atherosclerosis in the ascending aorta had a higher risk of dying then patients without.
5. The mortality rate for patients surviving a stroke during surgery was equal to patients who did not have a stroke.

Cost effectiveness analysis

We estimated the cost-effectiveness of the two strategies across various groups defined by well known determinants of life expectancy of surgical patients: gender, age (55, 65, 75 year old patients), and two estimates of the prevalence of distal ascending aorta atherosclerosis across the age categories: Low prevalence rates were 10%, 20% and 40% at age 55, 65 and 75 respectively, and high prevalence rates 15%, 30% and 50% respectively. We thus had cost-effectiveness estimates per strategy for 12 patients groups. For each patient group, a hypothetical cohort of 10,000 patients was simulated and the individual pathways of the patients were determined based on the above defined probabilities and corresponding distributions, along with the associated costs and effects for each patient(27). These were then averaged over the entire cohort. Per subgroup, this was repeated 5,000 times to account for sample uncertainty using Monte Carlo simulation based on the distributions defined in table 1. We defined two baseline groups: 65-year old men and 65-year old women, both with a prevalence of 20% atherosclerosis.

Results

As expected, for both the manual palpation strategy and the A-View strategy more adaptation occurred with increasing prevalence of atherosclerosis (Table 2). The risk of fatal and non-fatal stroke events also increased with this prevalence and with age, for both strategies. Obviously, the number of life-years after cardiac surgery decreased with patient age and with increasing prevalence of atherosclerosis for the manual palpation strategy but not for the A-View strategy. The risk of stroke was higher among women, as female sex is a risk factor in the EuroSCORE risk equation, though the life expectancy after surgery was still higher among women. For all patient subgroups the A-View strategy consistently resulted in more adapted procedures and, consequently, in a lower risk of stroke and a slightly higher number of life-years.

Given these figures, for the manual palpation strategy costs increased and effects decreased with increasing patient age and increasing prevalence of atherosclerosis. Age had a much larger influence on costs and effects than the prevalence (Table 3). For the A-View strategy, costs and effects also increased with increasing patient age, whereas the influence of the prevalence was almost negligible. For the 55-year-old patients, i.e. subgroups 1-4 (Table 3), the A-View strategy was (slightly) more expensive. The A-View strategy resulted in health benefits in all subgroups. Accordingly, the ICER was positive in subgroup 1-4 (i.e. the manual palpation strategy was more cost-saving and effective), with a maximum value of € 4937/QALY, and negative in all other subgroups. The cost-saving by the A-View strategy was higher for women, increased with patient age and with increasing prevalence of atherosclerosis. The same applied to the health gain only to a lesser extent. Figures 2A-C depicts the uncertainty surrounding the cost-effectiveness results shown in table 3. In all figures the largest proportion of the ellipsoids is located in the south-eastern quadrant of the CEA plane, indicating both cost savings and health gain in favour of the A-View strategy. Another substantial proportion of the ellipsoids fell in the north-eastern quadrant, indicating health gain at (though slightly) increased costs, less then € 700. A small proportion of points fell in the north-western quadrant, indicating increased costs and worse health outcomes for the A-View strategy. Comparing men and women in Figures 2A-C it appeared that the uncertainty was consistently larger for women than for men, and increased with the prevalence of atherosclerosis and age. Accordingly, larger proportions of the ellipsoids were located in the south-eastern quadrant. The probability of the A-View strategy resulting in cost saving and health gain became more certain although the exact cost-saving and health gain became more uncertain.

Subgroup	Gender	Age	% atherosclerosis	EuroSCORE predicted mortality risk	*Manual palpation strategy*					*A-View strategy*				
					Chance of minor adaptation	Chance of major adaptation	Risk of stroke		Life-years after surgery	Chance of minor adaptation	Chance of major adaptation	Risk of stroke		Life-years after surgery
							non-fatal	fatal				non-fatal	fatal	
1	Men	55 yr	10%	1,04%	5,00%	0,08%	1,12%	1,01%	23,04	27,69%	0,26%	1,01%	0,95%	23,08
2	Men	55 yr	15%	1,08%	6,38%	0,13%	1,20%	1,04%	23,02	31,43%	0,39%	1,04%	0,94%	23,08
3	Women	55 yr	10%	1,41%	4,99%	0,08%	1,52%	1,37%	26,07	27,71%	0,26%	1,37%	1,29%	26,13
4	Women	55 yr	15%	1,46%	6,41%	0,13%	1,63%	1,40%	26,02	31,37%	0,39%	1,40%	1,28%	26,11
5	**Men**	**65 yr**	**20%**	1,61%	7,81%	0,17%	1,84%	1,52%	15,13	35,03%	0,52%	1,52%	1,35%	15,21
6	Men	65 yr	30%	1,71%	10,61%	0,25%	2,05%	1,59%	15,09	42,48%	0,78%	1,58%	1,32%	15,20
7	**Women**	**65 yr**	**20%**	2,14%	7,82%	0,17%	2,44%	2,03%	17,44	35,07%	0,52%	2,03%	1,80%	17,55
8	Women	65 yr	30%	2,28%	10,61%	0,25%	2,74%	2,11%	17,37	42,45%	0,78%	2,12%	1,76%	17,55
9	Men	75 yr	40%	3,18%	13,40%	0,33%	3,98%	2,89%	8,65	49,87%	1,04%	2,90%	2,29%	8,81
10	Men	75 yr	50%	3,36%	16,20%	0,42%	4,35%	3,00%	8,61	57,28%	1,30%	3,01%	2,24%	8,81
11	Women	75 yr	40%	4,13%	13,43%	0,34%	5,13%	3,76%	10,33	49,84%	1,04%	3,77%	2,99%	10,57
12	Women	75 yr	50%	4,34%	16,21%	0,42%	5,62%	3,88%	10,27	57,27%	1,30%	3,90%	2,91%	10,57

Table 2: Expected costs and effects for the 12 predefined patient groups of patients (see text). For each subgroup the EuroSCORE predicted mortality risk is given, plus for both strategies the chance of adaptation of the surgical procedure, the risk of stroke and the expected number of life-years following surgery.

				Manual palpation strategy		*A-View strategy*		A-View strategy vs Manual palpation strategy		
Subgroup	Gender	Age	% atherosclerosis	Expected costs (€)	Expected effects (QALY)	Expected costs (€)	Expected effects (QALY)	Expected incremental costs (€)	Expected incremental effects (QALY)	Expected ICER (€ / QALY)
1	Men	55 yr	10%	26017	14.30	26116	14.32	99	0,02	4937
2	Men	55 yr	15%	26076	14.30	26124	14.32	49	0,02	2439
3	Women	55 yr	10%	26117	15.34	26194	15.36	77	0,02	3863
4	Women	55 yr	15%	26220	15.32	26234	15.35	14	0,03	466
5	**Men**	**65 yr**	**20%**	26842	10.74	26805	10.78	-37	0,04	-917
6	Men	65 yr	30%	27015	10.72	26860	10.78	-155	0,06	-2590
7	**Women**	**65 yr**	**20%**	27027	11.81	26940	11.87	-87	0,06	-1442
8	Women	65 yr	30%	27245	11.79	27012	11.87	-233	0,08	-2910
9	Men	75 yr	40%	28249	6.98	27830	7.07	-420	0,09	-4662
10	Men	75 yr	50%	28489	6.96	27912	7.07	-577	0,11	-5249
11	Women	75 yr	40%	29531	8.07	28737	8.20	-795	0,13	-6113
12	Women	75 yr	50%	29907	8.03	28854	8.20	-1052	0,17	-6191

Table 3: Cost and effect outcomes for each of the 12 predefined patient groups (see text). For both strategies the costs and effects are given, as well as the incremental costs and effects and the incremental cost-effectiveness ratio.

Figures 3A-C show the probability that the cost-effectiveness of the A-View strategy would be acceptable for various cost-effectiveness threshold (CET) values, i.e. maximum costs that a decision-maker might be willing to pay for a single additional QALY. Figure 3A shows that for 55-year-old patients this probability ranged from 10% for men (prevalence atherosclerosis 10%) to 41% for women (prevalence atherosclerosis 15%). Figure 3B shows that for 65-year-old patients this ranged from 57% for men (prevalence atherosclerosis 20%) to 84% for women (prevalence atherosclerosis 30%), and for 75-year-old patients this probability ranged from 92% for men (prevalence atherosclerosis 40%) to 97% for women (prevalence atherosclerosis 50%) (Figure 3C).

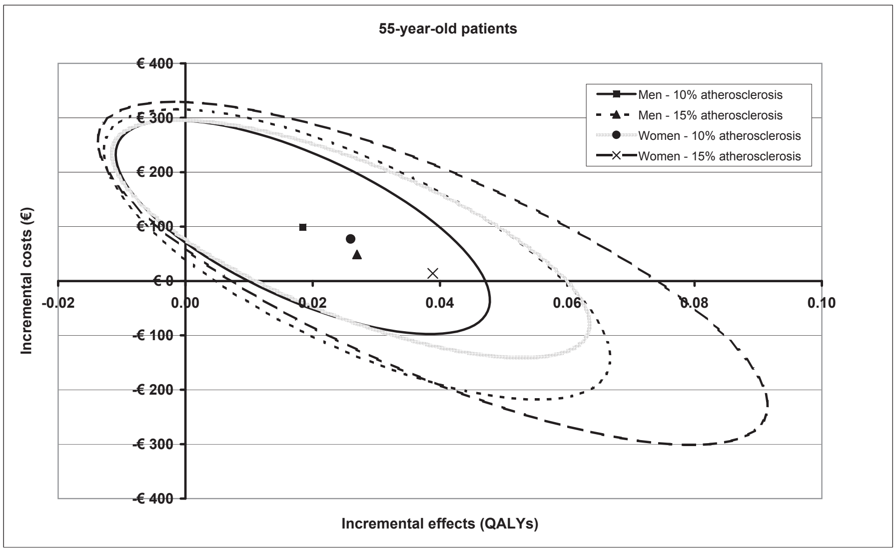
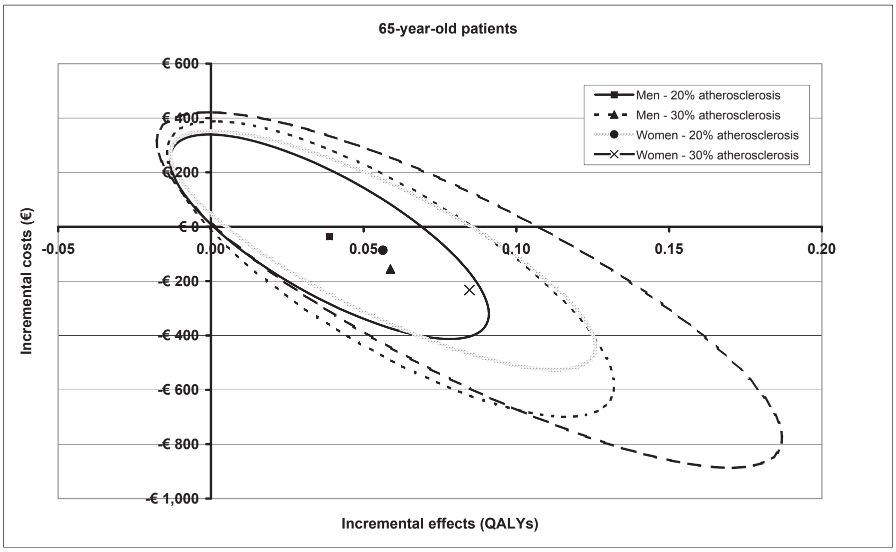


Figure 2A.

Figure 2: The cost-effectiveness plane with incremental costs and effects for 55-year old patients [A], 65-year old patients [B], and 75-year old patients [C]. These figures show the cost-effectiveness (CEA) plane for the 12 subgroups, with the additional effects of the A-View strategy on the horizontal axis and the additional costs of the A-View strategy on the vertical axis. Each subgroup is visualized by an ellipsoid that represents the combined bivariate 95% confidence interval (CI) for incremental costs and effects, and a symbol denoting the mean incremental costs and effects. The scales of the axes in Figures 2A-C are not similar, as the range of incremental costs and effects increases with patient age.



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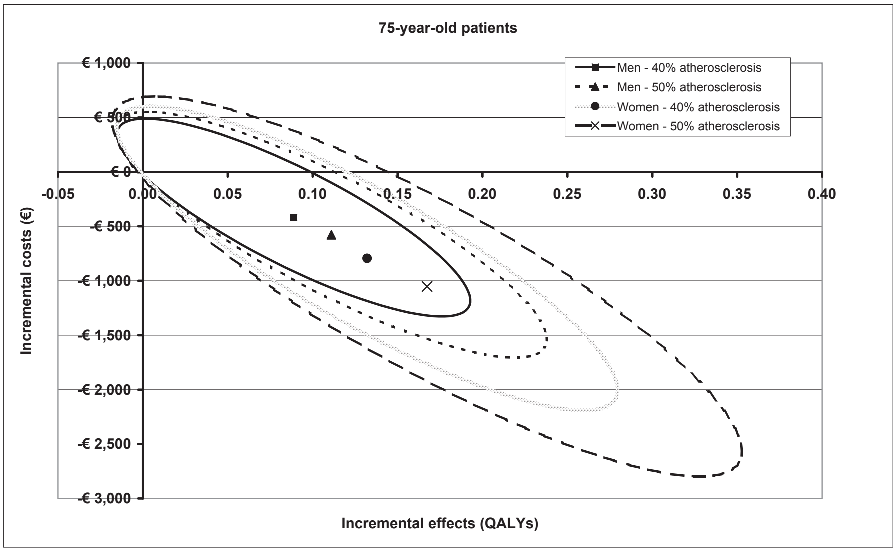

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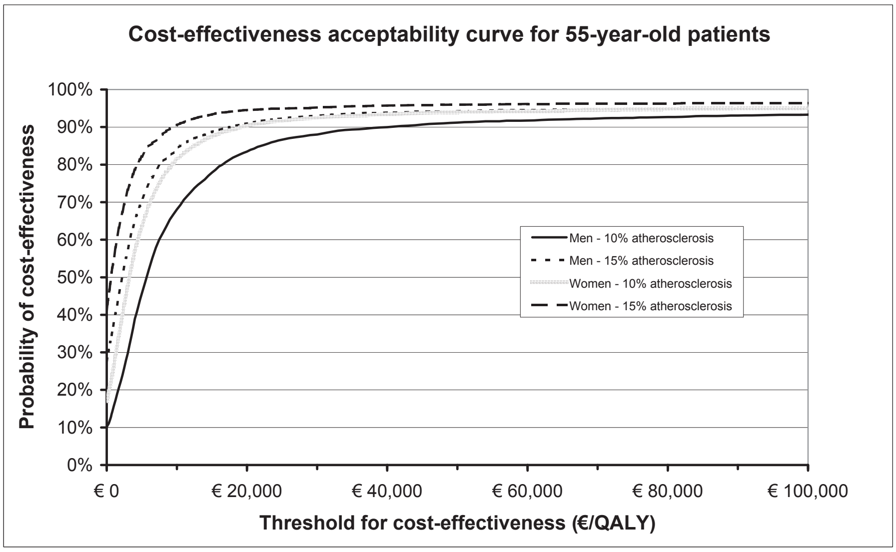

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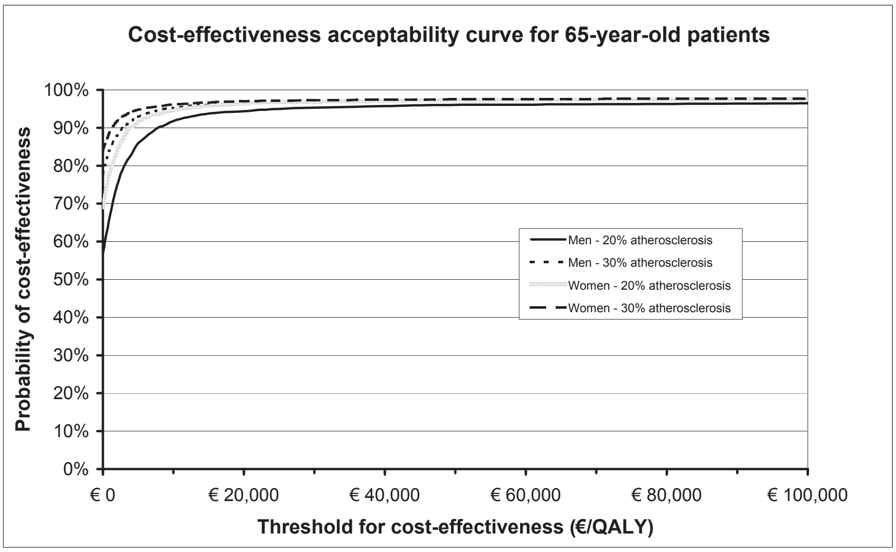

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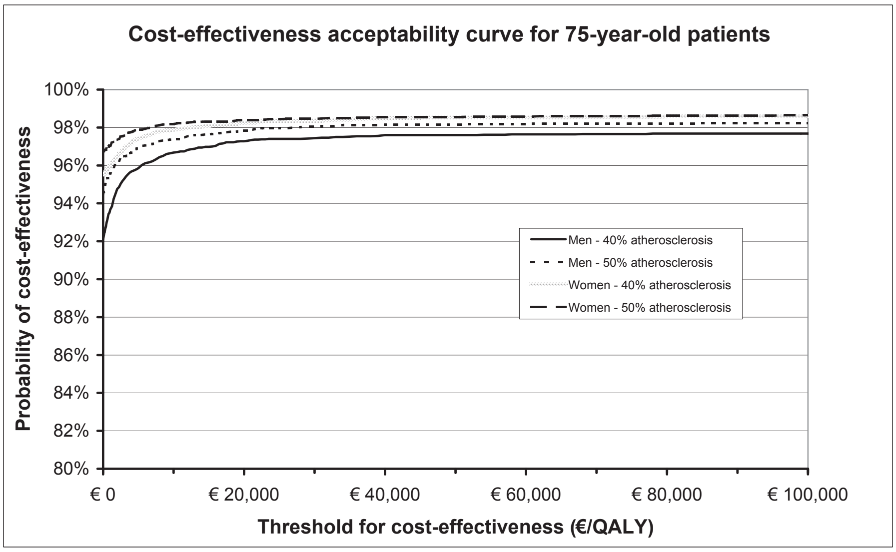

Figure 3C.

Figure 3: Cost-effectiveness acceptability curves indicating the probability that the A-View strategy is cost-effective compared with the manual palpation strategy, for 55-year old patients [A], 65-year old patients [B], and 75-year old patients [C], as function of a range of cost-effectiveness threshold values. The intersections of the curves with the vertical axis indicate the probability that the A-View strategy is cost-saving and results in health gain, i.e. the probability that the cost-effectiveness is still acceptable even if a decision-maker is unwilling to pay anything for additional health gain. Note that the vertical axis of Figure 3C was adjusted for clarity.

Discussion

The cost-effectiveness of the A-View strategy compared with the manual palpation strategy varies with patient age and gender, and with the prevalence rate of atherosclerosis of the ascending aorta. Nevertheless, results from our model based cost-effectiveness analysis shows that in comparison with manual palpation, the A-View strategy is expected to be cost-saving and beneficial in all patients undergoing cardiac surgery from the age of 65 years, also for conservative prevalence rates of atherosclerosis. In patients 55 to 65 year old, however, the A-View strategy is expected to result only in small health benefits at very low costs, though with an acceptable expected ICER. According to Dutch guidelines an intervention may be considered to have acceptable cost-effectiveness if the ICER falls below € 20,000 per QALY. The probability that this is indeed the case for the A-View strategy can be read from Figures 3A-C and ranges from 84% for 55-year-old men (prevalence atherosclerosis 10%) to over 97% for all 75-year old patients. The cost-effectiveness seems to improve with increasing age, which is uncommon, since potential health gain of medical interventions typically decreases with increasing age, commonly, elderly patients face death anyway, such that a substantial increase in (quality-adjusted) life-expectancy is often difficult to obtain. We have examined our results further in order to explain this effect. To this end we compared the risk of death from cardiac surgery as estimated by the EuroSCORE with the risk of death due to all causes in the general population as a function of age. This indeed shows that the potential health gain increases from age 60 years up to approximately age 85 years, and then starts to decrease again. The incremental costs of the A-View strategy are hardly influenced by age, thus the cost-effectiveness of this strategy can understandably improve with increasing age.

Limitations of our cost-effectiveness analysis

Our model has certain limitations. First, to obtain an estimate of the risk of death in patients with atherosclerosis in the ascending aorta after cardiac surgery we used the increased risk of patients with arteriopathy as based on the EuroSCORE. This assumption was necessary because rigorous data on the true excess risk of death due to atherosclerosis in the ascending aorta when undergoing cardiac surgery was not available from the literature. Testing this assumption in our sensitivity analyses revealed that decreasing the excess mortality risk due to atherosclerosis in the ascending aorta indeed resulted in less cost-effectiveness estimates of he A-View strategy, though still acceptable (certainly according to the Dutch threshold figure of €20,000 per QALY). Second there are no clear estimates of the prevalence of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery, certainly not as a function of patient age. We thus solved this issue by defining 12 different patient groups with two prevalence rates per age category. We found that the cost-effectiveness results were rather similar for both conservative (lower) and higher prevalence rates of atherosclerosis per age category.

Conclusions

In patients undergoing cardiac surgery older then 65 years, using the A-View strategy to pre-sternotomy diagnose the presence of aortic atherosclerosis and adjusting the surgical procedure based on the findings is likely to reduce health care costs and increase health benefits as compared to the current strategy where aortic atherosclerosis is often assessed by manual palpation after sternotomy. In some subgroups the A-View strategy is more expensive than the manual palpation strategy, though the cost-effectiveness was still acceptable.

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APPENDIX I

Surgical procedure	Description	Mean cost#
203	CABG or single valve	€ 21,259
204	Complex CABG , CABG + single valve, or Double valve	€ 27,243
205	CABG + complex valve, Aortic root replacement	€ 28,143
206	CABG + Aortic root replacement or triple valve	€ 29,638
207	Ascending aorta replacement with CABG	€ 28,363

Costs were recalculated to 2008 euros and included in-hospital post-surgery care.

	Final procedure (after possible adaptation)					Total fraction initial
Initial procedure	203	204	205	206	207	
203	0.6235				0.0135	0.637
204		0.3195			0.0135	0.333
205			0.01			0.01
206				0.01		0.01
207					0.01	0.01
Total fraction final	0.6235	0.3195	0.01	0.01	0.037	1

Appendix I table 1: Details of the predefined types of cardiac surgery procedures (top), and the occurrence of procedure types with the corresponding probability of a change of type (bottom). We incorporated both the probability of major adaptation and the associated changes in costs, separately for each of the original procedures. For example, almost 2/3 of all procedures are of type 203 and each of these procedures has a 1.35% probability of being adapted and become a type 207 procedure, due to detected atherosclerosis of the ascending aorta. Such an adaptation would then cause the costs to increase from € 21,259 to € 28,363, i.e. an increase of € 7,104.

	Event cost#		Annual costs after the event#	
Age category at the stroke event (years)	Men	Women	Men	Women
65	€ 23,272	€ 19,775	€ 5,166	€ 4,391
70	€ 24,925	€ 24,436	€ 5,646	€ 5,522
80	€ 20,345	€ 26,149	€ 4,620	€ 5,949
85	€ 20,030	€ 26,744	€ 4,604	€ 6,157

#All costs were recalculated to 2008 euros.

Appendix I - table 2: Event and annual cost of stroke, for men and women in different age categories(28)

Appendix II sensitivity and covariance analysis

Methods

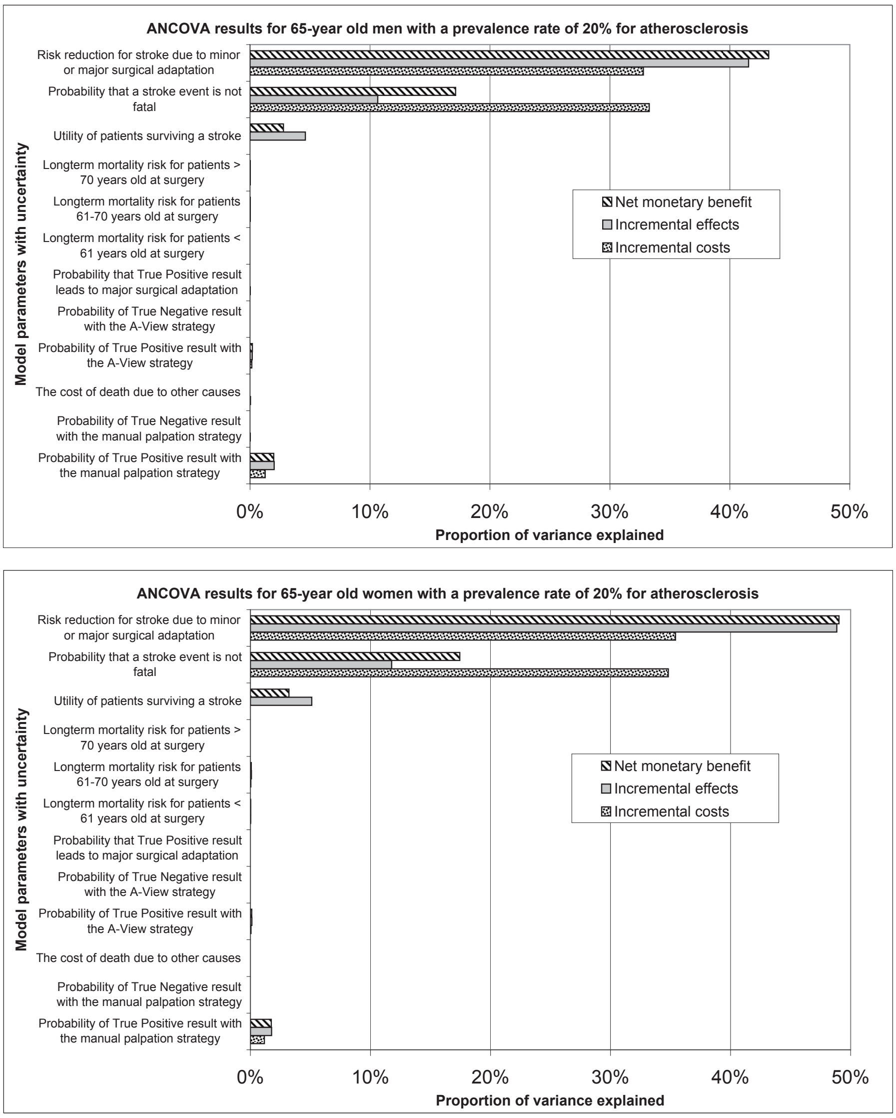
Sensitivity analyses were performed to investigate the effects of a discount rate of 1.5% per year, instead of 4% per year. Furthermore, the consequences of reducing the relative risk of 'arteriopathy' in the EuroSCORE risk equation by 50%, i.e., to exp(0.6558917*0.5) ~ 1.39, were assessed. Cost-effectiveness acceptability curves were used to visualize decision uncertainty(29). Analysis of covariance (ANCOVA) methods were applied to estimate the proportion of the variation in the model outcomes (i.e. costs and effects) that is 'explained' by variation in the individual input parameters(27). The R^2 statistic obtained from these methods relates the overall variance that is present in the model outcomes to the variance that can be explained by uncertainty in the individual input parameters, when a linear relation is assumed between model input and model output. A value of one for the R^2 statistic indicates that the linearity assumption is fully correct and that all variation in model outcomes can be explained by uncertainty in input parameters. A value less than one indicates that our model was (partly) non-linear, and only part of the variation in model outcomes can be explained by the uncertainty in input parameters.

Results

Aappendix II – table 1 shows the results of the sensitivity analyses applied to our two baseline subgroups (i.e. group 5 and 7 in the upper part of table 3). Decreasing the discount rate from 4% to 1.5% resulted in slightly larger cost-savings and health gain, causing the ICER to become more negative, in favour of the A-View strategy, for both men and women. Reducing the effect of arteriopathy in our model lowered the risk of stroke due to undetected atherosclerosis of the ascending aorta and therefore the benefits of the A-View strategy. For 65 year old men, the ICER was € 1,239/QALY and for women the A-View strategy dominated the manual palpation strategy. Appendix II Figure 1 depicts the results of the ANCOVA methods applied to our two baseline groups. Assuming a linear relation between model input and output values a large fraction of the variance in model output values could be explained, i.e. roughly 60-70% of the total variation in costs, effects, and net monetary benefit (NMB). Incremental costs, effects and NMB were influenced to the largest extent by the parameters 'risk reduction due to adaptation', and 'probability that a stroke event is not fatal', and to a lesser extent by the parameter 'utility of patients surviving a stroke'.

Gender	Age	% atherosclerosis	*Manual palpation strategy*		*A-View strategy*		A-View strategy vs Manual palpation strategy		
			Expected costs (€)	Expected effects (QALY)	Expected costs (€)	Expected effects (QALY)	Expected incremental costs (€)	Expected incremental effects (QALY)	Expected ICER (€ / QALY)
Men (discount rate = 1.5%)	65 yr	20%	27763	13.25	27687	13.30	-76	0,05	-1529
Men (beta arteriopathy halved)	65 yr	20%	26649	10.77	26686	10.80	37	0,03	1239
Women (discount rate = 1.5%)	65 yr	20%	28140	14.99	27992	15.06	-148	0,07	-2111
Women (beta arteriopathy halved)	65 yr	20%	26776	11.86	26773	11.90	-3	0,04	-73

Appendix II Table 1: Results from the sensitivity analysis with respect to discount rate and the relative risk of mortality associated with arteriopathy, in four additional subgroups. For both strategies the costs and effects are given, as well as the incremental costs and effects and the incremental cost-effectiveness ratio (ICER).



Appendix II - Figure 1: Results of the covariance analysis: the amount of variation in the model outcomes (i.e. costs, effects, and net monetary benefit (NMB)) that can be contributed to uncertainty in the individual input parameters. For the variation in NMB a cost-effectiveness threshold of € 20,000/QALY was used. All input parameters combined could explain 68% of the variation in costs, 59% of the variation in effects and 65% of the variation in NMB for men (top panel), and respectively 71%, 68%, and 72% for women (bottom panel). The length of the individual bars indicate the relative importance of the individual input parameters, i.e. the degree to which uncertainty in that particular input parameter is related to uncertainty in the model outcomes. The longest bars point towards parameters for which it is most relevant to reduce uncertainty as such a reduction would result in less variation in model outcome.

GENERAL DISCUSSION

9

A considerable number of patients undergoing cardiac surgery develop neurological complications ranging from subtle cognitive changes to clinically evident confusion, delirium, or stroke caused by atherosclerotic emboli(1-3). Atherosclerotic emboli are dislodged from the ascending aorta by manipulation during cardiac surgery. Timely identification and mapping of aortic pathology, preferably before sternotomy is crucial to implement appropriate changes in the surgical strategy. Indeed, improved diagnostic classification, i.e. accurate and timely identification of ascending aortic atherosclerosis, leads to improved treatment indications, and thus improved patient outcomes. The research described in this thesis was conducted to evaluate a possible improvement in diagnostic strategy, i.e. the A-View method, for ultrasound assessment of the presence and severity of atherosclerosis in the distal ascending aorta.

Main findings from this thesis

First, the A-View method offers a minimally invasive approach to preoperatively resolve the "blind spot" of TEE by replacing the air in the trachea, which hampers ultrasound conduction, with fluid by filling a endobronchial balloon-catheter (chapter 3 and 4) (4,5). Second, because of the very low sensitivity, conventional TEE seems not useful to exclude ascending aorta atherosclerosis before sternotomy (chapter 2). If the TEE result is positive, however, atherosclerosis can be considered present, and surgical strategies leading to less manipulations of the ascending aorta, such as off-pump surgery, might be indicated(6).

Third, the A-View method can be used without significant cardiopulmonary side effects, provided that the A-View catheter is introduced carefully (chapter 4 and 6). Fourth, the A-View method shows good accuracy for timely detection or excluding distal ascending aorta atherosclerosis. Depending on the threshold for presence of clinically relevant atherosclerosis, it seems suitable to exclude aortic atherosclerosis, given the high negative predictive value (97%) and sensitivity

(95%)(chapter 6). Diagnostic tests by themselves do not improve patient outcome, but they do when the treatment strategies are selected based on the results of a diagnostic test(7). It seems that one can safely proceed with surgery as planned in case of a negative A-View result. If the A-View examination is positive for ascending aorta atherosclerosis, one should anticipate that changes to the surgical plan have to be made to reduce manipulation of the ascending aorta. Fifth, the agreement across observers was poor to moderate, and the agreement within observers was moderate to good (chapter 7). Sixth, introduction of the A-View method may increase cost-effectiveness of cardiac surgery as compared to usual care (chapter 8).

Potential clinical impact of the A-View method

Modification of surgical management

Epiaortic ultrasound scanning, up to now the best available method to image the distal ascending aorta(6,8-14), leads to modifications in intra-operative surgical management in 4.1%-31% of patients undergoing cardiac surgery(15-20). Although not the aim of our diagnostic accuracy study, in 12% of the patients a modification of surgical treatment was made based on the epiaortic ultrasound scanning result (results not shown). As the A-View method is capable of adequately imaging the distal ascending aorta it is most likely that the rate of modifications of the surgical technique will be more or less the same as for epiaortic ultrasound scanning.

Aortic maneuvers, such as clamping or cannulation, can be associated with atherosclerotic embolization into the cerebral circulation, often resulting in vascular occlusion with concomitant stroke or cognitive decline(21). A large number of modifications to surgical technique have been proposed that may decrease the embolic risk, but no clear guidelines are established on when or where novel techniques should be employed. Moving cannulation and aortic cross-clamping away from the atherosclerotic sites may suffice(22). Some studies suggest that alternative cannulation sites and the use of different types of aortic cannulae can improve neurologic outcome. In addition to the above axillary artery cannulation has been suggested as a possible alternative in high-risk patients where cannulation is required(23,24). Nowadays a number of alternative techniques for standard cannulation are available ranging from the on-pump single or no aortic cross-clamp techniques to off-pump CABG with a "no touch" technique of the aorta with Y-grafts of the mammary arteries(25-27). Zingone and colleagues study, on aortic replacement in patients with severe atherosclerosis concluded that despite significant perioperative morbidity, replacement of the severely atherosclerotic aorta is worth consideration to avert expectedly higher death and stroke rates in patients undergoing valve surgery(28). Overall, most changes in surgical management consist of minor modifications, such as the aortic cannulation site or modifying the position of the aortic cross-clamp(29).

Atherosclerosis and stroke

An autopsy report involving 262 patients who had died shortly after cardiac surgery revealed presence of macro- and microhemorrhages, brain infarction, subarachnoid hemorrhages, and hypoxic brain damage in 49% of patients. The brain infarcts resulted from atheroemboli, fat or foreign body emboli, or from emboli originating from localized cerebral artery atherosclerosis(30). These findings were confirmed in studies using diffusion-weighted magnetic resonance imaging (DW-MRI). DW-MRI is a sensitive way to detect acute ischemic brain injury and to distinguish new from chronic brain lesions. New ischemic lesions were found in 26%-43% of patients and are related with neurocognitive decline after cardiac surgery(31-33). The relevance of these new lesions remains unclear, because many new lesions on DW-MRI are not associated with new focal neurologic deficit(33). But it also has been shown that elderly people with silent brain infarctions on DW-MRI have an increased risk of dementia and a steeper decline in cognitive function than those without such lesions(34). In accordance with this finding is Newman and colleagues' finding that early cognitive decline is a strong predictor of later cognitive deterioration (1).

At present acute post-operative cerebral infarcts are often considered to have occurred during or immediately after cardiac surgery, however a study by Maekawa and colleagues showed that in 4.5% of patients abnormalities are identified by DW-MRI already before cardiac surgery(35). Some of the per- and post-operative infarcts could therefore truly be a pre-operative infarction.

A small number of cohort studies have demonstrated that epiaortic ultrasound scanning was able to reduce perioperative stroke rates from 3% to 1% (29,36). The most dramatic advantage was observed in the "no touch" approach in patients with significant disease of the ascending aorta(16,25,36,37). Wareing and colleagues studied the stroke rate in patients with varying degrees of aortic atherosclerosis. In patients with moderate or severe atherosclerotic disease who only had minor modifications to their operation the stroke rate was 6.3%, whereas in 27 patients who had an ascending aortic replacement for severe atherosclerotic aortic disease there were no strokes. This study provides support for the hypothesis that minor modifications may be much less effective then major modifications in attempting to reduce the stroke rates in high risk patients(38). However, no definitive, mulitcenter, randomized trial has yet been performed on this issue.

Atherosclerosis and neurocognitive decline

The association between less aortic manipulations leading to a reduction of embolic load seems logical, although the evidence is inconsistent(17,20). Also, the link between cerebral embolization and neurocognitive dysfunction has been debated. In studies comparing on-pump versus off-pump coronary artery bypass grafting, a similar rate of cognitive decline was found despite a reduction of embolic load in the off-pump group(39-41).

However, the rate of cerebral embolization during cardiac surgery appears to be more related to the degree of atherosclerosis of the ascending aorta than to the number of manipulations(42,43). Therefore, several studies have tried to establish the relationship between the severity of atherosclerosis in the ascending aorta and neurocognitive decline after cardiac surgery(25,44-46). Goto and colleagues found a correlation between the extent of atherosclerosis and neurocognitive dysfunction(44). In studies by Royse et al and Hammon and colleagues, several modifications of surgical technique to reduce manipulation of a diseased aorta were investigated(25,45). They both found a reduction of the incidence of cognitive decline.

In contrast to the studies mentioned above, Bar-Yosef et al were not able to demonstrate a relationship between the extent of atherosclerosis and neurocognitive dysfunction(47). Although they avoided all the methodological flaws of previous studies, a major limitation of this study was the use of transesophageal echocardiography for the assessment of the ascending aorta instead of the reference standard (i.e. epiaortic ultrasound scanning)(6,8-14). This could have led to an underestimation of the severity and incidence of atherosclerosis in the distal ascending aorta.

Lessons learned

Introducing a new diagnostic device into clinical practice requires a thorough scientific evaluation (48-51).

Our very first study on the evaluation of the A-View method (chapter 3) was a small single observer study were the observer or operator of the A-View method was highly experienced, and involved with the development of the device(52). As often with imaging devices, using experienced observers commonly leads to an overestimation of the accuracy of the device. Given however, the promising initial results with the A-View method, we concluded it was ethical, necessary and safe to conduct additional studies in a larger series of patients using multiple observers to estimate more precisely the diagnostic accuracy and the intra- and inter observer variation of the A-View method.

In the subsequent large diagnostic accuracy study (chapter 6) we unfortunately encountered a considerable amount of missing data. However, most of these data were missing because there was a change in the operation-schedule leading to unavailability of a trained A-View observer. This often occurs in a busy cardiac anesthesia practice and can hardly be prevented. However the reason for missing indicated that the missing data was not completely at random. This was indeed confirmed by the slight differences between the patients with and without missing data. By multiply imputing the missing data we aimed to further reduce any potential for selectively missing values.

In the diagnostic accuracy study the epiaortic ultrasound scanning result was interpreted by the attending anesthesiologist, the same that a short time earlier interpreted the A-View method result (chapter 6). Although the surgeon, who was unaware of the A-View method result, performed the epiaortic ultrasound scanning, this still could have influenced the interpretation of the epiaortic ultrasound scanning images: incorporation bias. By not informing the surgeon we aimed to minimize this. The surgeon was not triggered to actively search for an atherosclerotic plaque that was seen with the A-View method. Moreover, we found that the A-View method detected a higher degree of atherosclerosis in 122 patients. This finding indicates that there was likely no incorporation bias. If the effect of incorporating the knowledge of the A-View result into the epiaortic ultrasound scanning reading would be large, one would expect that the result of the epiaortic ultrasound scanning was more often in line with the A-View result. Hence we feel that the effect of not blinding the epiaortic ultrasound scanning image for the A-View method result was small. To reduce incorporation bias we suggest that the reference standard (epiaortic ultrasound scanning) should not only be performed but also interpreted by an independent observer, for example the surgeon.

Transesophageal echocardiography and thus the A-View method is a dynamic investigation, which is strongly operator dependent, both for image quality and the interpretation of these images. In the diagnostic accuracy study (chapter 6) and in the observer variation study (chapter 7) images were obtained and reviewed by different observers with different levels of experience and expertise in the A-View method. We did realize that any new observer dependent diagnostic test requires time to develop the skills needed to acquire and interpret its results. We tried to minimize the effect of this learning curve by training all the participating observers, before patient inclusion started. However, despite this additional training the experience between different operators ranged from having performed 5-10 investigations to having performed a few hundred investigations. Also, when we started the studies included in this thesis there were no standard views of the A-View method and there had been no extensive plenary discussion on what was considered to be an adequate image of the distal ascending aorta. Furthermore, we had not discussed the grading of the images and when we would consider atherosclerosis as “present” or “absent”. In retrospect, we may consider this a limitation of our studies. This certainly may have had its influence on acquisition, and interpretation of the data, leading to increased diversity in acquiring, interpreting and the scoring of images among the observers than should be.

To minimize these limitations in future studies on the A-View method one should provide a more extensive and plenary training of performing and reading the new diagnostic technique to multiple operators. This will likely also reduce the number of missing data. Furthermore it may reduce the large differences in expertise, and certainly reduce the disagreement among the different observers. Previous studies on the reproducibility of conventional TEE for detecting proximal ascending atherosclerosis found uniformly high agreement for interpretation of the images(53,54). In one of these studies the authors also did not discuss or reached á priori consensus on grading atherosclerosis, similar to our studies(54). Conventional TEE is performed daily in cardiac anesthesia practice. As the A-View method is an extension of the conventional TEE examination, it is to be expected that also for the A-View method in the future higher agreement among (and within) observers can be reached, using the appropriate training, images, and scoring tables.

For the quantification of the observer variation the ideal design is to have each observer perform the complete examination in real time (for the interobserver variation) in the operation room and have him or her repeat the investigation after some time (intra-observer variation). Obviously the latter is not possible, since the time frame between two readings in the operating room is too small (only minutes) to rule out recall-effects. Repeating the examination by 4 different observers would expose the patient for a longer period to the potential risks associated with the A-View method, this was considered to be unethical. Hence, for the observer variation study (chapter 7) on the A-View method, we explicitly chose for repeated interpretation of stored loops. For technical reasons we could only store loops with a duration of two heartbeats (1-2 seconds) and not the complete examination, which would be second best. This was because the TEE machine did not have full-video recording facilities. This could have hampered interpretation of the loops since some information is only visible on longer loops, for example certain artifacts and whether or not mobile plaques are present, and thus decreased the observer agreement.

In the 386 included patients that underwent the A-View method in this thesis there were two (0.5%) unexpected events due to (the use of) the device. One patient had a decrease in arterial oxygen because of a dislodged endotracheal tube and one patient suffered a massive pulmonary hemorrhage. For the latter patient a protocol violation was observed. In contrast to the study protocol bronchoscopy was not considered necessary when blood was seen after removal of the catheter. Bronchoscopy could have prevented this complication by guiding treatment of the bleeding. We concluded that this event most likely was caused by the (traumatic) introduction of the A-View catheter into the left bronchus which led to bleeding from a small tear that increased during heparinization for extra corporeal circulation. As with therapeutic studies, diagnostic studies are almost never designed to obtain precise estimates of the unexpected event rates. The aim is rather to study in a (small) series of patients the safety of the device. Since there were some unintended effects we recommend as is common for drug therapies, additional safety and post-marketing studies.

Future Research

Given all the above, the evaluation process of the A-View method is not yet completed. Although the A-View catheter is commercially available, the inter- and intraobserver reproducibility of the A-View method should be improved by additional training and by creating consensus on the standard views, the grading of atherosclerosis and the standardization of data acquisition techniques. Furthermore, a study should be performed, which confirms the improved agreement (compared to the study presented in this thesis) and in which all the methodological flaws as earlier described are prevented.

If this can be shown, the question remains whether the use of the A-View method with surgery directed based on its results is indeed more cost-effective than care as usual. This requires a randomized comparison between a strategy where patients are managed by the A-View method with subsequent surgical choices and a strategy with care as usual and subsequent surgical choices, using a clinically relevant outcome (for example a reduction of embolic load or stroke) and additional modeling for the long term consequences and incremental cost-effectiveness ratio(7,55). The work described in this thesis was not designed to study effects on patient outcome but solely to quantify the diagnostic performance and the reproducibility of the A-View method with the epiaortic ultrasound scanning as reference standard.

In the studies included in this thesis, patient management was not directed by the result of the A-View method. Therefore, a logical next step is to investigate whether the use of the A-View method leads to changes in surgical management and subsequently a reduction of embolic events and clinical significant neurologic complications (stroke, cognitive decline, evident confusion or delirium). However, in our opinion it is still too early to design a large randomized study using clinically relevant outcomes as primary endpoint. This would first require a better inter- and intraobserver agreement, and a trial with over 2000 patients.

If the first requisite can be reached, an alternative to a full randomized trial using patient outcomes, is a randomized comparison between the A-view method with so-directed surgical management versus care as usual, using markers for the embolic load to the brain as primary outcome. The presence of embolic events in the brain can now be adequately measured with DW-MRI, a technique which has been widely used over the past years to identify the occurrence of embolic events after carotid stenting and more recently in cardiac surgery (31-33,42,56-58).

Furthermore, diagnosing a disease is nowadays considered to be a multivariable consecutive process starting with a medical history and physical examination, followed by more burdensome or costly diagnostic tests. Therefore, diagnostic research should aim to quantify which test increases or decreases the probability of having the disease based on the previous testing(51). If previous studies have satisfying results, the independent predictive contribution of the A-View method to existing diagnostic information in a clinical context can and must be quantified by a multivariable approach in subsequent studies and analyses as well.

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SUMMARY

10

Epiaortic ultrasound scanning of the ascending aorta is a safe and useful method to detect atherosclerosis in patients undergoing cardiac surgery. The use of epiaortic ultrasound can lead to modifications of the surgical technique notably less manipulations of the atherosclerotic aorta, which effectively reduces the post-operative incidence of stroke in case of severe ascending aorta atherosclerosis.
Although not widely used, epiaortic ultrasound scanning is considered the 'gold' standard for detecting atherosclerosis in the ascending aorta. However, epiaortic ultrasound scanning can only be applied after sternotomy. If then the atherosclerosis appears more severe than anticipated, decisions regarding possible changes in surgical strategy have to be made at a relatively late stage of the operation. In principle, it will be preferable to detect atherosclerosis in an earlier stage, i.e. pre-sternotomy.

Transesophageal echocardiography is a widely used imaging modality permitting evaluation of the extent of atherosclerosis in the thoracic aorta. However, assessment of the distal ascending aorta using transesophageal echocardiography is disturbed by the interposition of the air-filled trachea between the oesophagus and the ascending aorta: the so-called 'blind spot'. Recently the A-View (Aortic-view) method was introduced as a modification of conventional transesophageal echocardiography with the aim to overcome this limitation. An intra-tracheal balloon (the A-View catheter, Cordatec Inc, Zoersel, Belgium) filled with saline to replaces the air in the distal trachea and left main bronchus. Hence, it becomes possible to assess the distal ascending aorta and aortic arch for the presence and severity of atherosclerosis before cardiac surgery.

Various researchers investigated the ability of transesophageal echocardiography to discriminate between the presence and absence of ascending aorta atherosclerosis. It is acknowledged that transesophageal echocardiography has limited value in this, but it has never been supported by a meta-analysis estimating the true diagnostic accuracy of transesophageal echocardiography based on all quantitative evidence.

In **Chapter 2** this was done using state of the art methodology of diagnostic meta-analyses. We searched multiple databases for studies in which transesophageal echocardiography was compared to epiaortic ultrasound scanning for detection of distal ascending aorta atherosclerosis. A random-effects bivariate meta-regression model was used to obtain summary estimates of sensitivity and specificity, incorporating the correlation between sensitivity and specificity as well as covariates to explore heterogeneity across studies. In total 6 studies were extracted with a total of 346 patients of whom 419 aortic segments were analyzed, including 100 segments with atherosclerosis (median prevalence 25% (range 17% - 62%)). Summary estimates of sensitivity and specificity were 21% (95% CI 13 – 32%), and 99 % (96 – 99 %). We conclude that because of the low sensitivity of transesophageal echocardiography for the detection of ascending aorta atherosclerosis negative test results requires verification by additional testing using epiaortic ultrasound scanning. In case of positive test results, ascending aorta atherosclerosis can be considered present, and less manipulative strategies might be indicated.

It is widely acknowledged that in the scientific evaluation of a new diagnostic device, like the A-View method, a phased approach should be followed. After technical development and safety evaluation (first phase), but before investigating whether the test may replace current diagnostic techniques and actually improves the (cost)-effectiveness in terms of patient outcome, the test's reproducibility and potential discriminative accuracy must be quantified.

In **Chapter 3** the first phase of the evaluation process is described, i.e. whether the A-View method indeed visualizes the distal ascending aorta and the initial safety of this technology. In a cross-sectional diagnostic study, 41 patients undergoing cardiac surgery with sternotomy underwent the same work-up including transesophageal echocardiography, the A-View method, epiaortic ultrasound scanning and routine operative monitoring. With the A-View method the distal ascending aorta was visible in all (100%) patients. There were no clinical important side effects associated with use of the A-View catheter, however in one patient the endotracheal-tube was accidentally dislocated leading to a drop of oxygen saturation. Severity of atherosclerosis visualized with the A-View method compared to epiaortic ultrasound scanning results showed good agreement between the two methods (Kappa of 0.69 (0.50 - 0.88)). The Bland-Altman analysis showed poor agreement in plaque-size measurements (bias 0.05 cm2, limits of agreement -0.63 to 0.74 cm2). The A-View method offers a minimally invasive and safe approach to preoperatively resolving the blind spot of transesophageal echocardiography. Compared to epiaortic ultrasound scanning, the A-View method yielded satisfactory results in detection of ascending aorta atherosclerosis.

Chapter 4 describes the use of the A-View method, its standard views and the clinical indications and contra-indications of the method via various case reports. They include 4 cases with different types of distal ascending aorta pathology or monitoring indications such as distal ascending aorta atherosclerosis, vascular pathology such as aortic dissection or intramural hematoma and monitoring of cerebral blood flow.

In **Chapter 5** it is described that estimation of the confidence intervals of predictive values of diagnostic tests results in a nested case-control design is not straightforward. To obtain the correct estimates of these absolute probabilities, i.e. the predictive values, one applies a simple correction for the sampling fraction. But using this correction to calculate the corresponding standard error (SE) falsely increases the number of patients that are actually studied, yielding too small confidence intervals. Therefore, modifications have to be made to estimate the correct confidence intervals. We compared six methods for estimating the SE of predictive values in a nested case-control study, using simulations on empirical data from a large cohort among patients suspected of deep venous thrombosis. The methods were: 1. The standard formula for the SE of a proportion, 2. Adaptation of the standard formula with the sampling fraction, 3. A bootstrap procedure, 4. A method, which uses the sensitivity, the specificity and the prevalence, 5. Weighted logistic regression, and 6. Method 4 on the log odds scale. The methods were compared on the coverage probabilities and 95% confidence interval width of the predictive values. The bootstrap procedure appeared superior to all other methods showing a correct coverage probability, with a relatively small confidence interval width. To conclude, the bootstrap methods yields adequate confidence intervals for predictive values of diagnostic and prognostic test or biomarker results, in a nested case-control setting.

In **Chapter 6** the diagnostic accuracy of the A-View method in assessing atherosclerosis is quantified. In a cross-sectional diagnostic study, 465 patients over 65 years of age undergoing cardiac surgery underwent modified transesophageal echocardiography (the A-View method), epiaortic ultrasound scanning and routine monitoring. The positive predictive value of the A-View method was 67%, and the negative predictive value was 97%. The sensitivity was 95% and the specificity was 79%. One patient suffered from pulmonary hemorrhage, he recovered without further sequelae. We did not observe any clinical significant hemodynamic and ventilatory effect. The A-View method yields adequate diagnostic accuracy to detect ascending aorta atherosclerosis, without significant cardiopulmonary side effects provided that the A-View catheter is introduced carefully.

In **Chapter 7** the intra- and interobserver variability of the A-View method for determining the presence and severity of ascending aorta atherosclerosis in patients undergoing cardiac surgery is quantified. In a cross-sectional diagnostic study images, obtained with the A-View method, of 60 patients with atherosclerosis in the ascending aorta and 60 without were reviewed by 4 different observers at two moments. Agreement within and across observers was estimated, using (weighted) Kappa statistic. For the primary outcome (presence versus absence of atherosclerosis), the Kappa value ranged from 0.11 to 0.43 between observers and from 0.38 to 0.63 within observers. Indicating that the agreement across observers was slight to moderate and the agreement within observers was moderate to substantial. Given the promising accuracy of the method we have found in previous studies we have to and will further investigate how to improve this interobserver agreement to enhance the applicability, and thus to improve the effectiveness of the method when used in clinical practice.

In **Chapter 8** a cost-effectiveness analysis of the A-View method, compared with manual palpation (usual care), to detect atherosclerosis of the ascending aorta is performed. We used a Markov decision-analytical model and Monte Carlo sampling to assess the differences in health benefits and costs for cardiac surgery which was adapted based on (a) the presence of atherosclerosis as detected with manual palpation compared with (b) the presence of atherosclerosis as detected with the A-View method. In patients undergoing cardiac surgery older then 65 years, using the A-View strategy to pre-sternotomy diagnose the presence of aortic atherosclerosis and adjusting the surgical procedure based on the findings is likely to reduce health care costs and increase health benefits as compared to the current strategy where aortic atherosclerosis is often assessed by manual palpation after sternotomy.

In **Chapter 9** it is concluded that a logical next step is to investigate whether the use of the A-View method leads to changes in therapeutic management and a reduction of embolic events and subsequent clinical significant neurologic complications (stroke, cognitive decline, evident confusion or delirium). First, as the intermediate occurrence of intra- or early postoperative embolic events in the brain is the most likely causal pathway of these 'true' patient outcomes, we suggest it is first timely to do a randomized comparison between the A-view method with so-directed surgical management versus care as usual, using embolic load in the brain as primary outcome. This should be followed by a large randomized study using clinical relevant patient outcomes as primary endpoint, which requires a high number of patients.

SAMENVATTING

11

Epiaortic ultrasound scanning van de aorta ascendens is een veilige en bruikbare methode om atherosclerose te diagnosticeren en te kwantificeren in patiënten die cardiale chirurgie ondergaan. Als er sprake is van ernstige atherosclerose kan aanpassen van de operatietechniek op basis van epiaortic ultrasound scanning het aantal manipulaties van de atherosclerotische aorta verminderen en daarmee mogelijk het aantal postoperatieve herseninfarcten. Ondanks dat epiaortic ultrasound scanning niet veel wordt gebruikt, wordt het toch beschouwd als de "gouden" standaard. Epiaortic ultrasound scanning kan echter alleen worden gebruikt tijdens chirurgie, nadat er een sternotomie heeft plaatsgevonden. Als de mate van atherosclerose ernstiger is dan verwacht moeten beslissingen over het aanpassen van de chirurgische strategie in een relatief late fase worden genomen. Dit soort beslissingen worden bij voorkeur genomen in een vroege fase voor de sternotomie.

Een veel gebruikte methode die in staat is om de mate van atherosclerose in de thoracale aorta vast te stellen is transoesophageale echocardiografie. Het onderzoek van de distale aorta ascendens door middel van transoesophageale echocardiografie wordt echter gehinderd doordat de met lucht gevulde trachea zich bevind tussen de oesofagus en de aorta ascendens; de zogenoemde "blind spot". Onlangs werd de A-View methode, een aanpassing van conventionele transoesophageale echocardiografie, geïntroduceerd om deze beperking op te heffen. De A-View methode maakt gebruik van een intra-tracheale ballon (de A-View katheter, Cordatec Inc., Zoersel, België) die gevuld wordt met fysiologisch zout om zo de lucht in de distale trachea en in de linker hoofdbronchus te vervangen door vloeistof. Op deze manier wordt het mogelijk om de distale aorta ascendens te onderzoeken op de aanwezigheid en de ernst van atherosclerose.

Diverse onderzoekers hebben de mogelijkheden van transoesophageale echocardiografie onderzocht om te discrimineren tussen de aanwezigheid en de afwezigheid van atherosclerose in de aorta ascendens. Het is bekend dat transoesophageale echocardiografie een beperkte waarde heeft hierin, maar dit is nooit ondersteund door een meta-analyse waarin de werkelijke diagnostische nauwkeurigheid van transoesophageale echocardiografie wordt geschat op basis van al het beschikbare kwantitatieve bewijs. Hiervan is in **Hoofdstuk 2** met gebruik van "state of the art" methodologie van diagnostische meta-analyse een schatting gedaan. We doorzochten diverse databanken naar studies die transoesophageale echocardiografie vergeleken met epiaortic ultrasound scanning voor de detectie van atherosclerose in de distale aorta ascendens. Een random-effects bivariaat metaregressie model werd gebruikt om schattingen te verkrijgen van de sensitiviteit en specificiteit, waarbij de relatie tussen de sensitiviteit en de specificiteit werd meegenomen evenals diverse covariaten om heterogeniteit tussen de verschillende studies te onderzoeken. In totaal werden 6 studies geëxtraheerd met in totaal 346 patiënten van wie 419 segmenten van de aorta waren geanalyseerd. Hiervan waren er 100 segmenten met atherosclerose (mediane prevalentie 25% (spreiding 17 – 62%). Schattingen van de sensitiviteit en specificiteit waren respectievelijk 21% (95% CI 13 – 32%) en 99% (96 – 99%). We concludeerden dat vanwege de lage sensitiviteit van transoesophageale echocardiografie voor het detecteren van atherosclerose in de aorta ascendens een negatief resultaat bevestigd moet worden door additionele diagnostiek door epiaortic ultrasound scanning. Als de test positief is kan atherosclerose van de aorta ascendens als aanwezig worden beschouwd en zijn chirurgische strategieën met minder manipulaties mogelijk geïndiceerd.

Voor de wetenschappelijke evaluatie van een nieuw diagnosticum, zoals de A-View methode, moet een gefaseerde aanpak worden gevolgd. Nadat er een technische en veiligheidsevaluatie heeft plaatsgevonden, maar voordat er onderzoek gedaan wordt naar de mogelijkheden om de huidige diagnostische testen te kunnen vervangen en de kosten-effectiviteit in termen van patiënten uitkomst, moeten de reproduceerbaarheid en de diagnostische nauwkeurigheid van de test worden gekwantificeerd.

In **Hoofdstuk 3** wordt de eerste fase van dit evaluatie proces beschreven; is the A-View methode inderdaad in staat om de distale aorta ascendens in beeld te brengen en zijn er geen onverwachte bijwerkingen. In een dwarsdoorsnede diagnostisch onderzoek onder 41 patiënten die cardiale chirugie via sternotomie ondergingen werd transoesophageale echocardiografie, epiaortic ultrasound scanning, de A-View methode en routine intra-operatieve monitoring verricht. Met de A-View methode was de distale aorta ascendens zichtbaar in alle patiënten (100%). Er waren geen klinisch significante veranderingen in de cardiopulmonale parameters geassocieerd met het gebruik van de A-View katheter. Bij 1 patiënt raakte de endo-tracheale tube gedisloceerd wat leidde tot een daling van het arteriële zuurstofgehalte. De ernst van de atherosclerose zoals afgebeeld met de A-View methode in vergelijking met epiaortic ultrasound scanning kwamen goed overeen (Kappa van 0.69 (0.50 - 0.88)). De Bland-Altman analyse liet een zwakke overeenkomst zien tussen de metingen van de grootte van de atherosclerostische plaque (bias 0.05 cm^2, grenzen van overeenkomst -0.63 – 0.74 cm^2). De A-View methode biedt een minimaal invasieve en veilige benadering om preoperatief de “blind spot” van transoesophageale echocardiografie op te lossen. In vergelijking met epiaortic ultrasound scanning, liet the A-View methode bevredigende resultaten zien voor de detectie van aorta ascendens atherosclerose.

In **Hoofdstuk 4** is het gebruik van de A-View methode, de standaard opnamen, de indicaties en de contra-indicaties van de methode beschreven door middel van enkele case-reports. Het betreft 4 cases met verschillende typen van distale aorta ascendens pathologie of indicaties voor aanvullende monitoring met behulp van de A-View methode.

In **Hoofdstuk 5** wordt beschreven dat het schatten van betrouwbaarheidsintervallen van voorspellende waarden van een diagnostische test in een nested case-control design niet ongecompliceerd is. Om correcte schattingen te verkrijgen van deze absolute kansen, d.w.z. de voorspellende waarden, moet er een correctie gedaan worden voor de steekproef fractie. Indien deze correctie wordt gebruikt om de corresponderende standaard fout te berekenen wordt het aantal patiënten onterecht verhoogd in vergelijking met het aantal bestudeerde patiënten en dit leidt tot te smalle betrouwbaarheidsintervallen. Daarom moet er ook een aanpassing worden gedaan om correcte betrouwbaarheidsintervallen te kunnen berekenen. We vergeleken 6 methoden om de standaard fout van voorspellende waarden te schatten in een simulatie waarbij gebruik werd gemaakt van empirische data van een groot cohort patiënten die verdacht werden van diep veneuze trombose. De methoden waren: 1. de standaard formule voor de standaard fout van een proportie, 2. aanpassing van de standaard formule met de steekproef fractie, 3. een bootstrap procedure, 4. een methode die gebruik maakt van de sensitiviteit, de specificiteit en de prevalentie, 5. gewogen logistische regressie, en 6. methode 4 op een log odds schaal. De methoden werden vergeleken op basis van coverage probability en op de breedte van het 95% betrouwbaarheidsinterval van de voorspellende waarde. De bootstrap procedure bleek superieur in vergelijking met de andere methoden, het liet een correcte coverage probability zien met een relatief smal betrouwbaarheidsinterval. Concluderend kunnen we zeggen dat de bootstrap methode adequate betrouwbaarheidsintervallen geeft voor voorspellende waarden van diagnostische en prognostische testen in een nested case-control setting.

In **Hoofdstuk 6** is de diagnostische nauwkeurigheid van de A-View methode in het vaststellen van atherosclerose in de distale aorta ascendens gekwantificeerd. In een dwarsdoorsnede onderzoek onder 465 patiënten van 65 jaar of ouder die cardiale chirurgie ondergingen via een sternotomie, werd in iedere patiënt gemodificeerde transoesophageale echocardiografie (de A-View methode), epiaortic ultrasound scanning en routine intra-operatieve monitoring verricht. De positief voorspellende waarde was 67% en de negatief voorspellende waarde was 97%, de sensitiviteit was 95% en de specificiteit was 79% voor de A-View methode. Één patiënt had een massale longbloeding, hij herstelde zonder restverschijnselen. De A-View methode heeft een adequate diagnostische nauwkeurigheid voor het detecteren van atherosclerose in de aorta ascendens zonder significante cardiopulmonale bijwerkingen op voorwaarde dat de A-View katheter voorzichtig wordt ingebracht.

In **Hoofdstuk 7** wordt de intra- en interbeoordelaar variabiliteit van de A-View methode gekwantificeerd voor het vaststellen van de aanwezigheid en de ernst van atherosclerose in de aorta ascendens in patiënten die cardiale chirurgie ondergaan. In een dwarsdoorsnede diagnostisch onderzoek werden beelden, verkregen met de A-View methode, van 60 patiënten met atherosclerose en 60 patiënten zonder atherosclerose beoordeelt door 4 verschillende beoordelaars op twee verschillende momenten. Overeenstemming binnen en tussen beoordelaars werd geschat met behulp van de (gewogen) Kappa waarde. Voor het primaire eindpunt (aanwezigheid versus afwezigheid), had de Kappa waarde een spreiding van 0.11 tot 0.43 tussen beoordelaars en van 0.38 tot 0.63 binnen beoordelaars. Dit geeft aan dat de overeenkomst tussen beoordelaars licht tot matig was en binnen beoordelaars matig tot substantieel. Gegeven het feit dat de diagnostische nauwkeurigheid van de A-View methode die we vonden in eerdere studies veelbelovend is moeten en zullen we verder moeten onderzoeken hoe de intra- en inter-beoordelaar overeenkomst te verbeteren is. Daarmee wordt de toepasbaarheid en dus de effectiviteit van de methode groter indien die wordt gebruikt in de praktijk.

In **Hoofdstuk 8** is de kosten-effectiviteit van de A-View methode in vergelijking met manuele palpatie (normale zorg) in het detecteren van atherosclerose in de aorta ascendens onderzocht. We maakten gebruik van een Markov beslissingsanalyse model om de verschillen in gezondheidswinst en kosten van cardiale chirugie te onderzoeken. In het model werd gebruik gemaakt van 2 strategieën om cardiale chirurgie aan te passen, namelijk op basis van (a) de aanwezigheid van atherosclerose zoals vast gesteld door middel van manuele palpatie en op (b) de aanwezigheid van atherosclerose zoals vastgesteld met behulp van de A-View methode. In patiënten ouder dan 65 jaar die cardiale chirurgie ondergaan waarbij gebruik wordt gemaakt van de A-View strategie om voor sternotomie de aanwezigheid van atherosclerose in de aorta ascendens te diagnosticeren en op basis van de deze informatie de chirurgische strategie aan te passen is het waarschijnlijk dat de kosten voor de gezondheidszorg worden gereduceerd en dat er gezondheidswinst is in vergelijking met de huidige strategie waarbij atherosclerose van de aorta vaak wordt beoordeeld met manuele palpatie na sternotomie.

In **Hoofdstuk 9** wordt geconcludeerd dat het een logische volgende stap is om te onderzoeken of het gebruik van de A-View methode leidt tot veranderingen in therapie en daaropvolgend tot een reductie van embolieën en klinisch relevante neurologische complicaties (herseninfarct, cognitieve achteruitgang of delier). Omdat de tussenuitkomst intra- of vroeg postoperatieve embolieën in de hersenen de meest waarschijnlijke causale weg is naar deze "harde" patiënten uitkomsten, suggereren we dat er eerst een gerandomiseerde vergelijking wordt gedaan tussen de A-View methode met daarop gebaseerd beleid versus het normale beleid, met embolieën in de hersenen als primaire uitkomstmaat. Dit zal gevolgd moeten worden door een grote gerandomiseerde trial met neurologische complicaties als primaire uitkomstmaat.

LIST OF PUBLICATIONS

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List of Publications

1. van Zaane BA, van Woensel JB, Teeuw AH, Maes A, Bos AP. [Unnatural and unexplained death in a paediatric intensive-care unit, 1993-2002]. Nederlands Tijdschrift voor Geneeskunde 2004;148:1591-4.

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3. van Zaane B, Zuithoff NP, Reitsma JB, Bax L, Nierich AP, Moons KG. Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery. Acta Anaesthesiologica Scandinavica 2008;52:1179-87.

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DANKWOORD

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Promoveren en medisch specialist worden is een zware strijd, een strijd die niet alleen gestreden kan worden. Ik wil dan ook een ieder bedanken die mij in die strijd steunt en heeft gesteund. Een aantal mensen heeft hierbij een speciale rol gespeeld, die wil ik dan ook in het bijzonder bedanken.

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CURRICULUM VITAE

Curriculum Vitae

Bas van Zaane was born on the 3rd of april, 1976 in Nijmegen, the Netherlands. After graduating from university preparatory education at the Scholengemeenschap Lelystad in 1994, he started medical school in 1997 at the Academic Medical Center in Amsterdam and graduated in 2003. After a period working as a resident at the intensive care unit of the Isala Clinics, Zwolle he started the work described in this thesis (Promotores: Prof. Dr. K.G.M. Moons and Prof. Dr. C.J. Kalkman) in 2005. Simultaneously he started his specialist training in anesthesiology at the Department of Perioperative Care and Emergency Medicine of the University Medical Center Utrecht. He obtained his Master of Science in Clinical Epidemiology at the University of Utrecht in January 2007. He is currently finishing his specialist training.

Bas is married to Lottie and they have one son Tom.