The role of TTE in assessment of the patient before and following TAVI for AS

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The Role of Transthoracic Echocardiography in Assessment of the Patient before and following Transcatheter Aortic Valve Implantation for Aortic Stenosis

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Short Title: Role of transthoracic echocardiography before and after TAVI

Abstract (110/250 words)

Transcatheter aortic valve implantation is now accepted as a standard mode of treatment for an increasingly large population of patients with severe aortic stenosis. With the availability of this technique, echocardiographers need to be familiar with the imaging characteristics that can help to identify which patients are best suited to conventional surgery or transcatheter aortic valve implantation, and what parameters need to be measured. This article highlights the major features that should be assessed during transthoracic echocardiography prior to presentation of the patient to the 'Heart Team'. In addition, the article summarises the aspects to be considered on echocardiography during follow-up assessment after successful implantation of a transcatheter aortic valve.

Keywords: Transthoracic echocardiography

Transcatheter aortic valve implantation

Aortic stenosis

Transcatheter Aortic Valve Implantation (TAVI) is now firmly established as a treatment for symptomatic aortic stenosis (AS), in patients who cannot undergo or who are considered too high risk for conventional surgical aortic valve replacement (SAVR). Since the advent of the PARTNER trial [1, 2], the adoption of TAVI has increased exponentially worldwide as a method of treating symptomatic AS [3]. With further trials enrolling patients at intermediate as well as high risk [4], the indications for TAVI are set to grow and the demand for pre-procedural assessment will increase (Figure 1).

European and American guidelines highlight the central role of the multi-disciplinary (Heart) team when deciding on appropriate intervention in AS [5, 6]. This team is tasked with the selection of those who would benefit most from SAVR or TAVI, and those who should not undergo intervention on the basis that they would not benefit either in terms of symptoms (minimum expected gain more than one NYHA class) or life expectancy (minimum expected survival > 1 year following a successful procedure) [6]. While a large and growing body of literature has confirmed both survival advantage and symptom benefit compared to medical therapy with TAVI [1, 2], one in four patients report only limited improvement either in quality of life or functional status [7] and almost one in five do not live beyond the first year following implantation [3]. Scoring systems such as the Society of Thoracic Surgeons Risk Calculator or Euroscore fail to take into account patient specific factors including co-morbidity, major organ system compromise or patient frailty. A number of important factors however, may be identified by a comprehensive transthoracic echocardiogram (TTE) to inform decision-making for the patient and the aim of this article is to highlight those that should be emphasised in any report. There is recent evidence to suggest regular follow-up by TTE following implantation is important and this article will outline what should be assessed following TAVI.

Pre-Procedural Transthoracic Echocardiography

Aortic Stenosis (AS) Severity

The leading priority for the Heart Team is to ensure that each patient has a confirmed diagnosis of severe AS meeting class 1 indications for intervention [5]. In the absence of symptoms, there is no significant increase in age-adjusted mortality with mild, moderate or severe AS [8] as compared to a combined procedural and 30-day mortality rate of 6% with TAVI [3]. Therefore, confirmation that AS is severe and that symptoms are due to valve disease remains critical. One major and recurrent problem is inconsistency in grading severity of AS by TTE when using the standard haemodynamic parameters recommended for evaluation of severity, comprising maximal velocity, mean gradient and aortic valve area (AVA) [9, 10]. This inconsistency can be attributed to several factors:

i) **Measurement of maximum velocity and highest mean gradient across the stenotic valve** - This demands that multiple measures are made from different acoustic windows. In a recent study of 100 consecutive patients undergoing TTE for severe AS within a single department, the right parasternal window was superior for identifying maximal velocity (Figure 2) [11]. When sampling maximal velocity from only the apical window, nearly a quarter of patients were misclassified with two-thirds under-estimated as moderate AS, and a third with paradoxical low flow rather than normal flow severe AS. One of the factors thought to influence the non-apical location of the maximal peak velocity may be increasing angulation of the ventricular-aortic junction with advancing age.

ii) **Variability in acquiring the data and variability in measuring the data** - Velocity measurements have a very low inter- and intra-observer measurement variability once acquired but left ventricular outflow tract (LVOT) dimension measures may vary between 5-9% between echocardiographers even using the same image [12]. Even when reproducibility is optimised between echocardiographers, the LVOT is elliptical in many patients with AS and the 2D measure used for calculation of the area on 2D TTE is often the shortest dimension, such that the continuity equation may still under-estimate the AVA [13]. The variability is further accentuated in the hypertensive patient, in whom the LVOT orifice becomes progressively more elliptical, leading to under-estimation of stroke volume and AVA [14]. This means that 3D TTE should be used when technically possible to measure the LVOT area, since this improves accuracy in grading (Figure 3) [15]. Stroke volume derived from 3D LV datasets can also be used as an internal validator for accuracy. The use of the Doppler Velocity Index (DVI), a ratio of the velocity time integral in the LVOTvti/AVvti, avoids the need for LVOT measurements altogether overcoming some of these inaccuracies. A partition value below 0.25 has been shown to identify a group of patients with a high rate of valve-related events, including death [16].

iii) **Discrepancy in measurement of AS severity relative to a low aortic valve area (AVA <1cm2)** - typically with a low maximal velocity or mean gradient (Vmax<4.0m/s; mean <40mmHg). After exclusion of measurement inaccuracy, one of the main reasons for this presentation is LV dysfunction (LVEF <40%). Whilst exercise stress echocardiography has much to add to the assessment of aortic stenosis in patients with preserved LV function, low dose dobutamine stress echocardiography (to a maximum of 20mcg) is required in the assessment of AS severity and operative risk stratification in AS with impaired LV and low gradient. Confirmation that AS is severe requires demonstration of a maximal velocity above 4m/s or mean gradient above 40mmHg at any stage with AVA below 1.0cm2 at any flow rate [17]. This is important not only in identifying patients who would benefit from AVR but also selecting out those patients at higher peri-operative risk with SAVR (LV stroke volume or EF improvement <25%). The latter does not apply to TAVI, since LV impairment at time of procedure does not affect peri-procedural outcomes from percutaneous intervention but is a major factor in determining surgical survival [18].

The other main reason for a low maximal velocity or mean gradient, relative to a low aortic valve area (AVAi<0.6cm^2/m^2) is the presence of a low stroke volume (<35mL/m^2) in the context of preserved LV function (LVEF>40%). Sub-group analysis of the PARTNER data clearly demonstrated improved survival in patients with so-called low gradient, low flow, normal ejection fraction (LF LG nEF) severe AS following TAVI compared to medical therapy at 2 years (56.5% vs 76.9%) [19]. Given the limitations in measurement of LVOT-derived stroke volume on Doppler however, this diagnosis can be problematic and requires a systematic approach. Firstly, visual assessment of the 2D appearance and mobility of the aortic valve is important with severe AS being unlikely if a cusp tip opens well or one leaflet remains mobile. A small study suggested this had high specificity for the severity of aortic stenosis [20]. Secondly, grading extent of valve calcification is an important factor in predicting outcome in AS [21], although visual estimation on 2D has high inter-observer variability (Figure 4) [20]. Thirdly, concomitant valve lesions which may reduce transaortic flow need to be identified – particularly severe mitral valve disease. Finally, other supporting characteristics of patients with true LF LG nEF AS should be highlighted in the echo report, including small LV cavity size [22], concentric remodelling with increased LV mass [23], and high valvulo-arterial impedance (Zva>5.5mmHg/mL/m^2) (Figure 5) [24]. A simple additional marker of severity is M-mode-derived mitral annular plane systolic excursion, with a cut-off below 9mm having high accuracy in separating out those with low gradient, severe AS from those with low gradient, moderate AS [25]. Where these additional features are absent, imaging should be repeated to minimise measurement error and consideration given to the possibility that indexed AVA may be low as a result of a very low body surface area.

It should also be remembered that there are inconsistencies between Gorlin formula derived valve areas and mean gradients derived from Doppler used to generate guideline criteria partition values. Theoretical modelling has shown that with a normal flow rate and an EOA of $1cm^2$ that a mean gradient would be expected to be closer to 30mmHg than 40mmHg. This means that the presence of LG *normal flow* nEF AS confers a better prognosis than low flow [26].

Combined AS and aortic regurgitation can be difficult to assess when both are in the moderate range, although the peak velocity across the aortic valve still holds prognostic weight in this situation [27]. Identifying AR can be an important factor in determining management, for example, the presence of severe AR may prohibit palliative balloon valvuloplasty and would likely modify its use during the TAVI procedure itself.

Aortic Valve Morphology

There are important features of the aortic valve complex that deserve mention in the transthoracic report. Firstly, the diastolic sinus of Valsalva diameter and height, diastolic diameter of the sinotubular junction, as well as the systolic left main coronary artery position may influence the size of TAVI selected as well as decisions about valve placement, although some may be better assessed on TOE [28]. Secondly, consideration should be given to symmetry of opening of the aortic valve, in particular whether this is bicuspid or tricuspid. Congenital bicuspid AS presents earlier than degenerative disease and may affect the decision whether to proceed with surgery or TAVI. Although TAVI can be performed effectively in patients with a bicuspid valve, there is a higher incidence and greater severity of aortic regurgitation post procedure, as frequently as 28% of cases [29]. Thirdly, calcification beyond the leaflets themselves is predictive of post-procedural AR and should be noted, particularly if there are ectopic deposits in the LVOT, sinus or proximal root [30]. Calcific deposits around the coronary ostia increase the risk of coronary obstruction, while calcification within the aortic complex may increase risk of annular rupture, root perforation, aortic wall haematoma and dissection [31]. Finally, together with ectopic LVOT calcification, severe basal septal hypertrophy may influence the choice of prosthesis, although the latter is common in the elderly hypertensive patient. Balloon expandable valves have a lower profile compared to self-expanding valves; but the positioning of both can be influenced by a severely hypertrophied basal septum.

Mitral Regurgitation

Community studies have demonstrated that mitral regurgitation (MR) is the most common valve lesion, with prevalence increasing with age [32]. The presentation of patients to the Heart Team with both severe AS and mitral regurgitation is therefore common, and has been reported in up to 74% elderly candidates undergoing SAVR or TAVI [33]. Accurate quantification of MR on pre-procedural TTE is important. Firstly, the presence of moderate-severe MR will lower maximal velocity and mean gradient across a stenosed aortic valve, which may lead to misclassification. Secondly, recent data have highlighted the adverse morbidity and mortality associated with residual moderate or severe MR following isolated SAVR [34]. Several recent studies have considered the patient referred for TAVI who also has moderate-severe MR and these have focussed on two questions: firstly, does TAVI lead to change in severity of MR; secondly, if moderate-severe MR is left untreated, what impact does this have on early and late outcome? In contemporary TAVI cohorts, the incidence of moderate-severe MR appears to be around 15%, equally divided between primary (organic) and secondary (functional) aetiologies [33]. In a recent meta-analysis of 9 studies including over 8000 subjects, moderate MR was present at baseline in 386 (5%) and severe in 135 (2%) patients. After TAVI, moderate MR improved in 48.2%, remained the same in 48.7% and deteriorated in 3.1%, while in severe MR it improved in 57% and remained unchanged in the remainder [35]. While MR may therefore improve following TAVI, the same meta-analysis also highlighted that those with residual MR post-TAVI are exposed to a similar increase in mortality as following isolated SAVR (30-day mortality: HR 1.49, 95% CI 1.16 - 1.92; 1-year mortality HR 1.32, 95% CI 1.12 - 1.55). Though two earlier studies suggested outcomes were better with functional rather than primary organic MR [36, 37], these findings were not confirmed in a recent meta-analysis which showed outcomes were influenced by severity of MR but not aetiology [38]. It is therefore imperative that any pre-procedural echo identify both the presence and quantify severity of MR to optimise discussion of the patient in the Heart Team meeting (Figure 6).

Left Ventricular Function

The prognosis of patients with symptomatic and asymptomatic severe AS is worse when associated with LV dysfunction. Even at extremes of left ventricular (LV) dysfunction (ejection fraction <20%), patients who survive SAVR have a much better prognosis than those managed medically [39, 40]. In patients considered unfit for SAVR undergoing TAVI, there were no differences in 30-day or 1-year survival between those with LVEF above or below 50% (or in a smaller sub-group with LVEF<35%), and survival was higher than in patients treated medically [18]. Even patients with severely impaired LV function should therefore be referred for discussion by the Heart Team, with current data suggesting that such patients may fare better with TAVI than SAVR. Pre-procedural LV dysfunction did not affect 30-day mortality in the inoperable cohort, a finding confirmed in the high risk cohort of PARTNER (although those with LVEF <20% were excluded) [41]. This contrasts with the increased 30-day mortality following SAVR, particularly in those with prior myocardial infarction [42]. Interestingly in the PARTNER B cohort, improvement in LVEF by >10% after TAVI was observed in half of patients considered unsuitable for SAVR and was more likely to occur in those with smaller pre-procedural LV internal dimensions and less mitral regurgitation [18]. While improvement in LVEF does not appear to produce a survival benefit in inoperable patients, failure of LVEF to improve carries adverse prognostic significance in high risk patients at 1 year [41].

Right Ventricular Function and Pulmonary Hypertension

Pulmonary hypertension (PH) occurs in 25% of patients with severe AS and is more common in those with low LVEF, evidence of high filling pressure and moderate-severe MR [43, 44]. Patients with high pulmonary artery pressure (PAP) have a perioperative mortality as high as 35% with SAVR and is a major reason for “surgical turndown” [45]. Registry data have demonstrated that PH (defined on TTE by systolic PAP >40mmHg) does not adversely affect procedural success, early complication rate or 30-day mortality following TAVI but does increase 1-year mortality to 22% (28%>60mmHg sPAP) [46]. Despite the presence of high sPAP, patients continue to benefit symptomatically from TAVI and in some, PAP falls during follow-up. These echo data were supported in a retrospective analysis of 2180 patients undergoing invasive catheter studies from PARTNER A and the PARTNER registry, in which 1 year mortality was higher (25%) in those with moderate/severe PHT (mPAP >35mmHg) compared with those with no PHT (18%, mPAP <25mmHg) [47]. In the latter study, risk stratification was further improved with clinical variables, including 6-minute walk test, oxygen-dependent lung disease and impaired renal function but the only echo-derived haemodynamic parameter of use was lower mean gradient.

Tricuspid Regurgitation

TTE in patients with severe aortic stenosis requires a complete study of the tricuspid valve and right ventricle. Moderate or severe functional tricuspid regurgitation (TR) is present in about 5% patients referred for SAVR for severe AS (Figure 7) [48]. In these patients, residual TR following surgery does not improve in half of all patients, may be progressive and is associated with higher late mortality [49]. In patients following TAVI, registry data suggest that moderate or severe TR is more common (15%) and does not improve in the majority of patients following implantation [50]. Furthermore, TR was associated with a doubling of all-cause mortality at 2 years, an increase in risk that was found to be higher in an analysis of 542 patients from the inoperable PARTNER cohort [51]. In this group, randomised to TAVI or medical therapy, mortality at 1 year was 32.6% with moderate TR and 61.1% in those with severe TR on pre-procedural TTE, an increase in risk that was more marked in those with only mild or no mitral regurgitation. Both right atrial dilatation and RV dysfunction were associated with mortality but the association with outcome and RV dysfunction was lost on a multi-variate model. When assessing potential benefit from TAVI, the TTE needs to be reviewed for right atrial size from the apical four-chamber view, basal and mid right ventricular dimension, and RV function based on fractional area change [52]. The tricuspid valve needs to be assessed for severity of TR, aetiology and mechanism, with calculation of sPAP (Table 1).

Role of Pre- and Peri-Procedural Transoesophageal Echocardiography

Transoesophageal echocardiography (TOE) has traditionally been used as an integral part of pre-screening patients under consideration for TAVI and peri-procedurally to assess the degree of paravalular regurgitation and to detect complications (eg pericardial effusion) [28, 53]. Although most of the patients within the PARTNER series of trials were treated with the assistance of intraprocedural TOE, recent data have suggested that TOE may not be necessary for safe placement of the valve or monitoring during TAVI [54, 55]. One barrier to universal intraprocedural TOE has been the need for general anaesthesia (GA) and a purported increase in risk associated with general anaesthesia in an elderly population with multiple co-morbidities. Recent studies have shown similar safety and efficacy of conscious sedation (CS) compared to general anaesthesia [56], while others have demonstrated a benefit with CS in terms of reduced length of stay and lower cost [57]. One issue that remains to be decided is the impact of intraprocedural TOE on paravalvular regurgitation post TAVI, which has been associated with increased 1 year mortality [3]. The FRANCE 2 registry compared clinical outcomes for GA (n=1377) and CS (n=949), and showed a higher incidence of paravalvar leak > mild in the CS group (15.0% versus 19.1%; *P*=0.015) in whom TOE use was considerably less frequent (76.3% versus 16.9%; P<0.001) [58]. Longer term follow up is required to determine whether this difference has clinical consequence. While the role for intra-procedural TOE remains hotly debated, there is no question that the frequency of TOE during the TAVI procedure itself has declined.

In our centre, TOE is used pre-procedurally to clarify severity of aortic stenosis where this is uncertain on TTE and when TTE is inadequate to provide accurate data on LV size and function, presence and severity of mitral regurgitation, RV size and function, pulmonary pressure and presence and severity of tricuspid regurgitation as outlined. In many centres however, TOE is performed routinely as part of the pre-procedural assessment of the patient prior to TAVI and is vital in those centres that do not use alternative imaging modalities such as computed tomography to measure the annulus for valve sizing. There are a number of other published articles on the relative merits of TOE compared to other imaging modalities in measuring annulus size, extent of calcification and prediction of post-procedural outcomes that will not be discussed in this article [28].

Post-Procedure TTE

Data from the UK TAVI registry shows that over 80% of patients survive to 12 months and more than a third will be alive at 6 years, a figure likely to improve with advances in techniques and equipment [3]. Consensus agreement for echocardiographic assessment following discharge includes a baseline study at 30 days, at 1 year and annually thereafter – though supportive evidence for optimal frequency is lacking [45] (Table 2).

Post-procedural AR remains a problem following TAVI, and though platform designs evolve with the main aim of reducing this outcome, UK TAVI data have shown that the incidence has not changed significantly and remains an important predictor of outcome (incidence of moderate or severe AR approximately 14%) [3]. AR post TAVI is almost universally paravalvular in origin and can be difficult to assess on TTE, partly due to acoustic shadowing from the valve stent, contributing to significant variability in grading (Figure 8) [59]. Recent guidance has been published to both illustrate the complexities of assessment and inconsistencies of grading, as well as provide a framework for its assessment [60]. It is suggested that the echocardiographers should use 5 grades of severity (mild, mild-moderate, moderate, moderate-severe, severe) with a view to increasing flexibility while over time, improving accuracy and reproducibility. A multi-parametric and multimodality approach should be used, with the key features including: structural appearances of the THV stent, features of the AR jet (number, jet path and vena contracta), jet width as percentage of LVOT, and circumferential extent of the jet relative to the annulus. As yet, this grading system needs to be validated both against other imaging modalities and with outcome data. It is also important to remember that the presence of AR results in increased maximal forward velocity and mean gradient through the implanted TAVI, which must be taken into consideration if stenosis or obstruction is a possibility in follow-up.

Recent evidence has emphasised the importance of the baseline study in which the haemodynamic parameters of the newly implanted TAVI valve are measured, including maximal velocity, mean gradient, effective orifice area and DVI. Although early TAVI thrombus is uncommon [61], late valve thrombosis at a median of 6 months that cannot be visualised using TTE has been identified only through change in haemodynamic parameters, with explanted valves clearly demonstrating thrombus within the stent structure (Figure 9) [62]. It is important when making such measures to ensure pulsed wave Doppler interrogation is performed proximal to the stent of the prosthetic valve (pre-stent) rather than proximal to the leaflets (in-stent), since the latter can result in underestimation of the effective orifice area and over-diagnosis of prosthetic valve dysfunction and prosthesis mismatch [63]. Though early reports have come from CT based studies, analysis of bioprosthetic valve failure suggests that > 50% increase in mean gradient from baseline over 5 years of follow up is an important predictor of valve thrombosis [64].

Four other distinct causes of TAVI failure have been identified, including device migration, structural valve failure, compression and prosthetic valve endocarditis. Device migration, defined as ‘late’ when occurring greater than one hour post procedure, accounts for around 10% of the total number of device embolisations [65]. Cases have been reported up to a year post procedure and occur more commonly in balloon expandable valves (83%) [66]. Most are retrograde into the LV outflow tract and are associated with rapid haemodynamic collapse, although cases have been reported on identification with TTE alone. Risk factors for embolization include low valve implant within the LV, absence of calcification to act as an anchor and basal septal bulge leading to loss of apposition. Valve stability should be scrutinised with reference to the baseline study to ensure prosthetic position is maintained.

Structural valve failure with TAVI has been described rarely. Mylotte et al identified 13 cases occurring within 5 years follow-up and sharing a common aetiology to surgical bioprosthetic valve failure: pannus formation, leaflet degeneration and calcification, and rarely leaflet tear [66]. On TTE, these complications present with unexpected valvar stenosis, regurgitation or combined lesions. Mylotte et al also identified 7 cases of TAVI compression, only with balloon expandable valves, and only on post mortem analysis. In each of these cases, there was deformation of the stainless steel or cobalt-chromium stent, possibly as a result of chest wall compression during cardiopulmonary resuscitation. This mandates repeat TTE for any patient resuscitated with CPR following TAVI implantation.

A large multi-centre registry reported the incidence of infective endocarditis (IE) at one year following TAVI to be 0.5%, with the median time from implantation 6 months [67]. The most frequent causal organisms were typical (81.8%), including coagulase negative staphylococci, staphylococcus aureus and enterococci in similar proportions. Orotracheal intubation and the self-expanding Corevalve system were both associated with IE. Vegetations were identified in 77.4% of cases on echocardiography, though it is not clear the proportion of these that were identifiable on TTE. Vegetations were identified on the valve leaflets, stent frame and mitral valve in 39.6%, 17% and 20.7% respectively.

Conclusion

Transcatheter aortic valve implantation is now accepted as a standard mode of treatment for an increasingly large population of patients with symptomatic severe AS. With the availability of this technique, echocardiographers will need to be familiar with the imaging characteristics of patients that are best suited to conventional surgery or TAVI, and what parameters need to be assessed. Whilst there are clinical factors that will heavily influence patient selection and outcomes; echocardiography plays an essential role in confirming the diagnosis of severe aortic stenosis as well as identifying factors that influence 1 year mortality, including aetiology and severity of MR, LV function, TR, RV dysfunction and pulmonary hypertension. TTE should then be repeated within 30 days of the procedure, to establish baseline parameters for follow-up including maximal velocity, mean gradient, valve area, position and competence of valve.

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