

Clinically Important Misclassification of Aortic Valve Stenosis Severity Using Non-Invasive Techniques: Simultaneous Echocardiography and Cardiac Catheterization During Transcatheter Aortic Valve Implantation in Awake Patients

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ABSTRACT

Background: Suitability for transcatheter aortic valve (AV) implantation (TAVI) is determined by using transthoracic echocardiography (TTE), although left-sided cardiac catheterization (LCC) provides directly measured pressure data. TAVI in awake patients permits simultaneous comparison of TTE and LCC under physiologically relevant left ventricular loading conditions. We hypothesized that clinically important discrepancies between TTE and LCC would be identified.

Methods and results: TAVI was performed in 108 awake patients undergoing intra-procedural TTE and LCC between January 1, 2016 and December 31, 2016, based upon pre-procedure TTE data. Intra-procedural assessments simultaneously were performed before and after prosthesis implantation. Based upon mean trans-AV systolic ejection pressure gradient (MSEPG), AS was graded as: mild (<20 mm Hg; grade 1), moderate (20 - <40 mm Hg; grade 2), or severe (≥40 mm Hg; grade 3). In 79 of the 108 (73.1%) patients, intra-procedural TTE and LCC assessments were concordant. In 2 of the 108 (1.9%) patients, TTE overestimated AS severity by ≥1 grade. In 27 of the 108 (25.0%) patients, TTE underestimated AS severity by ≥1 grade. In total, AS severity reclassification occurred in 29 (26.9%) patients. Overall, TTE underestimated MSEPG by 8.9 ± 1.2 mm Hg (TTE MSEPG versus LCC MSEPG; $P < .001$).

Conclusion: Current TTE criteria appear to frequently and importantly underestimate AS severity. Because decision-making regarding TAVI often exclusively is based upon TTE data, these findings suggest either a continued role for LCC in the diagnostic assessment of AS in patients who do not meet standard TTE criteria or lowering TTE cutoffs for TAVI.

Highlights:

- TTE is the benchmark standard methodology for AS assessment prior to TAVI
- Simultaneous TTE and catheterization assessments of AS were compared prior to TAVI
- TTE frequently and importantly underestimated AS severity relative to catheterization
- In patients suspicious for severe AS, if TTE data identifies less than severe AS, pre-TAVI catheterization may be valuable

INTRODUCTION

Aortic valve (AV) stenosis (AS) is the most or second most common form of valvular heart disease [Andell 2017]. Classic studies have demonstrated the aggressive and malignant natural history of symptomatic and severe AS [Braunwald 2018]. As a mechanical disease in which left ventricular (LV) outflow during systolic ejection is impeded, mechanical strategies are the cornerstone of therapy for hemodynamically important severe AS. Historically, open cardiac surgical aortic valve replacement (AVR) has been the standard treatment of severe AS, with a wide range of artificial mechanical and biological (stented xeno-prostheses, stentless xeno- and allo-prostheses, and autografts) prosthetic options [Reineke 2016]. Over the past two decades, however, transcatheter aortic valve implantation (TAVI), also termed transcatheter aortic valve replacement (TAVR), has emerged as an alternative mechanical therapy for AS. In high and intermediate surgical risk patients, TAVI provides effective treatment of AS, with superior peri-procedural mortality and morbidity compared with AVR [Leon 2010; Smith 2011; Popma 2014; Adams 2014].

Regardless of whether AVR or TAVI is chosen as the treatment strategy for AS, accurate assessment of the physiological severity of AS is vitally important. Underestimating AS severity will result in under-treatment of patients; overestimating AS severity, in contrast, will result in over-treatment of patients. Assessment of the pressure gradients between the LV and proximal aorta during LV systolic ejection – either

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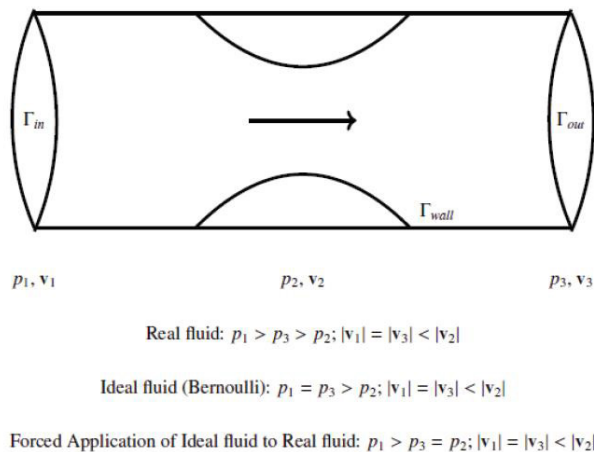


Figure 1. Depiction of fluid mechanics of AS, demonstrating assumptions and conceptual flaws in conventional Bernoulli equation-based non-invasive calculation of transvalvular pressure gradients. Modified from Svihlova et al, terms are pressure (p), velocity (v), and cross-sectional area (Γ) [Svihlova 2017]. Zones 1, 2, and 3, refer to the inlet, stenosis, and outlet, with the arrow indicating the direction of flow. Catheterization-measured findings are what are observed under the first heading of “real fluid.” The inlet pressure p_1 is $>$ the outlet pressure p_3 , with the difference across the stenosis ($p_1 - p_3$) being what is clinically termed the “pressure gradient.” The intra-stenosis pressure p_2 is the lowest value, and typically is some amount lower than p_3 . Energy is dissipated and expressed in the ($p_1 - p_3$) pressure gradient. The second, “ideal fluid,” constitutes the circumstance under which the Bernoulli equation holds. The inlet pressure p_1 is the highest value, and inlet velocity v_1 is the lowest value. However, if the cross-sectional area of the inlet and outlet are identical without alternate flow paths (single conduit), then the inlet and outlet pressures are the same ($p_1 = p_3$), and the inlet and outlet velocities are the same ($v_1 = v_3$). No energy dissipation occurs. Within the stenosis, velocity increases and pressure decreases; if the Bernoulli equation holds, then the extent of velocity increase and pressure decrease occur in order to satisfy $p + (\rho v^2/2) + \rho gh = \text{constant}$, where ρ = fluid density and h = height relative to baseline (this is assumed to be constant for the purposes of this study). The first term is the pressure component of potential energy, the second term is kinetic energy, and the third term is gravitational potential energy. Echocardiography calculations fall under the third heading of “forced application of ideal fluid to real fluid.” The Bernoulli equation is used, but does not actually hold true across the entire length of the conduit even in the forced application. Here, p_1 still is the highest value, with $p_2 = p_3$, but both lower than p_1 . Because the Bernoulli equation holds in Zones 1 and 2, the degree to which v increases from v_1 to v_2 can be used to calculate the degree to which p decreases from p_1 to p_2 . However, the entirety of the pressure decrease within the stenosis is held constant into Zone 3. Consequently, the trans-stenosis pressure difference ($p_1 - p_3$) happens to be equal to ($p_1 - p_2$), but v_3 is still lower than v_2 , and equal to v_1 . There is no formal rational basis for this, however. Specific mention is made of three additional points. First, conservation of mass (the “continuity equation”) holds under all circumstances. This is why v_1 and v_3 must be equal under both ideal and real fluids circumstances, if the cross-sectional areas at the inlet and outlet are identical, with no alternate flow paths (single conduit). Second, “pressure recovery,” namely p_3 being some amount higher than p_2 , commonly occurs under real circumstances, but is assumed not to occur in non-invasive assessments. In non-invasive assessment via Bernoulli equation-based

methods, p_2 , the pressure within the stenosis, is conveniently assumed to be equal to p_3 , the pressure downstream of the stenosis. In contrast, pressure recovery is partial under real circumstances, and total under ideal circumstances. Third, it may seem that non-invasive approaches thus ought to systematically overestimate trans-stenosis pressure drop, rather than mis-estimate via underestimation. However, systemic underestimation would mean that the Bernoulli equation-calculated value of p_2 (which equals p_3 in the calculated model) is consistently lower than the measured value of p_3 , even if one were to fix identical values for p_1 between calculated and measured circumstances. There is no rational basis for this. In non-invasive assessment, within the stenosis, the amount by which kinetic energy increases necessarily must be balanced by the amount that potential energy (pressure) decreases, because energy is conserved in this segment since the Bernoulli equation – which expresses conservation of energy – is assumed to be true. All of the energy losses for the real fluid “forced” to operate under ideal circumstances within Zones 1 and 2 are assumed to occur in Zone 3, such that all of the fluid energy lost across the stenosis can be expressed in kinetic energy losses (velocity decrease in the post-stenotic segment). In contrast, for a real fluid, with measurements undertaken via catheterization, the decrease in p_2 conceptually is not constrained by the increase in v_2 , because total energy is not conserved, i.e., energy dissipation may occur such that the real p_2 , from which pressure increases to the real p_3 to an extent determined by what v_3 must be as dictated by conservation of mass, is much less than the idealized Bernoulli equation-based p_2 (which equals the idealized p_3).

by measurement or calculation [Svihlova 2017], or calculation of “valve resistance” (impedance, in the context of unsteady flow) [Ford 1990], are the best-known methods to determine the physiological severity of AS. In contrast, AV area (AVA) determination relates to the anatomic severity of AS.

Transthoracic echocardiography (TTE) and left-sided cardiac catheterization (LCC) are the most common approaches to assess AS prior to TAVI. Current criteria for TAVI are specifically TTE-based (and are physiologic as opposed to anatomic, with the exception of AVA), as outlined in the 2017 American College of Cardiology Expert Consensus Decision Pathway [Otto 2017]. However, LCC measures pressure, whereas all non-invasive assessments calculate pressure. Moreover, the theoretical bases for such calculations used to determine physiological stenosis severity have limitations (Figure 1). Most importantly, LCC-measured and TTE-calculated trans-AV systolic ejection pressure gradients long have been known to have substantial discrepancies. Oh et al [Oh 1988], in an early TTE study from the Mayo Clinic, found that TTE had only a 40-50% sensitivity in the identification of severe AS, with underestimation of trans-AV systolic ejection pressure gradients. Conversely, with respect to anatomic severity of AS, TTE can measure or calculate AVA, whereas LCC only calculates AVA. Recently, Gertz et al demonstrated poor correlation between TTE- and LCC-determined AVA area [Gertz 2012]. Consequently, exclusive reliance upon TTE to determine appropriateness for TAVI, particularly with respect to physiologic parameters that are calculated rather than measured, may result in clinically important inaccuracies.

Awake TAVI [Lauck 2014] provides physiologically more relevant and uniform hemodynamic and LV loading conditions under which AS severity can be assessed simultaneously

using LCC and TTE, in contrast to general anesthesia. The empirical validity of standard TTE approaches to calculating trans-AV pressure gradients thus can be directly compared with LCC. We examined an institutional series of awake transfemoral TAVI, in order to directly compare LCC and conventional TTE assessments and identify any discrepancies with regard to AS severity.

METHODS

Overview and patients: A series of 108 consecutive patients undergoing awake transfemoral TAVI and simultaneous intra-procedural LCC and TTE performed by a single interventional cardiologist (PL) at Memorial Hermann-Texas Medical Center between January 1, 2016 and December 31, 2016, were analyzed. All patients underwent pre-TAVI TTE. Intra-procedural TTE was interpreted in a blinded fashion. Severe AS was determined based upon a peak trans-AV systolic ejection velocity ≥ 4.0 m/s [corresponding to a peak instantaneous trans-AV systolic pressure gradient (PISEPG) ≥ 64 mm Hg] and/or a calculated mean trans-AV systolic ejection pressure gradient (MSEPG) of ≥ 40 mm Hg (calculation described below). Of the patient group, 106 had severe AS based upon these criteria. Two patients had predominant AV regurgitation (AR) as an off-label indication for TAVI, one of whom did not have AS; both were included. This cohort of patients corresponds to the initial experience of our group with awake TAVI.

TAVI procedure, TTE and LCC: Monitored anesthesia care (MAC) was used for all procedures. Intravenous anesthetic agents, comprised of either propofol or dexmedetomidine (the latter only used in patients with preserved LV systolic function), along with small amounts of fentanyl as needed, were used in concert with local anesthetic agents (2% lidocaine administered subcutaneously) at vascular access sites. All procedures in this series were transfemoral TAVI using the Edwards Sapien TAVI system (Edwards Lifesciences, Irvine, CA).

Bilateral common femoral arterial and venous access was obtained, typically percutaneously; when deemed clinically warranted, open femoral arterial access was obtained. The more anatomically suitable femoral artery was used for large-bore sheath placement, through which retrograde trans-AV aortic root-to-LV access was obtained. Simultaneous LV and ascending thoracic aortic pressures were measured using the newly placed LV catheter and a secondary aortic catheter (LV catheter 6 Fr = 2.00 mm, aortic catheter 5 Fr = 1.67 mm diameter) as functions of time. MSEPG and peak-to-peak systolic ejection pressure gradients (PPSEPG) were determined, but PISEPG was not recorded. MSEPG was computed via catheterization laboratory software using the definition of the mean values of functions in calculus, integrating through the systolic ejection time, from AV opening to closure: $[\int P_{LV}(t) - P_{aorta}(t) dt] / t_{\text{systolic ejection}}$. TTE was performed simultaneously. Long- and short-axis views of the AV were obtained, and velocities in the LV outflow tract and aortic valve orifice/aortic root were measured as functions of time. Trans-AV

PGs were calculated from these velocity data using the modified Bernoulli equation [$\Delta P_{LV-aorta} = 4v_{AV}^2$; the PISEPG was determined using the peak systolic ejection velocity, whereas the MSEPG was determined using the mean systolic ejection velocity, in turn determined by numerically calculating the velocity-time integral (VTI) during systolic ejection, and dividing the VTI by the systolic ejection time]. Thereafter, the LV catheter was withdrawn over a guidewire, and the valve prosthesis mounted onto the delivery system was advanced retrograde through the systemic arterial circulation, until the valve prosthesis was in an intra-annular position. Rapid ventricular pacing was initiated, and the valve was deployed. Thereafter, the delivery system was withdrawn antegrade, and a pressure-transducing catheter was advanced over the guidewire until it resided within the LV cavity. Repeat AV assessments by LCC and TTE were performed as described. Based upon MSEPG, AS was graded as: mild (< 20 mm Hg; grade 1), moderate (20 - < 40 mm Hg; grade 2), or severe (> 40 mm Hg; grade 3).

Data analysis: Comparisons were made between simultaneously obtained intra-procedural TTE and LCC data, with only intra-patient comparisons being performed. Consequently, paired Student's t-tests were used to compare LCC and TTE data. The Receiver Operator Characteristic (ROC) curves were used to analyze the diagnostic accuracy of TTE vs. LCC derived AV assessments intra-procedurally. The area under curve (AUC) ranges from 0 to 1. TTE that correctly classifies all AV assessments based on the gold-standard LCC will have an AUC of 1.0, and a TTE with an AUC of 0.5 or less will have no discriminatory value. Data were analyzed using SPSS Version 25 (IBM, Armonk, NY).

RESULTS

Patient characteristics and peri-procedural TAVI outcomes: As stated in Methods, 108 patients underwent awake transfemoral TAVI with simultaneous LCC and TTE assessments performed pre- and post-AV prosthesis implantation. Native valve TAVI accounted for 107 cases, while valve-in-valve TAVI accounted for one case. Hospital mortality was 0.9% (one out of 108). Median length of stay was two days. Complications assessed included: need for emergent open cardiac surgery, shock requiring institution of mechanical circulatory support (typically peripheral veno-arterial extracorporeal membrane oxygenation), major bleeding (> 4 units of exogenous blood products), lower extremity ischemic complications, and pacemaker implantation. These data are displayed in [Table 1](#).

Intra-procedural LCC and TTE assessments of AS severity: We assessed the correlation between pre-implantation LCC and TTE assessments of AS. As stated in Methods, LCC determined MSEPG and PPSEPG, but not PISEPG. In contrast, TTE calculated both PISEPG and MSEPG. Consequently, LCC-assessed MSEPG and PPSEPG were compared only with TTE-assessed MSEPG. As shown in [Figure 2](#) and [Table 2\(A\)](#), TTE MSEPG was substantially and significantly lower than LCC MSEPG, as well as LCC PPSEPG. The mean difference between TTE and LCC MSEPG was -8.9 ± 1.2

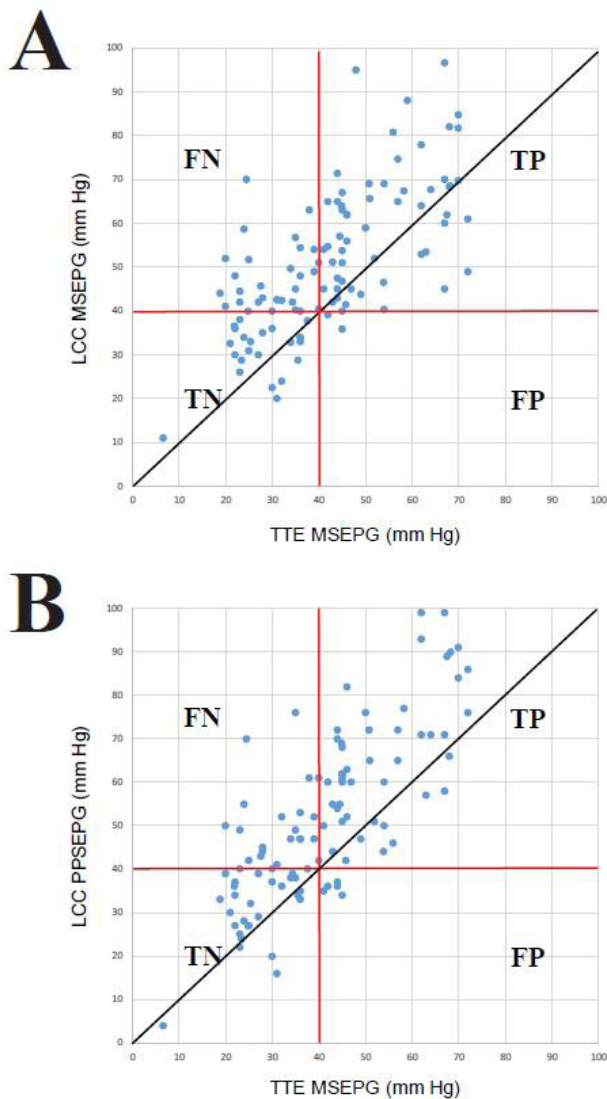


Figure 2. Graphs of LCC-derived versus TTE-derived SEPG, with TTE assessment resulting in underestimation relative to LCC. A) LCC MSEP (y-axis) versus TTE MSEP (x-axis). B) LCC PPSEP (y-axis) versus TTE MSEP (x-axis). The line $y=x$ denotes ideal correlation between LCC and TTE; values above the line denote underestimation by TTE, while values below the lines denote overestimation by TTE. The red lines indicate 40 mm Hg PGs, the cutoff value for severe stenosis. True and false positive and negative data are relative to this value.

(SEM) mm Hg ($P < .001$), while the mean difference between TTE MSEP and LCC PPSEP was -13.3 ± 1.8 (SEM) mm Hg ($P < .001$) (Figure 2 and Table 2).

Although TTE calculations underestimated LCC measurements, since all patients were thought to have severe AS based upon pre-TAVI TTE, the clinical consequences of this underestimation were not clear. We assessed whether the intra-procedural TTE estimates would result in different classifications of AS severity in comparison to LCC. As shown in Figure 2 and Table 2(B), TTE underestimation of AS severity resulted in a substantial degree of severity misclassification.

Table 1. Demographic and clinical outcomes data for patients undergoing awake transfemoral TAVI with simultaneous LCC and TTE assessment of AS. Peri-procedural mortality is defined as index hospitalization mortality. Need for emergent cardiac operation is defined as an operation on the heart and/or great vessels, excluding percutaneous procedures such as pericardiocentesis. Mechanical circulatory/pulmonary support includes de novo (intra- or post-procedural) intra-aortic balloon pump placement, percutaneous/endovascular or surgical ventricular assist device placement, and percutaneous/endovascular or surgical cannulation for extracorporeal membrane oxygenation. Major bleeding is defined as transfusion of ≥ 4 units of exogenous blood products.

Details	N (%)
Total number of patients: 108	
Native valve TAVI	107 (99.1%)
Valve-in-valve TAVI	1 (0.9%)
Peri-procedural mortality	1 (0.9%)
Median length of stay \pm SD (days)	2 \pm 3.5
Need for emergent cardiac surgery	0 (0%)
Peri-procedural mechanical circulatory support	1 (0.9%)
Major bleeding	2 (1.9%)
Lower extremity ischemia	4 (3.7%)
Surgical femoral arterial repair	11 (10.2%)
Pacemaker implantation	8 (7.4%)

Of 108 patients, based upon MSEP, LCC identified severe AS in 84 patients, moderate AS in 23 patients, and mild AS in one patient. TTE identified severe AS in 59 patients, moderate AS in 47 patients, and mild AS in two patients. By examining intra-patient comparisons between LCC and TTE, AS severity was found to be concordant in 79 of the 108 ($79/108 = 73.1\%$) patients. Of the 29 cases ($29/108 = 26.9\%$) of discordant data, TTE overestimated AS severity by ≥ 1 grade in two patients ($2/108 = 1.9\%$). In contrast, TTE underestimated AS severity by ≥ 1 grade in 27 patients ($27/108 = 25.0\%$).

Similar findings were observed for TTE MSEP in comparison to the LCC PPSEP (Figure 2 and Table 2(B)). Of 108 patients, based upon PPSEP (using MSEP criteria), LCC identified severe AS in 76 patients, moderate AS in 30 patients, and mild AS in two patients. Relative to LCC PPSEP, TTE MSEP was found to be concordant in $79/108$ ($81/108 = 73.1\%$). Of the 29 cases ($29/108 = 26.9\%$) of discordant data, TTE overestimated AS severity by ≥ 1 grade in six patients ($6/108 = 5.6\%$). In contrast, TTE underestimated AS severity by ≥ 1 grade in 23 patients ($23/108 = 21.3\%$). Importantly, because all patients met criteria for TAVI based upon pre-TAVI TTE determination of severe AS along with a consistent history and physical examination, TAVI was yet performed in patients in whom AS was assessed as not severe by either or both intra-procedural modalities.

Table 2. Comparison of LCC and TTE assessments of AS. A. LCC-derived MSEPG and PPSEPG, compared to TTE-derived MSEPG. B. Relative concordance and discordance between LCC- and TTE-determined AS severity grade. C. True positive (both LCC and TTE demonstrating severe AS), true negative (both LCC and TTE demonstrating less-than-severe AS), false positive (LCC demonstrating less-than-severe AS, TTE demonstrating severe AS), and false negative (LCC demonstrating severe AS, TTE demonstrating less-than-severe AS) rates of TTE MSEPG versus LCC MSEPG; calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TTE MSEPG at ≥ 40 , ≥ 35 and ≥ 30 mm Hg thresholds for severe AS.

A.	TTE MSEPG	LCC MSEPG	LCC PPSEPG
AS grade			
Mild (<20 mm Hg; grade 1)	2	1	2
Moderate (20 - <40 mm Hg; grade 2)	47	23	30
Severe (≥ 40 mm Hg; grade 3)	59	84	76
Mean \pm SEM (mm Hg)	41.9 \pm 1.5	50.8 \pm 1.6	55.2 \pm 2.4
Mean TTE MSEPG – LCC SEPG \pm SEM (mm Hg)	-8.9 \pm 1.2	-13.3 \pm 1.8	

B.	Discrepancy of TTE MSEPG	Relative to LCC MSEPG	Relative to LCC PPSEPG
No Discrepancy			
No discrepancy	79 (73.1%)	79 (73.1%)	
Discrepancy			
Greater by 1 grade	2 (1.9%)	6 (5.6%)	
Less by 1 grade	26 (24.1%)	23 (21.3%)	
Less by 2 grades	1 (0.9%)	0 (0%)	
Mis-classification rate			
By ≥ 1 grade	29 (26.9%)	29 (26.9%)	

C. Values	TTE MSEPG: 40	TTE MSEPG: 35	TTE MSEPG: 30			
	Relative to LCC MSEPG	Relative to LCC PPSEPG	Relative to LCC MSEPG	Relative to LCC PPSEPG	Relative to LCC MSEPG	Relative to LCC PPSEPG
TP	57	57	66	65	71	67
TN	22	22	18	21	13	17
FP	2	2	6	9	11	15
FN	27	27	18	13	13	9
Sensitivity	67.9%	67.9%	78.6%	83.3%	84.5%	88.2%
Specificity	91.7%	91.7%	75.0%	70.0%	54.2%	53.1%
PPV	96.6%	96.6%	91.7%	87.8%	86.6%	81.7%
NPV	44.9%	44.9%	50.0%	61.8%	50.0%	65.4%

Effects of decreasing TTE threshold criteria on concordance with LCC: Because we observed underestimation of AS severity by TTE, we sought to ask whether lowering this threshold of TTE MSEPG of ≥ 40 mm Hg for defining severe AS might result in improved correlation with LCC data. Therefore, reassessments were performed using a TTE MSEPG cutoff of ≥ 35 or ≥ 30 mm Hg for defining severe AS. As shown in Table 2(C), the sensitivity

of TTE using a 35 mm Hg cutoff relative to LCC improved to 78.6% and 83.3%, relative to MSEPG and PPSEPG, respectively; NPV increased as well, to 50.0% and 61.8%, respectively. However, this was offset by reduced specificity and PPV. Specificity was reduced to 75.0% and 70.0%, relative to LCC MSEPG and PPSEPG, respectively; PPV was reduced to 91.7% and 87.8%, respectively.

Receiver operator characteristic (ROC) relationships between TTE and LCC: ROC relationships between TTE MSEPG and LCC MSEPG as well as TTE MSEPG and LCC PPSEPG were derived as an additional approach to evaluating the quality of TTE assessments of AS (Figure 3). A value of LCC MSEPG of ≥ 40 mm Hg was used as a gold standard to define severe AS. When TTE MSEPG was compared with LCC MSEPG, the area under the curve (AUC) was 0.842, as depicted in Figure 3(A). Similarly, when TTE MSEPG was compared with LCC PPSEPG, the AUC was 0.868, as shown in Figure 3(B). Furthermore, various cut-off values for TTE MSEPG of ≥ 30 , ≥ 35 or ≥ 40 mm Hg and their corresponding sensitivities have been included in these ROC curves. These data suggest that TTE exhibits a decent ability to identify severe AS as assessed by LCC. However, underestimation and significant misclassification of AS yet occurred by using TTE.

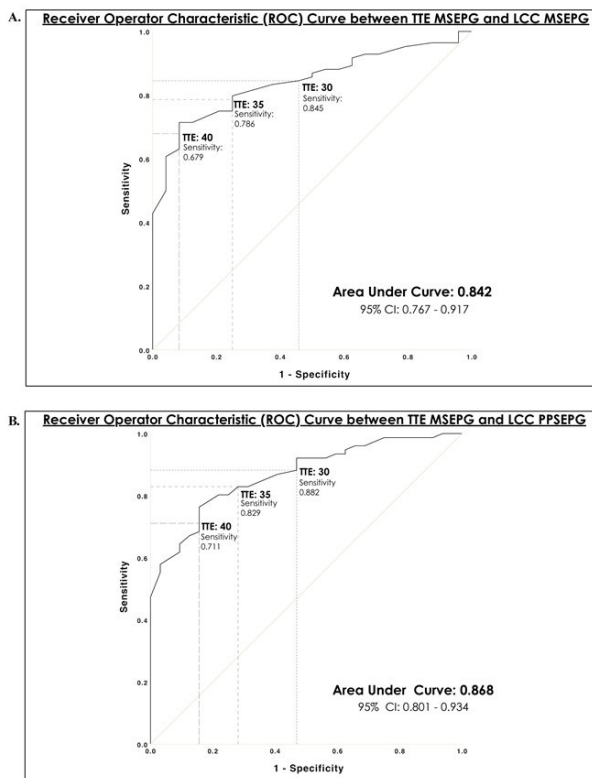


Figure 3. Diagnostic accuracy of intra-procedural TTE for AV assessment compared with LCC. Receiver operator characteristic (ROC) curves and corresponding areas under the curve (AUC) for various TTE cut-offs are shown. A) Comparison of TTE MSEPG (ROC) versus LCC MSEPG ($y=x$). B) Comparison of TTE MSEPG (ROC) versus LCC PPSEPG ($y=x$).

DISCUSSION

In this study, we conducted a retrospective comparison of invasively (LCC) and non-invasively (TTE) determined trans-AV systolic ejection pressure gradients, in the context of transfemoral TAVI undertaken in awake patients. Based upon our review of the literature, this appears to be the first such study in the setting of TAVI. We found that TTE commonly underestimates the MSEPG in a clinically important way. From a screening perspective, using non-standard lower TTE cutoffs improved sensitivity and NPV, albeit with reduced specificity and PPV. All patients met pre-procedural TTE criteria for undergoing TAVI, and thus subsequently thus underwent it regardless of the intra-procedural assessments (see discussion below). Thus, our data would suggest that if simultaneous LCC were hypothetically undertaken, even higher-pressure gradients would be identified.

However, if TTE underestimates SEPG in a clinically important way, then utilization of screening TTE to ascertain the severity of AS is called into question. Current TAVI criteria are reliant upon non-invasive assessments; this may be particularly problematic, as screening studies in principle should have low false-negative and high-sensitivity rates. Thus, it is plausible that a substantial percentage of patients undergoing isolated pre-TAVI (i.e., in a separate setting prior to TAVI, rather than intra-procedurally but pre-implantation) TTE assessments are denied AVR or TAVI that would be identifiably indicated if pre-TAVI LCC were undertaken. Our findings suggest that patients with other clinical data (history, physical examination, etc.) consistent with severe AS should undergo LCC assessment if TTE demonstrates the presence of moderate AS. However, based upon our study of lower TTE cutoff values, it is unclear as to what range of patients (or all) with moderate AS ought to undergo subsequent LCC.

We do not have information on patients who were screened by TTE and failed to demonstrate severe AS by echocardiographic criteria, only on those who qualified and underwent TAVI based upon these pre-procedural TTE assessments. In addition, because of potentially physiologically complex effects of MAC under which LCC is performed, outpatient TTE in an unsedated state cannot be compared with a temporally distinct LCC under MAC. Finally, resting TTE assessments may not reveal clinically important and hemodynamically significant AS, whereas studies under stressed conditions, in which systolic ejection trans-AV flow rates are higher, might reveal functionally severe AS [Johnson 2018].

If pre-procedural TTE findings are consistent with severe AS and intra-procedural LCC fails to confirm severe AS, this presents a different dilemma. All of the patients in our series had a pre-TAVI TTE identifying severe AS, but a substantial percentage of patients had intra-procedural LCC and TTE data that failed to identify at least moderate-severe AS (24/108 = 22.2% for LCC, and 49/108 = 45.4% for TTE). This highlights the high degree of variability in LV contractility and loading conditions between temporally distinct assessments, as well as potential operator dependence and other methodological variations between even the same techniques of assessments conducted at different times. However,

because TTE predominantly appears to underestimate AS severity, our data suggest that if a TTE assessment identifies severe AS, it is probably reasonable to proceed with AVR or TAVI. As previously discussed, it is not possible to fairly compare a pre-procedural TTE with a potential pre-procedural LCC because the latter is performed under conscious sedation (MAC), whereas the former is not.

Important limitations exist in our study. It is a retrospective review of a single interventional cardiologist's experience. With respect to methodology, although LCC is the gold standard for assessment of AS severity because pressure data are measured, the presence of even a small bore catheter spanning the AV orifice may exacerbate severe AS (Carabello effect) [Carabello 1979], even more so when AS is critical. However, the cross-sectional area of the LV pressure-transducing catheters in this study are only $\sim 3.1 \text{ mm}^2$, much smaller than AV orifice areas even in critical AS. Pre-procedural TTE data is not being reported. PISEPG data were not obtained during LCC; thus, we were unable to compare LCC- and TTE-derived PISEPG. In addition, operator dependence with respect to TTE assessments is well-described [Sacchi 2018]; it is conceivable that TTE performed at our institution consistently underestimated AS severity.

In LCC, pressure data are measured directly; valve resistance can be calculated if the cardiac output, and thus stroke volume, are known. In contrast, non-invasive imaging techniques, most notably echocardiography, rely upon approaches to calculate pressure. It has been shown [Svihlova 2017; Svihlova 2016] that standard non-invasive approaches for calculating transvalvular pressure differences have both conceptual and methodological drawbacks (Figure 1; see below). Moreover, using state-of-the-art fluid mechanics theory, solving inverse problems in the Navier-Stokes equations [Svihlova 2016], rigorous approaches to ascertaining LV pressure, intra-AV orifice velocity, and energy dissipation, from pre-specified LV outflow tract velocity and proximal aortic pressure data, have been developed [Svihlova 2017].

Currently used non-invasive approaches to calculating transvalvular pressure gradients employ the Bernoulli equation. However, the Bernoulli equation assumes inviscid flow, i.e., zero blood viscosity in the context of blood flow, and expresses conservation of energy. Viscosity is the physical property of fluids that is necessary for energy losses (dissipation) that occur with flow. Consequently, if the Bernoulli equation is invoked – expressing energy-conservative inviscid flow – concepts expressing energy-dissipative flow such as “resistance” and for time-varying (e.g., pulsatile) flow, “impedance,” are zero. The defining characteristic of a stenosis is that it poses an impedance to flow, i.e., fluid energy is lost due to energy dissipation across the stenosis. There is thus only one circumstance under which the Bernoulli equation can be appropriately applied to a stenosis in order to determine its hemodynamic importance. This is if the pressure within the stenosis happens to be equal to the pressure distal to the stenosis. The entirety of energy losses of flowing blood must occur just distal to the stenosis, where cross-sectional area acutely increases, and are mathematically captured in toto by losses in blood kinetic energy in the immediate post-stenotic

segment (although, as forms of energy are equivalent and interconvertible, this is simply an “accounting” tool with respect to mathematically expressing energy losses). In this situation, even though the Bernoulli equation still does not actually hold in that energy is dissipated, it can be used to calculate pressure gradients if the velocity data are known. However, the aforementioned assumptions are not well-supported. So-called “pressure recovery,” in which the pressure distal to the stenosis is higher than that within the stenosis, is impermissible if the circumstances above are invoked, but commonly occurs in vivo in the setting of valvular stenoses [Rijsterborgh 1987].

While it might be hypothesized that TTE should systematically overestimate LCC-derived pressure gradients (the lack of conceptual basis for this notion is described in the Figure 1 Legend), there is substantial variability in the literature regarding correlation between LCC- and TTE-derived data. Some of the earliest studies [Stamm 1983; Currie 1985] demonstrated good correlation between LCC and TTE, although a degree of underestimation via TTE was identified; yet, TTE appeared to have a low rate of mis-classification of AS severity in these studies. However, as previously noted, Oh et al [Oh 1988] identified large discrepancies between TTE and LCC, with clinically relevant mis-classification of AS severity by TTE. In addition, larger and/or more recent studies have identified less predictable and more complex non-linear, albeit yet roughly proportional, relationships between LCC- and TTE-determined assessments [Otto 1992; Parameswaran 2009].

Finally, it remains unknown whether the clinical importance of AS is in fact related to physiological stenosis severity, as opposed to simply anatomic severity. It is well-known in fluid mechanics that the relationship between conduit cross-sectional area and energy losses is non-linear; as such, anatomically significant stenoses that do not result in substantial energy dissipation may exist. However, it is possible that clinically important sequelae of AS are not only related to energy dissipation, but simply the anatomic extent of AS. For example, a non-dissipative stenosis yet could be associated with low aortic root and thus coronary arterial pressures, thereby resulting in impaired myocardial perfusion and resultant ischemia.

In our view however, the principal aim and impact of this study relates to clinical practice, regardless of potential conceptual advantages to LCC versus non-invasive approaches. Because TAVI criteria are based upon non-invasive modalities, inaccuracies in these modalities warrant either invasive assessment, or refinement of non-invasive criteria. Future studies are essential in order to better delineate both of these diagnostic options.

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