Valvular Heart Disease

Estimation of the End of Ejection in Aortic Stenosis
An Unreported Source of Error in the Invasive Assessment of Severity

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Background—All indices of aortic stenosis (AS) rely on measurements of mean transvalvular pressure gradient ($\overline{\Delta P}$) and flow rate. Because the gradient is reversed during late ejection, the late systolic left ventricular (LV)–aortic pressure crossover may be an erroneous landmark of end-ejection. The aortic incisura should be a better reference to calculate indices of AS invasively.

Methods and Results—The accuracy of the pressure crossover and the incisura to define end-ejection was assessed in a chronic AS experimental model (9 dogs) with the use of an implantable flowmeter and Doppler echocardiography as reference. In 288 hemodynamic recordings analyzed (aortic valve area [AVA]: 0.74 ± 0.46 cm^2), ejection ended 37 ± 29 ms after the pressure crossover but almost simultaneously with the incisura (2 ± 17 ms). Pressure crossover error accounted for significant errors in the measurement of $\overline{\Delta P}$ (95% limits of agreement, $+0$ to $+7$ mm Hg) and AVA (-0.1 to $+0.2$ cm^2). These errors were reduced to less than half with the use of the incisura to define end-ejection. Additionally, the agreement with Doppler-derived AS indices was best with use of the incisura. Pressure crossover error was maximal in situations of higher output, moderate orifice narrowing, higher arterial compliance, and lower vascular resistance. In 32 consecutive patients undergoing cardiac catheterization for AS, the pressure crossover induced a clinically important overestimation of the $\overline{\Delta P}$ from $+22$ to $+50\%$. Errors in AVA estimation were considerably smaller (-2% to $+6\%$) because of simultaneous and offsetting errors in the measurements of $\overline{\Delta P}$ and flow.

Conclusions—The aortic incisura and not the second pressure crossover should be used to obtain invasive indices of AS. (***Circulation*. 2004;110:1114-1120.**)

Key Words: valves ■ stenosis ■ catheterization ■ hemodynamics ■ animal experimentation

Cardiac catheterization is established as the gold standard technique for quantifying aortic stenosis (AS), and noninvasive methods have been validated with catheterization used as reference.[1] Invasive assessment of AS relies on accurate measurements of mean systolic ejection transvalvular pressure gradient ($\overline{\Delta P}$) and mean ejection flow rate ($\overline{Q}$), from which aortic valve area (AVA) is calculated.[1] Obviously, both $\overline{\Delta P}$ and $\overline{Q}$ need to be measured throughout the full systolic ejection period (SEP).[2]

Surprisingly, the method for measuring SEP has not been definitely established in AS. Ejection starts when intraventricular pressure rises above aortic pressure and ends with aortic valve closure. Most textbooks recommend using the second left ventricular (LV)–aortic pressure crossover to identify end-ejection when aortic and LV pressures are

obtained simultaneously.[3–5] However, we[6] and others[7,8] have demonstrated a reversed ΔP between the LV and the aorta during end-ejection in AS. Thus, measuring the SEP from the second LV-aortic pressure crossover may be erroneous. The aortic incisura may be a more accurate landmark of end-ejection,[9] and this criterion is used by some authors to calculate $\overline{Q}$.[10–12] However, whatever landmark is used to define end-ejection, not only flow but also ΔP should be averaged for the full SEP.

The present study was designed to clarify which landmark of end-ejection should be used for the most reliable assessment of AS during cardiac catheterization. An experimental animal model of chronic AS was used in which high-fidelity pressure, flow, and Doppler echocardiographic data were obtained. The implications of the animal findings were then

TABLE 1.   Summary of Hemodynamic Variables of Animal Study

	Median±IQR	Range
Cardiac catheterization		
Heart rate, bpm	118±30	33–196
Mean arterial blood pressure, mm Hg	94±24	43–147
Stroke volume, mL	20±11	5–46
Mean ejection transvalvular flow rate, mL/s	101±67	30–219
Cardiac output, L/min	2.4±1.5	0.6–5.9
Total systemic arterial compliance, mL/mm Hg	0.6±0.71	0.25–2.99
Systemic vascular resistance, dyne · s/cm^5	3101±1707	1425–11 018
Mean transvalvular pressure gradient, mm Hg	13±11	2–71
Aortic valve area, cm^2	0.74±0.46	0.17–2.1
Strouhal No.	0.14±0.11	0–0.96
Doppler echocardiography*		
Vena contracta mean pressure gradient, mm Hg	18±12	2–56
Net mean pressure gradient, mm Hg	14±12	0–44
Aortic valve area, cm^2	0.47±0.32	0.14–1.13
Energy loss coefficient, cm^2	0.53±0.43	0.15–1.44

IQR indicates interquartile range.
*Doppler data available for 7 animals.

assessed in 32 consecutive patients undergoing cardiac catheterization for AS.

Methods

Animals and Surgical Protocol

Nine mongrel dogs (weight, 18 to 24 kg) of both sexes underwent surgery to create a chronic model of degenerative valvular AS characterized by stiff leaflets without commissural fusion.[6,13,14] Studies were approved by the University of Washington Institutional Animal Care Committee and conform with the *Guide for the Care and Use of Laboratory Animals*. An implantable 16-mm transit-time flow probe (Transonics) was placed immediately above the sinotubular junction. Table 1 summarizes the hemodynamic data.

Animal Hemodynamic Studies

Postoperatively, 3 cardiac catheterization studies were performed in each animal, under general anesthesia, at 2-week intervals. A high-fidelity, dual-micromanometer (5 cm apart) catheter (Millar Instruments) was inserted across the aortic valve via the carotid artery. Transvalvular $\bar{Q}$ was measured with a factory-calibrated T101D Transonics flowmeter. Flow, pressure signals, and a lead II ECG were digitized simultaneously at 200 Hz over a 30- to 60-second period. Cardiac output was subsequently varied with saline and dobutamine, and measurements were repeated when hemodynamics stabilized.

Digital Signal Analysis of Hemodynamic Data

Signal processing was performed with the use of custom-developed algorithms in Matlab (version 6.2, The Mathworks, Inc). Measurements were performed on an individual beat basis and then averaged for the whole 30- to 60-second run. Beats with a cardiac cycle variation >10% were rejected.

Onset of ejection was established as the first pressure crossover of the LV and aortic pressure signals.[6] Reference end-ejection was established as the second zero crossing of the flow signal (Figure 1). Thus, reference SEP was calculated as the difference between these 2 time instants. Against this reference, we ascertained the accuracy of 3 end-ejection criteria: (1) the second crossover of the

LV-aortic pressures (detected automatically); (2) the valley of the aortic incisura (detected manually, blinded to the flow and LV pressure signals); and (3) the time of the peak negative first temporal derivative of the pressure signal (T$_{-dP/dt\,min}$, detected automatically).[15] Interobserver variability of the identification of the incisura (75 randomly selected beats) was 3±23 ms. Stroke volume was obtained as the positive time integral of flow during ejection, and $\bar{Q}$ was obtained as stroke volume divided by the SEP. Similarly, instantaneous ΔP (LV−aortic pressure) was averaged for each SEP to obtain $\overline{\Delta P}$. AVA was computed according to the Gorlin formula with the use of the following: (1) $\overline{\Delta P}_{flow\,probe}$ and $\bar{Q}_{flow\,probe}$ (reference); (2) $\overline{\Delta P}_{pressure\,crossover}$ and $\bar{Q}_{pressure\,crossover}$; (3) $\overline{\Delta P}_{incisura}$ and $\bar{Q}_{incisura}$; and (4) $\overline{\Delta P}_{pressure\,crossover}$ and $\bar{Q}_{incisura}$. This latter method for measuring AVA[10,12,16] was designated AVA$_{combined}$.

Total systemic arterial compliance was calculated from the aortic pressure signal by the area method.[17] The Strouhal number was calculated as follows:

$$\text{Strouhal Number} = \frac{\text{Inertial } \Delta P}{\text{Convective } \Delta P} = 2.87 \times \frac{Q_{max}}{\bar{Q}} \times \frac{\text{AVA}^{3/2}}{\text{Stroke Volume}},$$

where Q_{max}=peak ejection flow rate.[6,18] The Strouhal number is a dimensionless index used to describe unsteady flow systems and accounts for the relative contribution of inertial and convective forces.[8,18] In AS, the DP is the consequence of adding the forces related to (1) frictional energy losses (dissipated as heat); (2) local inertial acceleration (the change in velocity with time in a given point, due to ventricular pulsatility); and (3) convective acceleration (the change in velocity with space at a given instant, due to lumen tapering caused by the valvular stenosis). The Strouhal number accounts for the ratio between the latter 2 components. Thus, a value >1 reflects predominance of inertial forces (eg, a normal subject), whereas a value close to 0 reflects almost exclusive convective forces (eg, a critical orifice narrowing; see Discussion).[8,18]

Doppler Echocardiography

In 7 animals, pulsed- and continuous-wave Doppler spectrograms of the LV outflow tract (LVOT) and AS (Ao) jets were obtained from the apical 5-chamber view.[13,14] The $\overline{\Delta P}$ at the level of the vena contracta was obtained from mean velocities ($\bar{V}$) as $\Delta P = 4(\bar{V}^2_{Ao} - \bar{V}^2_{LVOT})$. Doppler AVA was obtained with the use of the
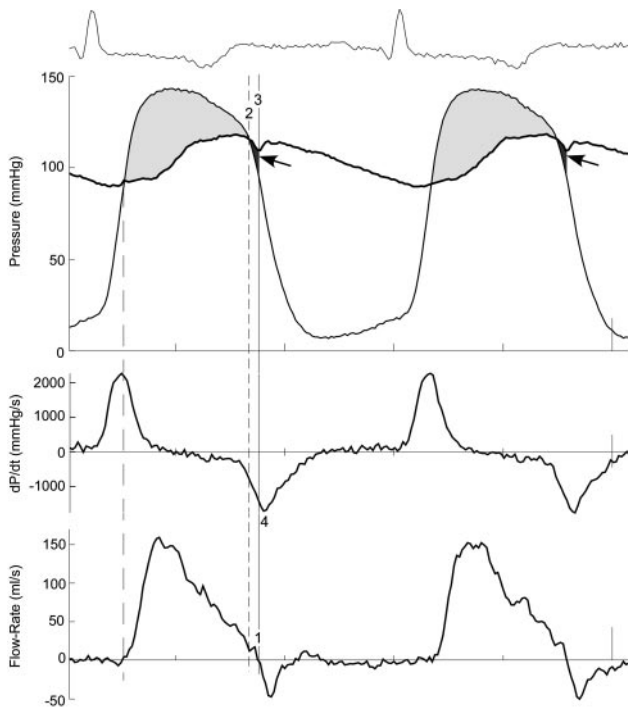
Figure 1. Recordings from an animal with AS. Lead II ECG (top) LV (thin line) and aortic (thick line) pressures (middle top), the first temporal derivative of LV pressure (dP/dt, middle bottom), and transvalvular flow rate (bottom) are shown. Onset- (wide dashed line) and end-ejection (continuous line, 1) are readily identified from the flow signal. The second pressure crossover (narrow dashed line, 2) occurs 18 ms earlier than end-ejection. The incisura (3) is recorded simultaneously, and the $T_{-dP/dt\ min}$ (4) takes place slightly later than end-ejection. The $\Delta P_{pressure\ crossover}$ is shown in light gray, and the negative gradient is shadowed in dark gray (arrow).

continuity equation as stroke volume divided by the AS time-velocity integral. To allow comparison with invasive parameters, Doppler indices of AS were corrected for the effect of pressure recovery, calculating the net $\overline{\Delta P}$ (LV−ascending aortic pressure) and the energy-loss coefficient (physiologically equivalent to Gorlin-derived AVA).[19,20]

Clinical Study

Hemodynamic data from 38 consecutive patients undergoing cardiac catheterization for AS were studied. Simultaneous LV and aortic pressures were recorded with the use of fluid-filled, 8F double-lumen pigtail catheters (Cordis Corp). Cardiac output was obtained by the Fick and thermodilution methods and averaged. High-quality paper pressure tracings were automatically digitized (Digitize-Pro Software, version 4.1) at 1000 Hz and processed in a manner identical to that of the animal signals. Six patients were excluded because of suboptimal superimposition of the 2 waveforms seen while both ports resided within the aorta, and therefore 32 patients (31 male; aged 73±7 years; LV ejection fraction=0.54±0.18) are the basis of this report. The aortic incisura could not be identified clearly in 19 subjects because of overdamping. In 9 patients, the clear point of slope change of the aortic pressure recording was used to identify end-ejection.[21] In the remaining 10 patients, the $T_{-dP/dt\ min}$ of the LV signal was used to estimate zero systolic flow. Because $T_{-dP/dt\ min}$ is close but not simultaneous to end-ejection,[21] this landmark was first calibrated by linear regression in the subset of patients showing a clear visualization of the incisura ($T_{incisura}=1.232 \cdot T_{-dP/dt\ min} -0.038$; $R=0.96$, n=36 beats).

Statistical Analysis

Data are presented as median±interquartile range. Agreement between indices was assessed by the intraclass correlation coefficient (R_{ic}) and Bland-Altman analysis. Errors are reported as mean±SD (limits of agreement). The analysis of the determinants of SEP error was based on prior evidence suggesting a relationship with the Strouhal number,[6,8,18] arterial compliance, and vascular resistance.[22] Hence, this association was assessed by multivariate regression accounting for factor interaction where the Strouhal number was first fitted to a 3-knot restricted cubic spline function. All analyses were performed with S-plus software (Insightful, version 2000), expanded by public-domain libraries.[23] A probability value <0.05 was considered significant.

Results

Accuracy of End-Ejection Criteria and Impact on AS Indices

End-ejection took place 37±29 ms (range, 0 to 146 ms) after the second LV-aortic pressure crossover (288 hemodynamic data sets, 2532 beats; Figure 1). The pressure crossover was a very inaccurate criterion to measure the SEP, and agreement with the reference was far better for the SEP$_{incisura}$ (Figure 2). Reference SEP could also be closely predicted by the $T_{-dP/dt\ min}$. Compared with Doppler-derived SEP, SEP$_{incisura}$ was also more accurate (error=−6±8%, R_{ic}=0.82) than the SEP$_{pressure\ crossover}$ (error=+14±11%, R_{ic}=0.53).

The SEP$_{pressure\ crossover}$ error caused significant bias and imprecision in the estimation of $\overline{\Delta P}$ and $\overline{Q}$ (Table 2). These errors in $\overline{\Delta P}_{pressure\ crossover}$ and $\overline{Q}_{pressure\ crossover}$ partially balanced each other in the calculation of AVA$_{pressure\ crossover}$. The incisura criterion highly improved the accuracy of $\overline{\Delta P}$ and $\overline{Q}$ measurements, yielding a more accurate AVA$_{incisura}$. The most inaccurate method of measuring AVA was AVA$_{combined}$. Compared with Doppler-derived indices, agreement was also better for the incisura than for the pressure crossover ($\overline{\Delta P}$: error=−5±49%, R_{ic}=0.74, versus −21±47%, R_{ic}=0.68; AVA: error=−3±20%, R_{ic}=0.92, versus −12±21%, R_{ic}=0.88, respectively).

Hemodynamic Predictors of Error

Relative SEP$_{pressure\ crossover}$ error correlated with a higher Strouhal number (total, interaction, and nonlinear factors: all $P<0.0001$), a higher arterial compliance (total and interaction factors: $P<0.0001$), and a lower vascular resistance (total and interaction factors: $P<0.0001$; adjusted R^2 for the final model=0.70). The slope of SEP error was very steep at low Strouhal numbers, particularly when arterial compliance was high and vascular resistance was low (Figure 3).

Clinical Study

Differences in AS indices due to the method used to estimate end-ejection are summarized in Table 3 and Figure 4. As shown, AVA$_{combined}$ may cause a >33% underestimation of AVA. Errors in the 13 patients showing a clear identification of the incisura were similar to those of the full group ($P>0.4$ for all AS indices).

Discussion

To assess the severity of AS, current textbooks recommend measuring $\overline{\Delta P}$ by averaging the area inside the LV and aortic
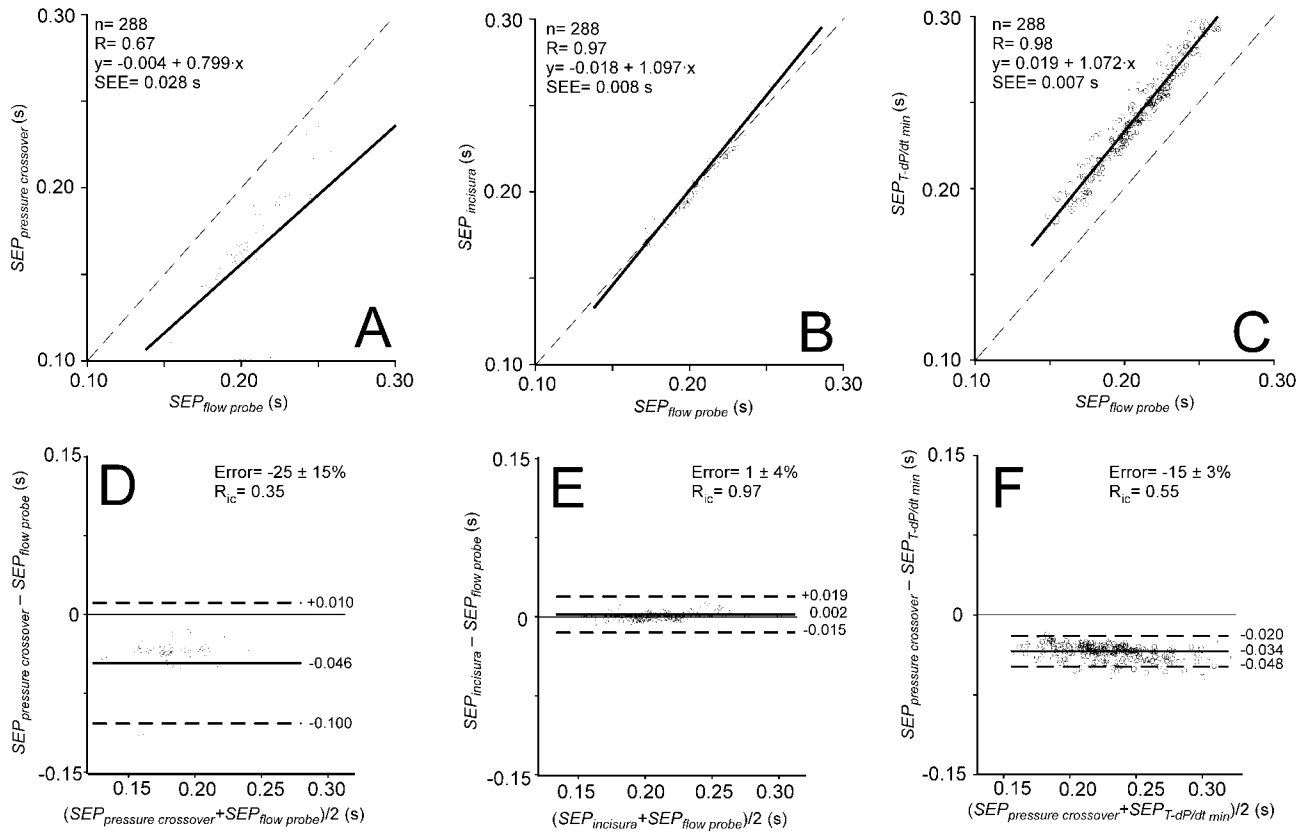
Figure 2. Accuracy of the end-ejection criteria. Linear regression and Bland-Altman analyses of the pressure crossover (A, D), the aortic incisura (B, E), and the $T_{-dP/dt\ min}$ (C, F) against reference SEP are shown.

pressure tracings.[3–5,11] Mean flow rate is calculated by dividing stroke volume by the SEP, measured as the time between the first and second LV-aortic pressure crossover. Our study demonstrates potential errors in this methodology. First, during end-ejection, the ΔP between the LV and the aorta is frequently reversed. The planimetry method for measuring $\overline{\Delta P}$ will therefore overestimate the total ejection gradient in such cases (up to +31%). Second, for the same reason, SEP measured from the pressure crossover may be shorter than actual ejection period, thus also overestimating $\bar{Q}$. Because the errors in $\overline{\Delta P}$ and $\bar{Q}$ partially compensate each other in the Gorlin formula, the inaccuracy in estimating AVA is smaller (+6% error) but may increase to as much as −33% error when real ejection $\bar{Q}$ is combined with the $\overline{\Delta P}_{pressure\ crossover}$ to calculate AVA.[11] These errors in quantifying the severity of

AS may become clinically relevant in situations in which there are discrepant noninvasive findings or associated coronary heart disease or in the setting of low-flow AS (see below).

Systolic Ejection Period in AS
Although never considered in the clinical assessment of AS, the fact that forward flow continues in the systemic circulation despite a negative ΔP was recognized several years ago.[24,25] The term *hangout interval* was coined to designate the time interval between the LV pressure (measured not at the time of pressure crossover but at the pressure value of the incisura) and the aortic incisura.[7] The basis of the reverse ejection gradients was further established in humans with the use of high-fidelity micromanometers.[26] End-ejection ΔPs

**TABLE 2.   Accuracy of AS Measurements Obtained Using Different End-Ejection Criteria in Animal Data Set**

	Pressure Crossover				Aortic Incisura			
	Absolute Error	Relative Error	R	R_{ic}	Absolute Error	Relative Error	R	R_{ic}
Mean transvalvular pressure gradient	3.1±1.8 mm Hg (−0.4 to +6.5)	21±12% (−3 to +45)	0.989	0.950	0.0±1.0 mm Hg (−2.1 to +2.1)	0±8% (−16 to +16)	0.996	0.995
Mean transvalvular flow rate	36±37 mL/s (−35 to +107)	29±30 % (−30 to +88)	0.876	0.628	0±4 mL/s (−8 to +8)	0±4% (−8 to +8)	0.997	0.996
Aortic valve area	0.08±0.08 cm² (−0.09 to +0.24)	10±11% (−12 to +32)	0.986	0.954	0±0.05 cm² (−0.09 to +0.10)	1±7% (−13 to +15)	0.990	0.990

Errors are expressed as mean±SD (95% limits of agreement). R indicates Pearson's correlation coefficient; R_{ic}, intraclass correlation coefficient.
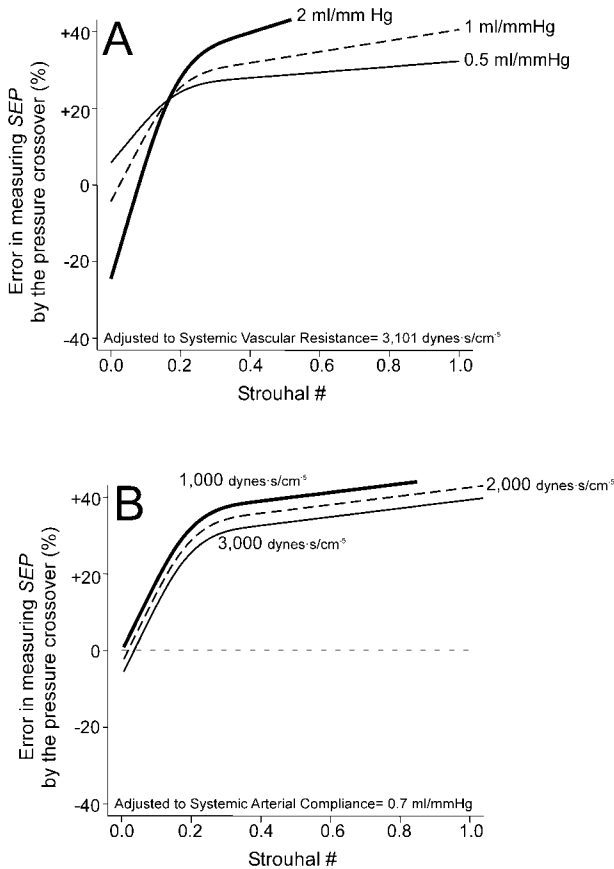
Figure 3. Correlates of SEP error using the second LV-aortic pressure crossover: results of the nonlinear multivariate analysis. The association between the Strouhal number and SEP error is shown, calculated for 3 values of total systemic arterial compliance (A) and for 3 values of systemic vascular resistance (B). Multivariate model accounts for nonlinearity of the Strouhal number effect, as well as for interactions between arterial compliance and the other 2 factors (P<0.0001 for total, nonlinear, and interaction terms; adjusted R^2=0.70).

have been also characterized in AS. Clark[8] demonstrated reverse ΔPs in an experimental model of supravalvular AS, and Shaver[22] reported a wide hangout interval in a patient with severe AS. The latter author further suggested a rela-
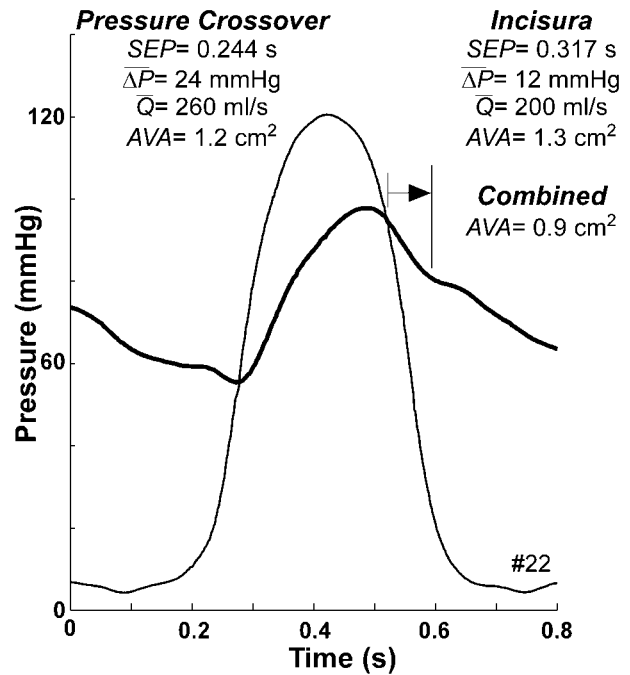
Figure 4. Simultaneous aortic (thick) and LV pressure (thin) tracings from a patient with moderate or severe AS according to the criterion used to identify end-ejection.

tionship of the hangout interval with aortic compliance.[22] The present study demonstrates that these concepts of basic ejection hemodynamics need to be incorporated in the clinical assessment of AS.

As expected,[6,8,18] the Strouhal number was the most important variable related to SEP error. In very tight orifice stenoses, convective forces predominate, the Strouhal number is close to 0.05,[1] and SEP-related error is small. However, in AS there may be situations in which inertial forces cannot be neglected. If inertial acceleration increases, and orifice narrowing is moderate, the Strouhal number rises to 0.1 to 0.2. In this range, SEP error is dramatically augmented, particularly in patients with high total systemic arterial compliance and low systemic resistance (Figure 3). It is precisely these

TABLE 3.   Differences in AS Indices Related to Using the Pressure Crossover or the Incisura as Surrogates of End-Ejection to Measure Severity of AS

	Method			Difference	
	Pressure Crossover	Aortic Incisura	Combined	Absolute	Relative
Systolic ejection period, s	0.271±0.027	0.337±0.025	...	−0.063±−0.009 (−0.799 to −0.040)	−21±3% (−27 to −15%)
Mean transvalvular pressure gradient, mm Hg	37±9	24±8	...	11±2 (+7 to +16)	36±7% (+22 to +50%)
Mean ejection transvalvular flow rate, mL/s	250±97	200±72	...	49±13 (+24 to +74)	21±5% (+11 to +31%)
Aortic valve area, cm^2	0.90±0.33	0.88±0.36	...	0.02±0.02 (−0.02 to +0.06)	2±2% (−2 to +6%)
Aortic valve area$_{combined}$, cm^2	...	0.88±0.36	0.71±0.31	−0.16±0.06 (−0.3 to −0.05)	−19±7% (−33 to −5%)

Data are from 32 consecutive patients undergoing simultaneous LV and aortic catheterization. Variables are expressed as median±interquartile range. Errors are expressed as in Table 2, of the pressure crossover–aortic incisura differences.

patients with an "intermediate" degree of valve narrowing who require an accurate determination of AS severity, because arriving at the correct clinical decision on the necessity of valve surgery can be difficult and challenging.

Clinical Implications: Moderate Disease and Low-Flow AS

A mild or moderately reduced valve orifice associated with a hyperdynamic state constitutes a typical scenario resulting in a relatively high Strouhal number. Inotropic stimulation during cardiac catheterization has been advocated to ascertain the severity of AS in patients with impaired systolic function.[1] In the presence of contractile reserve, dobutamine markedly increases inertial forces.[6,27] Consequently, the Strouhal number rises, and transvalvular pressure reversal is expected. Accounting only for the positive component of $\overline{\Delta P}$ may therefore induce significant overestimation of disease severity in the hypercontractile state. An illustrative example of this phenomenon is demonstrated in a recent study by Nishimura et al[28] on the value of dobutamine challenge for assessing the severity of low-flow AS. In the example shown in Figure 2B of their article, the authors display the tracings of a patient with only mild AS at the time of operation. Reported values of $\overline{\Delta P}$ at rest and peak stress are 17 and 20 mm Hg, respectively. Of note, the baseline tracing shows almost no SEP error. However, with dobutamine infusion, the pressure crossover anticipates end-ejection by $>50\%$, as determined by the aortic incisura. Consequently, the "actual" ejection $\overline{\Delta P}$ during dobutamine infusion is reduced to only 10 mm Hg. This drop in $\overline{\Delta P}$ is inconsistent with "fixed" severe AS and clearly identifies the patient as having pseudosevere AS. Thus, we believe that this example illustrates the advantages of using the aortic incisura.

Study Limitations

The absence of an independent gold standard method for assessing AS severity is a limitation of all in vivo studies of AS hemodynamics. Pulse wave propagation from the distal to the proximal measuring stations may cause a certain delay in pressure recordings between the transducers. The fact that the first LV-aortic pressure crossover closely matches flow probe–defined ejection in our experimental model[6] corroborates that correction for pulse wave propagation is not necessary. As found in our clinical study, the incisura may be difficult to identify from aortic pressure tracings obtained with the use of fluid-filled catheters. In those cases in which the incisura remains impossible to recognize despite careful catheter damping, high-fidelity catheters and/or the $T_{-dP/dt\ min}$ may be a suitable alternative. Whether an exact identification of end-systole is amenable by processing LV-aortic pullback pressure recordings deserves further investigation. Unfortunately, the methods proposed in our study are not suitable if the femoral artery sheath pressure is used as a surrogate of central aortic pressure.

Conclusions

The potential existence of reverse pressure gradients during end-ejection should be taken into consideration when the severity of AS is assessed invasively, particularly in patients with moderate orifice narrowing and increased cardiac output. Therefore, end-ejection landmarks such as the aortic incisura, and not the LV-aortic pressure crossover, should be used to measure the SEP and calculate $\overline{Q}$; additionally, the ΔP must be averaged up to the aortic incisura to measure the full ejection $\overline{\Delta P}$. These considerations improve the invasive assessment of disease severity.

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