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Severe Aortic Stenosis and Myocardial Function

Diagnostic and Prognostic Usefulness of Ultrasonic Integrated Backscatter Analysis

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Background—The aim of this study was to assess the myocardial reflectivity pattern in severe aortic valve stenosis through the use of integrated backscatter (IBS) analysis. Patients with aortic stenosis (AS) were carefully selected in the Department of Cardiology.

Methods and Results—Thirty-five subjects (AS: valve orifice ≤ 1 cm^2; 12 female; mean age, 71.8 ± 6.2 years) and 25 healthy subjects were studied. All subjects of the study had conventional 2D-Doppler echocardiography and IBS. Backscatter signal was sampled at the septum and posterior wall levels. Patients with AS were divided into 2 groups: 16 patients with initial signs of congestive heart failure and a depressed left ventricular systolic function (DSF) (ejection fraction [EF] range, 35% to 50%) and 19 asymptomatic patients with normal left ventricular systolic function (NSF) (EF $>50\%$). Myocardial echo intensity (pericardium related) was significantly higher at the septum and posterior wall levels in DSF than in NSF and in control subjects. IBS variation, as an expression of variation of the signal, appeared to be significantly lower in AS with DSF than in NSF and in control subjects, at both the septum and posterior wall levels. Patients with DSF underwent aortic valve replacement, and, during surgical intervention, a septal myocardial biopsy was made for evaluation of myocardium/fibrosis ratio. Abnormally increased echo intensity was detected in left ventricular pressure overload by severe aortic stenosis and correlated with increase of myocardial collagen content (operating biopsy).

Conclusions—One year after aortic valve replacement, we observed a significant reduction of left ventricular mass, and, only if pericardial indexed IBS value (reduction of interstitial fibrosis) decreased, it was possible to observe an improvement of EF and of IBS variation. **(*Circulation*. 2004;110:849-855.)**

Key Words: hypertrophy ■ ultrasonics ■ aorta ■ stenosis ■ valves

Fibrosis is an early morphological alteration in patients with aortic stenosis (AS); it is a major determinant of diastolic dysfunction and systolic pumping capacity, and it is one of the structural substrates for arrhythmogenicity, thus playing a major role for sudden death and the progression of congestive heart failure (CHF).[1] Cell loss, mainly by autophagy and oncosis, significantly contributes to the progression of left ventricular (LV) systolic dysfunction.[2] Hemodynamic severity of AS is another important element, which, together with clinical findings, is fundamental in decision-making about patients.[3] Once patients with AS become symptomatic with angina, syncope, or CHF, average survival significantly decreases, and for those patients, operative risk increases and mortality rates are higher.[4] Current hemodynamic assessment of AS severity relies on indexes such as transvalvular pressure gradient (ΔP) and aortic valve area (AVA), obtained by Doppler echocardiography. These indexes are suboptimal because they correlate poorly with patient symptoms, provide little prognostic information, and depend on flow rate; furthermore, the appropriate cutoff values of ΔP and AVA for establishing disease severity are unclear.[5]

Quantitatively assessed ultrasonic backscatter signal (IBS) is directly related to morphometrically evaluated collagen content in human beings. Analysis of its dynamic aspects (cycle-dependent variation of IBS) is useful to obtain information about myocardial intrinsic contractile performance, independent of wall motion.[6,7] Furthermore, myocardial reflectivity (IBS) in humans is directly related to myocardium collagen content.[8]

The aim of the study was to assess diagnostic and prognostic values of integrated backscatter indexes in patients with severe AS and in particular to test if these textural indexes could have a real incremental value in comparison to conventional echocardiographic systolic and diastolic functional indexes in decision-making of this valvular pathology.

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Methods

Study Population

Two groups of strictly age-matched subjects were studied (case-control study): 35 patients with AS, selected in the Department of Cardiology (AS: valve orifice ≤ 1 cm^2; 12 female; mean age, 71.8±6.2 years) and 25 healthy subjects of comparable age (70.5±5.5 years), sex (9 female), and body mass index (AS: 25.1±2.7 versus control: 23.6±3.8; NS). Apart from no previous myocardial infarction and a negative history of renal and connective tissue disease, selection criteria included absence of malignant or accelerated hypertension, severe CHF, cardiomyopathy, obesity, and diabetes. Once selected, all the participants underwent echocardiography, thus reserving eligibility for coronary angiography and cardiac catheterization; none had coronary artery disease. Hemodynamic aortic valve area (AVAc), according to the Gorlin equation, and peak-to-peak gradient were calculated. Patients with AS were divided into 2 groups: 16 patients with initial signs of CHF and a depressed LV systolic function (DSF) (ejection fraction [EF] range, 35% to 50%) (all in New York Heart Association [NYHA] class II) and 19 who were asymptomatic and with a normal LV systolic function (NSF) (EF >50%) (all in NYHA class I).

The 16 patients with symptomatic AS underwent aortic valve replacement (10 with biological prosthesis and 6 with mechanic prosthesis), and during surgical intervention, 10 underwent myocardial biopsy at the proximal anterior interventricular septum level (left side). Furthermore, they all were examined after 1 year for evaluation of LV function by conventional echocardiographic and by backscatter analysis (operating with the same system settings of the echocardiograph in comparison with the previous study). The study was approved by local ethical committee.

Experimental Procedures: Doppler Echocardiography

Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Korotkoff phase V) were measured at the time of echocardiographic examination by mercury sphygmomanometer with patients in the supine position. The reported value was the mean of several indirect recordings taken over a 30-minute period. Body surface was calculated according to standard formulas.

Conventional Doppler echocardiographic studies were performed with a digital Philips Sonos 5500 echocardiograph with S3 probe. Apart from conventional echocardiographic parameters previously described,[9] AVA and relative ΔP were calculated by using continuity and Bernoulli equations, respectively. Aortic regurgitation was graded on the basis of color Doppler flow imaging (patients with medium or severe aortic insufficiency were excluded). Valve aortic resistance was calculated as $28 \cdot \sqrt{\Delta P}/AVA(AVR)$.[10] Left ventricular stroke work loss was expressed as a percentage and obtained as $100 \cdot \Delta P/(\Delta P + SBP)$.[11]

Acoustic Densitometry

Integrated backscatter imaging technology has been commercially applied to provide a robust signal (calibrated in decibels) for purposes of tissue characterization research. Acoustic densitometry measurement is independent from nonlinear compression and postprocessing functions of the ultrasound imaging chain. The images were obtained through the use of harmonic imaging mode, which is able to determine an improvement of 2D image quality.[12] A detailed IBS methodology was used, as previously described.[9]

Other important control settings of the imaging chain such as preprocessing, focus position, persistence, compression, frame rate, and postprocessing were maintained constant for all patients, accurately avoiding the signal saturation (ie, backscatter value sampled at maximum value for the dynamic range of the system) at every level (pericardium, valve, myocardium) for the possibility of estimation errors. End-diastolic IBS parameters (IBS_{ed}) were then indexed for IBS pericardial values, both at the septum (IBS_{si}) and the posterior wall (IBS_{pwi}). The measurements obtained for each cardiac cycle were intensity of IBS at end-diastole (IBS_{ed}), intensity of IBS at end-systole (IBS_{es}), IBS variation ($IBSV = IBS_{ed} - IBS_{es}$), and cyclic variation index at the septum (CVI_s) and posterior wall levels (CVI_{pw}), which were computed by use of the formula $([IBS_{ed} - IBS_{es}]/IBS_{ed}) \cdot 100$.

Operating Myocardial Biopsy and Data Processing

During open heart surgery, biopsy samples weighting 30 to 80 mg were removed from the LV septum, immediately frozen in liquid nitrogen, and stored at −80°C. Tissues were fixed in 10% formalin and embedded in paraffin. Sections (5 μm) were stained with hematoxylin and eosin and modified trichrome stain for histological evaluation. Digitized pictures were visualized on a high-resolution color display (SAMPO, Tao-Yuan-Hsien). The true color image analysis software package KS300 version 1.2 (Kontron Elektronik GmbH) was run for interactive manipulation, quantification of the images, and data collection. Geometric calibration was set with erythrocyte diameter (7 μm). The different components of the myocardial biopsy were marked, calculated by computer analysis, and expressed as micrometers squared. In particular, the following parameters were analyzed: total area: the overall area occupied by the myocyte and connective tissue; myocyte area: the overall area occupied by the myocyte; connective area: the area covered by fibrous connective tissue; and myocyte area/connective area: the ratio between the area occupied by myocyte and the area covered by connective tissue. All measurements were made without knowledge of the clinical data.

Statistical Analysis

Continuous variables are expressed as mean±1 SD. A multiple group comparison was performed through an ANOVA, followed by Scheffe's test. Intragroup differences were evaluated by means of the Student's t test. The intraclass correlation coefficient (r_i) was calculated according to Bland and Altman's procedure, with a 1-way ANOVA used for repeated measurements.[13] Relations between IBS and 2D echocardiographic measurements were expressed in terms of linear regression analysis. Receiver operating characteristic (ROC) curve analysis was generated by a nonparametric method[14] to test the predictive discrimination of IBS parameters by the aortic and control groups and between the aortic subgroups. A probability value of <0.05 was considered significant.

Results

Blood pressure and heart rate overlapped in patients with AS and in the control group. Interventricular septum and posterior wall thicknesses were greater in AS, and both left ventricular mass index (by body surface, in g/m^2) (LVM_{bs}) and left ventricular mass index (by height, in g/m$^{2.7}$) (LVM_h) were significantly higher in the AS subgroups compared with control subjects (Table 1). Left ventricular end-diastolic diameter was slightly higher in the DSF subgroup compared with the NSF subgroup and control subjects (Table 1). The E/A ratio was significantly higher in control subjects (Table 1). Ejection fraction and fractional shortening were significantly lower, by definition, in the DSF subgroup (Table 1). The echo-derived hemodynamic data regarding the aortic valve showed that both peak and mean ΔP were significantly higher in the DSF group, and the AVA was significantly lower in the DSF group compared with the asymptomatic AS subgroup. AVR and stroke work loss were significantly higher in the group with DSF (Table 1). Regarding IBS, in DSF the cyclic variation index and IBS variation, both at the proximal level of the septum and of the posterior wall, were significantly lower than in NSF and in control subjects (Table 2). If we consider the IBS_{si} and IBS_{pwi}, their values were significantly higher in DSF than in NSF and in control subjects.

TABLE 1. Conventional Echo Doppler Parameters

Parameters	Aortic Stenosis DSF (A) (n=16) Mean	SD	Aortic Stenosis NSF (B) (n=19) Mean	SD	Control (C) Mean	SD	ANOVA P<
EDD, mm	54.2‡	3.3	45.3†	4.6	50.2	4.1	0.05
FS, %	25.2‡	4.4	40.5	6.3	35.1*	5.4	0.05
EF, %	41.4‡	2.4	56.2	3.7	60.7*	4.3	0.05
DS_{th}, mm	16.3	3.3	15.5†	3.7	9.7*	1	0.001
DPW_{th}, mm	12.2	1.3	11.7†	1.8	9.6*	2.4	0.01
LVM_{bs}, g/m^2	186.8	44.5	158.7†	37.4	101.3*	12.4	0.001
LVM_h, $g/m^{2.7}$	85.4	23.6	78.4†	27	43.5*	5.5	0.001
mESS	77.8‡	16.7	55.7	16.5	66.1	17.9	0.05
Peak E, m/s	0.85	0.1	0.76	0.1	0.72	0.1	NS
Peak A, m/sec	0.92	0.2	0.81†	0.2	0.47*	0.1	0.01
E/A ratio	0.96	0.2	0.99†	0.3	1.6*	0.3	0.03
IVRT, mms	78.6	7.9	81.6	5.9	85.8	8.3	NS
AS peak vel, m/s	4.7‡	1.1	3.8†	1.3	1.3*	2.5	0.001
ΔP Aortic peak, mm Hg	88.3‡	14	78.5†	18	5.2*	3.1	0.001
ΔP Aortic mean, mm Hg	67.9‡	10.5	46.2†	10.2	4.3*	2.7	0.001
AVA, cm^2	0.74‡	0.13	0.97	0.16	...	...	0.05
AVR, dyn/s per cm^{-5}	349.8‡	39	235.8†	59	22.4*	8.3	0.01
SWL, %	39.5	10.2	19.4	10.5	4.5	0.5	0.01
AVAc, cm^2	0.67‡	0.12	0.88	0.15	...	...	...
Peak-to-peak gradient, mm Hg	78.5‡	11.3	68.5	14.2	...	...	...

EDD indicates end-diastolic diameter; FS, fractional shortening; DS_{th}, diastolic interventricular septum thickness; DPW_{th}, diastolic posterior wall thickness; mESS, meridional end systolic stress; IVRT, isovolumic relaxation time; and SWL, stroke work loss. Other abbreviations as defined in text.

*Comparison between C and A ($P<0.05$).

†Comparison between C and B ($P<0.05$).

‡Comparison between A and B ($P<0.05$).

For separating patients with AS with DSF and those with NSF by using ROC curve analysis (Figure 1), (A) CVIs yielded an area under curve of 0.93±0.04 ($P<0.001$) (95% CI, 0.86 and 0.99); (B) IBS_{si} showed the higher discriminating power, with an area under the curve of 0.97±0.00 ($P=1$) (95% CI, 1.00 and 1.00), whereas (C) the variation index at proximal septum level ($IBSV_s$) showed an area under the curve of 0.95±0.03 ($P<0.0001$) (95% CI, 0.87

TABLE 2. Tissue Characterization Parameters

Parameters	Controls (n=25) (C) Mean	SD	Aortic Stenosis (n=16) Symptomatic (A) Mean	SD	Aortic Stenosis (n=19) Asymptomatic (B) Mean	SD	ANOVA P<
IBS_{Si}, %	42.6	5.3	64.6‡	5.7	52.4*†	6.2	0.01
IBS_{PWi}, %	47.1	6.1	62.2‡	5.3	55.3†	7.7	0.01
CVI_S, %	30.4	5.0	12.7‡	3.5	18.3*†	4.5	0.001
$IBSV_S$, %	7.1	1.5	2.3‡	1.5	4.5§*	1.3	0.001
CVI_{PW}, %	41.2	6.6	13.2‡	4.6	16.9†	5.3	0.001
$IBSV_{PW\ (dB)}$	8.2	2.2	3.4‡	1.8	5.4†	1.5	0.001

IBS_{Si} indicates diastolic backscatter at proximal septum (by pericardium) (%); IBS_{PWi}, diastolic backscatter at proximal posterior wall (by pericardium) (%); CVI_S, cyclic variation index at proximal septum level (%); CVI_{PW}, cyclic variation index at proximal posterior wall thickness (%); and $IBSV_{PW}$, variation index at proximal posterior wall thickness (dB).

*Comparison between A and B ($P<0.05$).

†Comparison between C and B ($P<0.05$).

‡Comparison between C and A ($P<0.05$).

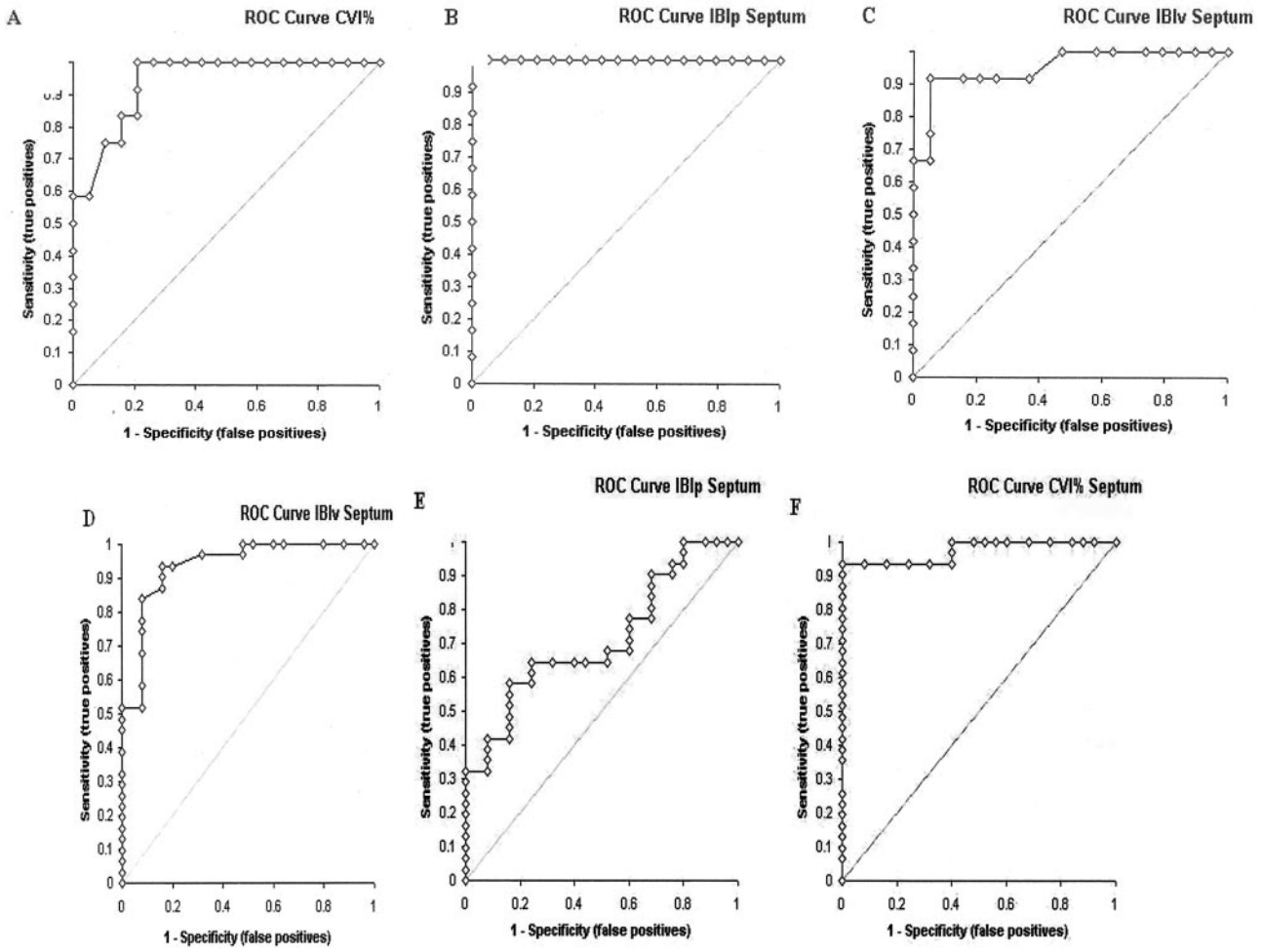

Figure 1. A, Receiving operating characteristic curve analysis for separating patients with AS with DSF and those with NSF (curves A through C). B, Receiving operating characteristic curve analysis for separating patients with AS and control subjects (curves D through F). For details, see text.

and 0.99). By using an IBS_{si} >56.6% as a cutoff, patients were discriminated as DSF and NSF, with a sensitivity of 100% and a specificity of 100% (Figure 1). For separating patients with AS and control subjects through the use of ROC curve analysis, (D) $IBSV_s$ pointed out an area under curve of 0.93 ± 0.03 ($P<0.0001$) (95% CI, 0.87 and 0.99); (E) IBS_{si} yielded an area under curve of 0.71 ± 0.06 ($P<0.001$) (95% CI, 0.58 and 0.84), whereas (F) CVI_s showed the higher discriminating power with an area under curve of 0.97 ± 0.01 ($P<0.0001$) (95% CI, 0.93 and 100). Using a CVI_s <22.2% as a cutoff, patients were identified with a sensitivity of 93% and a specificity of 100% (Figure 1).

Histopathological Parameters Correlation With IBS Variables

In each specimen, the main microscopic change was the presence of abundant interstitial fibrosis. Connective tissue surrounded isolated or small groups of myocytes. Myocytes frequently showed size and shape variability and disarray of myofibrils. No inflammatory infiltrate was found (Figure 2) The histopathology data of the end-operative biopsy at the septum level showed in particular the myocardial digitized area ($12.5 \cdot 10^3$ μm^2 $\pm 3.5 \cdot 10^3$), compared with digitized fibrotic area ($47.3 \cdot 10^3$ μm^2 $\pm 8.6 \cdot 10^3$), and the relative ratio between myocytes and fibrotic area (0.26 ± 0.06). We obtained relevant and significant correlations between myocyte/fibrosis ratio and IBS parameters: with IBSV septum

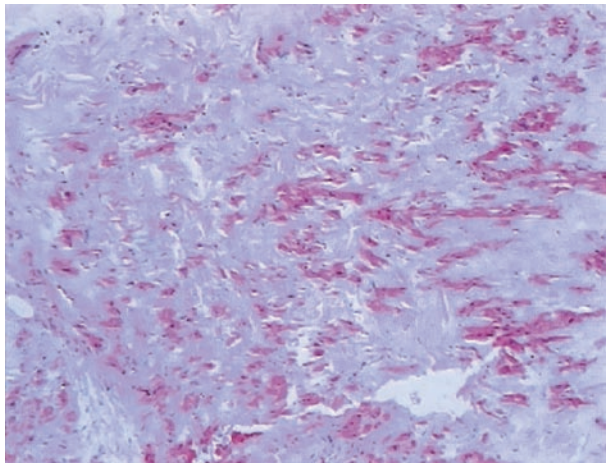

Figure 2. Histopathology of aortic stenosis (operating biopsy).

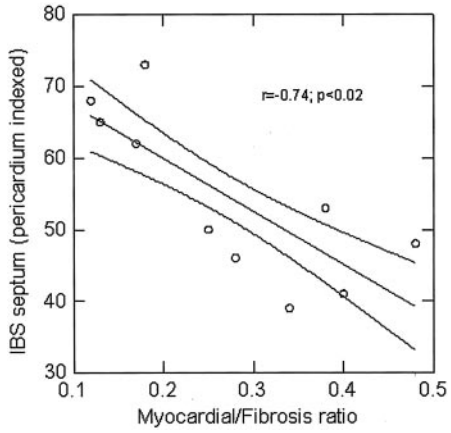

Figure 3. Plot of correlation between IBS_{si} and myocyte/fibrosis ratio (operating biopsy).

($r=0.70$; $P<0.04$), with CVI at septum level ($r=0.72$; $P<0.05$), and with IBS_{si}, ($r=-0.74$; $P<0.02$) (Figure 3).

Relation Between Quantitative Backscatter Analysis Data, Echocardiographic, and Hemodynamic Aortic Valve Parameters

Both cyclic variation index (CVI) and IBS variation at the septum and posterior wall levels showed an inverse, significant correlation with LVM_{bs} (Table 3). Furthermore, both CVI and IBSV at the septum and posterior wall levels showed a significant inverse correlation with ΔP both at peak and mean (Table 3). A lesser degree of correlation was found between IBS_{si}, IBS_{pwi}, and structural and functional aortic stenosis parameters. AVA and AVR showed a lesser degree of correlation with backscatter parameters than the previous described variables (Table 3).

Follow-Up Results

All patients with AVR had a good follow-up, with no prosthetic dysfunction. If we considered the percentage of variation of LVM_{bs} after 1-year follow-up, we could point out that in all patients, in a different amplitude, there was a reduction of LVM_{bs}; however, if we considered the EF variation, we could note that 10 of 16 patients showed an increased or constant EF. These patients were characterized by a parallel decrease of IBS_{si}, whereas in the other 6 patients the IBS_{si} value remained constant. Considering the IBS_{si} mean before the AVR of the patients who showed EF improvement, it was 56.2 ± 2.6 and for other 6, it was 65.7 ± 4.6 ($P<0.003$). It is relevant to note the concordance of this value with the cutoff derived by ROC curve analysis for this variable in discriminating patients with DSF by NSF. Another relevant observation was the correlation between ΔLVM_{bs}, ΔEF, and ΔIBS_{Si}, in particular between ΔLVM_{bs} and ΔIBS_{Si} ($r=0.58$; $P<0.01$), between ΔEF and ΔIBS_{Si} ($r=-0.76$; $P<0.003$), and ΔLVM_{bs} and ΔEF ($r=-0.62$; $P<0.01$) (Table 4 and Figure 4).

Discussion

Main findings of the study were (1) a significant inverse correlation between backscatter parameters and aortic valvular pressure gradient (peak and mean); (2) a significant relation between IBI parameters and histopathology parameter such as the myocardium/fibrosis ratio; (3) high discriminating power between patients with AS and control subjects of CVI at the septum level, whereas IBS_{si} was the best variable in identifying patients with DSF and patients with NSF (ROC curves); (4) 1 year after aortic valve replacement, we observed a significant reduction of LV mass, and only if pericardial indexed IBS value (reduction of interstitial fibrosis) decreased, it was possible to observe an improvement of IBSV and EF; on the contrary, EF and IBSV remained constant or slightly decreased.

These data confirmed the previous observations that IBS is able to detect the increase of collagen tissue (fibrosis), which occurs in aortic stenosis (inverse correlation between IBS indexed by pericardium reflectivity and operating biopsy myocardial/fibrosis ratio), and to point out precocious impairment of LV myocardial intrinsic contractility (through CVI and IBS variation). Furthermore, the pressure gradient across the aortic valve is one of the independent factors that induces intense fibrosis at the myocardial level in aortic stenosis.

A close correlation was described between cardiac function and myocardial morphology in patients with AS; with worsening of fibrosis and myocyte degeneration, LV end-diastolic pressure increases, and later EF decreases.[15] This should be taken into account for any decision of surgical intervention. Myocyte hypertrophy and reactive fibrosis are the first adaptive elements to LV pressure-overload of AS; it follows myocyte degeneration under complex humoral stimuli (ACE and TGF-β_1), which interact with cellular genomic transcription capacity.[16,17] Reduction of capillary density, myocardial cellular loss, and replacement fibrosis complete this complex adaptive mechanism.

Our operating biopsy observations confirm that severe aortic stenosis in old age is able to determine an abnormal

TABLE 3. Correlation Matrix (Pearson's Method)

	LVM_{bs}	ΔP_{peak}	ΔP_{mean}	AVA	AVR
CVI_s	−0.63 ($P<0.005$)	−0.65 ($P<0.005$)	−0.77 ($P<0.001$)	−0.45 ($P<0.01$)	−0.43 ($P<0.04$)
CVI_{pw}	−0.56 ($P<0.003$)	−0.84 ($P<0.001$)	−0.85 ($P<0.001$)	−0.40 ($P<0.05$)	−0.31 (NS)
$IBSV_s$	−0.54 (P<0.001)	−0.64 (P<0.01)	−0.73 (P<0.001)	−0.37 NS	−0.22 (NS)
$IBSV_{pw}$	−0.48 ($P<0.004$)	−0.72 ($P<0.001$)	−0.76 ($P<0.001$)	−0.43 ($P<0.05$)	−0.34 (NS)
IBS_{si}	0.46 ($P<0.05$)	0.50 ($P<0.01$)	0.52 ($P<0.02$)	0.31 (NS)	0.53 ($P<0.05$)
IBS_{pwi}	0.42 ($P<0.03$)	0.55 ($P<0.01$)	0.57 ($P<0.01$)	0.30 (NS)	0.42 ($P<0.03$)

Abbreviations as defined in text and Table 2.
Only aortic stenosis patients (n=35). *R* and *P* values are shown for each correlation.

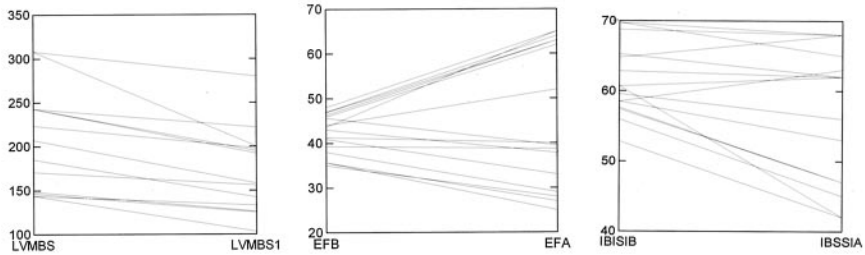

Figure 4. Individual plot of values of LV mass; EF, and IBS_{si} before and after AVR (1-year follow-up).

increase of fibrotic tissue with a disproportionate ratio with myocardial cellular components. These evident changes in myocardial texture are reflected in an increase in absolute myocardium reflectivity, as detected by IBS.

According to these observations, we can discriminate, with a high level of power, aortic patients with DSF by AS with NSF (ROC curves) essentially on the basis of IBS parameters. The progressive increase of fibrosis, related to LV pressure overload of aortic stenosis, induces an impairment of myocardial function linked to an increase of myocardial stiffness, which causes an increase of LV end-diastolic pressure and a progressive reduction of contractility indexes.

One year after AVR, we observed in several patients a collagen network resetting (as demonstrated by significant reduction of IBS_{si} and IBS_{pwi}), LVM_{bs} reduction, and EF improvement (as confirmed by CVI and IBSV significant increase, for both the septum and posterior wall).[18,19]

IBS could integrate conventional echo evaluation of LV function in two ways: (1) the cross-point of increase in IBS_{si} over which degenerative myocardial alterations in LV hypertrophy could develop into CHF (see ROC), and (2) the initial functional CVI and IBSV alterations, which reflect the intrinsic myocardial contractility abnormalities. Both early impairment of IBS indexes, together with clinical findings (increasing dyspnea, inserting angina pectoris, or syncope) and Doppler evaluation of aortic stenosis hemodynamics, allow identification of the patients with CHF and aortic stenosis, separating them from those with cardiomyopathy and AS. Therefore, IBS could identify those patients most suitable for AVR before irreversible myocardial damage is realized and with the best chance of postoperative recovery and improvement.[20]

Study Limitations and Conclusions

One study limitation was the relatively low number of patients, but on the contrary, the strength was strict inclusion criteria. We did not enroll patients with EF <35% because we were interested in testing the early capability of IBS in precociously detecting myocardial alterations before CHF developed in patients with AS. Further investigation in a greater AS study population, also with systolic dysfunction, is needed to definitely confirm the diagnostic and prognostic value of IBS parameters. Recent technological development

TABLE 4. Individual Change Percent Variation Before and After One Year of Aortic Valve Replacement

Patients*	ΔLVM_{bs}	ΔEF	ΔIBS_{Si}	$\Delta IBSV_s$
1*	−23, 6	+36, 2	−19, 6	48, 9
2*	−14, 5	+35, 0	−18, 5	31, 3
3	−19, 7	−3, 1	+6, 0	−7, 7
4	−8, 6	−1, 5	+5, 0	−5, 2
5	−11, 4	−29, 9	−1, 1	−30, 8
6*	−23, 2	+35, 4	−18, 2	51, 9
7	−20, 9	−23, 7	+6, 8	−3, 3
8	−15, 1	−12, 2	+2, 1	−49, 2
9	−7, 4	−13, 4	+7, 7	−54, 4
10*	−35, 1	+34, 3	−20, 5	41, 5
11	−11, 4	−24, 3	+5, 0	−6, 2
12*	−23, 2	+36, 1	−18, 2	38, 3
13	−8, 6	−20, 0	−2, 5	−26, 7
14*	−15, 1	+18, 1	−10, 8	44, 4
15*	−28, 3	+39, 0	−19, 4	37, 8
16	−9, 1	−19, 3	−1, 4	−38, 9
Mean before AVR	LVM_{bs} 183.8±48.5	EF 40.4±2.2	IBS_{si} 65.6±5.9	$IBSV_s$ 3.1±1.5
Mean after AVR	143.5±36.5	48.7±4.9	49.8±6.7	4.8±2.4
P (*t* paired)	0.05	0.05	0.01	0.05

Abbreviations as in text.
*Patients with improvement of LV function.

of acoustic densitometry, consisting in high-frame IBS, might greatly improve the analytic capability of the method.

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References

1. Krayenbühl H, Hess OM, Monrad ES, et al. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation*. 1989;79:744–755.
2. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overload human heart: structural deterioration and compensatory mechanisms. *Circulation*. 2003;107:984–991.
3. Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *Circulation*. 1998;98:1949–1984.
4. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis. *Circulation*. 1990;82:124–130.
5. Smucker ML, Manning SB, Stuckey TD, et al. Preoperative left ventricular wall stress, ejection fraction, and aortic valve gradient as prognostic indicators in aortic valve stenosis. *Cathet Cardiovasc Diagn*. 1989;17:133–143.
6. Wickline SA, Thomas TJ III, Miller JG, et al. A relationship between ultrasonic integrated backscatter and myocardial contractile function. *J Clin Invest*. 1985;76:2151–2160.
7. Mottley JG, Miller JG. Anisotropy of the ultrasonic backscatter of myocardial tissue, I: Theory and measurements in vitro. *J Acoust Soc Am*. 1988;83:755.
8. Lythall D, Bishop J, Greenbaum RA, et al. Relationship between myocardial collagen on echo amplitude in nonfibrotic hearts. *Eur Heart J*. 1993;14:344–350.
9. Di Bello V, Pedrinelli R, Bertini A, et al. Cyclic variation of the myocardial Integrated backscatter signal in hypertensive cardiopathy: a preliminary study. *Coron Artery Dis*. 2001;12:267–275.
10. Rodrigo FA, Snellen HA. Estimation of valve area and valvular resistance. *Am Heart J*. 1953;45:1–12.
11. Bermejo J, Odreman R, Feijoo J, et al. Clinical efficacy of Doppler echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. *J Am Coll Cardiol*. 2003;41:142–151.
12. Spencer KT, Bednarz J, Rafter PG, et al. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol*. 1998;82:794–799.
13. Bland JM, Altman DG. Measurement error and correlations coefficients. *BMJ*. 1996;313:341–342.
14. Beck JR, Schultz EK. The use of receiver operating characteristic (ROC) curves in test performance evaluation. *Arch Pathol Lab Med*. 1986;110:13–20.
15. Hein S, Schaper J. The extracellular matrix in normal heart and diseased myocardium. *J Nucl Cardiol*. 2001;8:188–196.
16. Weber KT. Angiotensin II and connective tissue: homeostasis and reciprocal regulation. *Regul Pept*. 1999;82:1–17.
17. Schultz J, Witt SA, Glascock BJ, et al. TGF-β1 mediates the hypertrophic cardiomyocyte growth induced by angiotensin II. *J Clin Invest*. 2002; 109:787–796.
18. Kolh P, Lahaye L, Gerard P, et al. Aortic valve replacement in the octogenarians: perioperative outcome and clinical follow-up. *Eur J Cardiothorac Surg*. 1999;16:68–73.
19. Fuster RG, Argudo JA, Albarova OG, et al. Left ventricular mass index in aortic valve surgery: a new index for early valve replacement? *Eur J Cardiothorac Surg*. 2003;23:69–74.
20. Finch-Johnston AE, Gussak HM, Mobley J, et al. Dependence of "apparent" magnitude of time delay of cyclic variation of myocardial backscatter. *Ultrasound Med Biol*. 1999;25:759–762.