JACC Vol. 25, No. 2
February 1995:500–8



# Clinical Evaluation of Left Heart Doppler Contrast Enhancement by a Saccharide-Based Transpulmonary Contrast Agent

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***Objectives.*** **A multicenter study was carried out to evaluate the efficacy with which SHU 508A enhances left heart Doppler signals and improves the clinical quantification of valve disease.**

***Background.*** **Poor signal-to-noise ratio often limits the Doppler interrogation of left heart flows. This problem may be resolved by the enhancement of Doppler signals by an ultrasound contrast agent capable of pulmonary transmission, such as the recently developed SHU 508A.**

***Methods.*** **Left heart contrast enhancement was tested for 1) continuous wave Doppler evaluation in 51 patients with aortic stenosis, 2) pulsed Doppler transthoracic evaluation of pulmonary venous flow in 85 patients, and 3) color Doppler evaluation of mitral regurgitation in 60 patients. Studies were performed immediately before and during the intravenous administration of SHU 508A (16 ml of 200 mg/ml) and compared with unenhanced transesophageal data in representative subsets of patients.**

***Results.*** **SHU 508A had no serious adverse effects. A significant increase in left heart Doppler signal intensity lasted for 30 to 300 s. The continuous wave Doppler velocity envelope was enhanced for all jets, but Doppler peak velocity was not altered in high quality baseline studies. However, Doppler contrast enhancement resulted in higher measured peak gradients ($p < 0.001$) in 29 patients with aortic stenosis who had poor quality baseline studies. This improved the overall correlation with invasive pressure measurements ($r = 0.73$ vs. $r = 0.89$, $p < 0.01$). The enhanced pulsed Doppler traces of transthoracic pulmonary venous flow allowed quantitative analysis in 92% patients (vs. 27% at baseline) and correlated well with peak velocities and velocity profiles obtained by transesophageal echocardiography ($r = 0.91$, $p < 0.001$). The enhanced color Doppler display of regurgitant jets increased jet area with a high interindividual variability (mean 276%), resulting in almost identical jet areas as unenhanced transesophageal values ($r = 0.97$, $p < 0.001$).**

***Conclusions.*** **SHU 508A is a safe transpulmonary contrast agent that significantly enhances both spectral and color Doppler signals in the left heart. In specific patient subsets, the increase in signal-to-noise ratio improved the quantitative assessment of aortic stenosis, pulmonary venous flow and mitral regurgitation.**
***(J Am Coll Cardiol 1995;25:500–8)***

Doppler echocardiography allows the noninvasive assessment of normal and pathologic intracardiac flow and the accurate determination of intracardiac velocities and pressure gradients. Its value has been widely accepted in clinical cardiology. However, the diagnostic accuracy of the Doppler technique depends, in part, on the quality of Doppler recordings. The actual display of intracardiac flow is limited, particularly in structures more remote from the transducer, such as the atria, because of increased absorption and scattering of ultrasound. The color Doppler modality in particular is subject to these limitations and has, so far, led the cardiologist to accept the reduced sensitivity of flow detection as "normal." However, cardiac cavities are full of flowing blood and should be displayed in full color by the color Doppler technique if this technique is supposed to mirror reality. Efforts to compensate for the apparent loss of diagnostic flow information have led to the acceptance of transesophageal Doppler echocardiography in clinical routine. An alternative method of compensating for reduced precordial Doppler sensitivity is to enhance the relatively low intensity Doppler signals by contrast agents, a method that has been reported from both experimental and human studies (1–4). However, this augmentation has previously been limited to the right heart chambers (5). Preliminary results for Doppler contrast enhancement of the left cardiac chambers using intravenous injections have recently been reported (6–8).

The present investigation was designed as a multicenter clinical study to systematically evaluate the potential clinical role of Doppler contrast enhancement for the evaluation of aortic stenosis, pulmonary venous flow and mitral regurgitation and to assess the efficacy and patient tolerance of SHU 508A. The results of contrast-enhanced Doppler techniques were

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Manuscript received March 3, 1994; revised manuscript received August 25, 1994, accepted August 31, 1994.

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0735-1097/95/$9.50
0735-1097(94)00404-E

**Table 1.** Exclusion Criteria for Phase III Multicenter Clinical Study With SHU 508A

| |
|---|
| Galactosemia |
| Critically ill patients (e.g., <2 wk after myocardial infarction, life-threatening arrhythmia, severe heart failure) |
| Patients in whom drug therapy or radiotherapy might initiate a change in chemical laboratory variables |
| Patients who had an angiographic study within 24 h |
| Patients with mental retardation |
| Patients who had participated in another drug study within 30 days of the present one |
| Pregnant or lactating women |

also compared with those of transesophageal technique in a selected patient subset.

## Methods

This study was carried out as a prospective multicenter collaborative study in five European cardiology centers under the auspices of the Levovist Cardiac Working Group and as a subsection of a European multicenter phase III clinical study. Before the investigations began, the study protocols were approved by the individual institutional review boards of the participating institutions (established according to the Food and Drug Administration guidelines).

**Study patients.** Patients of either gender were invited to participate in the study if they met the following inclusion criteria: a suboptimal precordial Doppler study of left-sided cardiac flows and age ≥18 years. Because of the intrinsic sensitivity problems of color Doppler, almost every patient entering the echocardiographic laboratory had <70% of the left atrium color coded from normal anterograde flow and thus proved eligible for the study. Patients were excluded from the study if they met the criteria shown in Table 1. One hundred fifty-two patients (90 men, 62 women; mean age 59 years, range 23 to 90; mean weight 72 ± 12 kg, mean height 169 ± 9 cm) were studied between June and December 1992. Sinus rhythm was present in 121 patients, and atrial fibrillation in 31.

Native or prosthetic valvular *aortic stenosis* was evaluated in 51 patients. Mixed native aortic valve disease was present in 12 of these patients. Six patients with an aortic valve prosthesis were included. Correlative invasive pressure measurements were performed in 24 of these patients. *Pulmonary venous flow* was assessed in 85 patients. These included patients with mitral valve disease (n = 20), mitral valve prosthesis (n = 7), aortic valve disease (n = 4), aortic valve prosthesis (n = 6), ischemic heart disease (n = 28), hypertensive heart disease (n = 2), dilative cardiomyopathy (n = 7) and 10 clinically normal subjects. Sinus rhythm was present in 64 patients, atrial fibrillation/flutter in 20 and paced rhythm (VVI mode) in 1. Immediately before the transthoracic contrast study, transesophageal echocardiography was performed in 13 patients, 12 of whom had atrial fibrillation.

*Mitral regurgitation* was evaluated in 60 patients. Mitral valve prosthesis was present in 14 patients, mixed mitral valve disease in 5, isolated regurgitation in 12, ischemic heart disease in 18, dilative cardiomyopathy in 4 and aortic valve stenosis or prosthesis, or both, in 7. On the basis of clinical indications, a left ventricular angiogram was performed in 23 of these patients within 3 days of the ultrasound study and was used to grade the severity of mitral regurgitation according to the classification of Nagle et al. (9): 0 = none; 1 = mild; 2 = moderate; and 3 = severe. Transesophageal Doppler echocardiography was performed for clinical reasons in 14 patients just before the transthoracic contrast study.

**Study protocol.** After the patients had signed the informed consent form, they underwent a baseline clinical evaluation consisting of medical history, physical examination, electrocardiogram (ECG), biochemical screen and a blood count. This clinical evaluation was repeated 0.5 and 24 h after the contrast study. Pulse rate and blood pressure were measured at baseline and 5 min after each contrast injection. Continuous ECG monitoring was maintained during the contrast study. Patients were monitored for the development of adverse symptoms during the test period and immediate follow-up period and were questioned about the presence of side effects or subjective complaints during and after the contrast study.

**Injection of SHU 508A.** The contrast agent SHU 508A is a suspension of galactose microparticles (median diameter 2 μm) in water that is prepared 2 min before injection by adding sterile water to the vial with 4 g of galactose particles: 17 ml water for a concentration of 200 mg microparticles/ml, 11 ml for 300 mg/ml and 8 ml for 400 mg/ml. Each patient received 16 ml of SHU 508A, with 200 mg/ml as standard dose. If modified doses were required according to the degree of contrast enhancement in the individual patient, the dosage could be reduced (10 ml of 200 mg/ml) or increased (10 ml of 300 mg/ml or 8 ml of 400 mg/ml). Injections could be repeated only 5 min after the contrast effects had completely disappeared. Up to six injections were possible if diagnostically required. The contrast agent was injected at a rate of 1 to 2 ml/s through a 20-gauge cannula positioned in an antecubital vein, followed by a 5-ml flush of saline solution.

**Doppler examination.** Transthoracic Doppler echocardiography was performed at baseline before the first injection of SHU 508A and for 10 min after each contrast injection, using commercially available ultrasound devices (Acuson 128 XP10, Hewlett-Packard 1000, Toshiba SSH 270 or Vingmed 750). Examinations were performed with the use of 2- to 2.5-MHz transducers. Optimized setting of filters, pulse repetition frequency and gain for the individual Doppler studies were kept constant during the study. Color, continuous wave and pulsed Doppler were used as clinically appropriate for the individual cardiac lesions. All studies were stored on VHS videotape for off-line analysis by two independent observers. Transesophageal studies were performed in a standard manner using 5-MHz imaging.

**Measurements.** The duration of diagnostically usable signal intensity increase within the left-side heart chambers was assessed in seconds. Anterograde jets from aortic stenosis and retrograde jets from mitral regurgitation were recorded by

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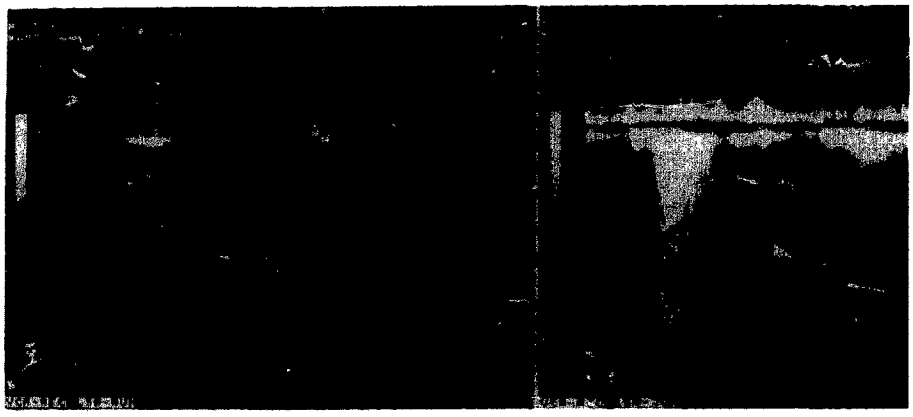

**Figure 1.** Original continuous wave Doppler of anterograde aortic flow velocities in a patient with aortic stenosis. **Left,** Baseline recording had a vague envelope. **Right,** Contrast enhancement provided a clear envelope and allowed confident measurement of peak velocity.

continuous wave Doppler for the measurement of peak velocity and the calculation of the peak gradient, using the simplified Bernoulli equation. Pulsed Doppler recordings of the pulmonary venous flow from the right upper pulmonary vein were analyzed for the peak velocities and velocity–time integrals of anterograde flow during systole and diastole, for the duration of the retrograde flow during atrial contraction and systolic reversed flow from mitral regurgitation. In the four- and two-chamber views, the color Doppler frames with the maximal jet area of mitral regurgitation were selected for planimetry of these areas of disturbed flow (coded as turbulence plus immediately contiguous blue). Cavity area was measured from the same frame to allow calculation of jet area as a percent of cavity area. Color Doppler and spectral Doppler signal intensity was graded from 0 to 5 (0 = no flow detected; 1 = scarce signals; 2 = weak signals; 3 = moderate signals; 4 = good signals; 5 = signals too strong or artifactual) as previously described (4,8).

**Statistical analysis.** Differences in data obtained in individual groups were assessed using nonparametric tests. These were the Wilcoxon signed-rank test and the Friedman test for paired data. The differences were considered significant if $p < 0.05$ for two-tailed testing. Results are presented as mean value ± SD in text and tables. Simple linear regression analysis was used to correlate transesophageal with transthoracic contrast-enhanced measurements. The effect of contrast enhancement on the correlation between Doppler and catheter-derived peak gradients or mitral regurgitation jet area and angiographic degree of severity was tested by multiple regression analysis.

## Results

**Patient tolerance.** In the course of the study, heart rate, blood pressure and the ECG did not change. There were no clinically relevant changes in blood chemistry or the complete blood count. Eight patients (5%) mentioned a brief burning sensation at the injection site; two (1.3%) had transient headache; and one (0.7%) had taste sensations. There were no serious adverse events.

**Dose and duration.** In 50% of the patients, the initial dosage of SHU 508A for Doppler enhancement (16 ml of 200 mg/ml) provided good quality images. In the remaining patients, 60% required 10 ml of 300 mg/ml for better images; 10% required 8 ml 300 mg/ml; and in 30% of the patients a reduction to 10 ml 200 mg/ml was required.

Mean duration of significant signal intensity increase was 120 s (range 30 to 300) for color Doppler, 140 s (range 30 to 300) for pulsed Doppler and 100 s (range 30 to 180) for continuous-wave Doppler.

**Aortic stenosis.** Signal intensity of continuous-wave Doppler recordings increased significantly in the anterograde jets of aortic stenosis after injection of SHU 508A (score 3.8 ± 0.5 vs. 2.0 ± 1.1, $p < 0.001$) (Fig. 1). In only two patients was there hardly any contrast enhancement effect on the poor quality rest velocity envelopes. In the subgroup of patients with good quality baseline studies (score 3 and 4) ($n = 22$), peak jet velocity and peak gradient did not change after contrast injection. In the patients with ambiguous envelopes at baseline (score 0 to 2) ($n = 29$), peak gradients after contrast enhancement significantly increased by 2 to 88 mm Hg (mean 26 mm Hg, $p < 0.001$) (Fig. 2). Thus, the correlation with invasive pressure measurements improved ($p < 0.01$) from $r = 0.73$ before to $r = 0.89$ with contrast enhancement (Fig. 3).

**Pulmonary venous flow.** When color Doppler was used in the four-chamber view, pulmonary venous inflow into the left atrium was clearly visualized after contrast enhancement so that the sample volume of pulsed Doppler could be accurately placed for recording pulmonary venous flow velocities. Pulsed Doppler flow envelopes improved (Fig. 4) in all patients after intravenous SHU 508A (score 3.1 ± 0.8 vs. 1.7 ± 1.1, $p < 0.001$). At baseline study, quantitative assessment of systolic and diastolic flow velocities was possible in 23 (27%) of 85 patients and after contrast enhancement in 78 (92%). In the former group of patients, the duration of atrial reversal did not change after contrast enhancement, but systolic and diastolic indexes increased after Doppler enhancement if baseline signal intensity was <3 (Table 2). These indexes remained unchanged in those patients with good baseline signal intensity (score ≥3). Of the seven patients with persisting poor quality

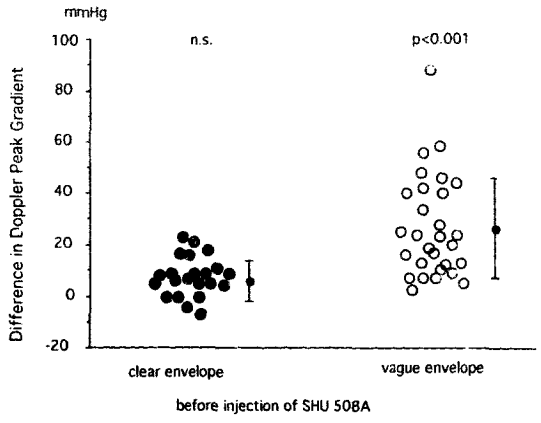


**Figure 2.** Apparent difference in peak Doppler gradients between recordings before and after intravenous injection of SHU 508A (Peak gradient$_{SHU\ 508A}$ − Peak gradient$_{baseline}$). Recordings were differentiated with regard to baseline quality as clear envelope (score 3 and 4) or vague envelope (score 0 to 2). Significant increase in peak gradient was observed in the vague envelope subgroup only.

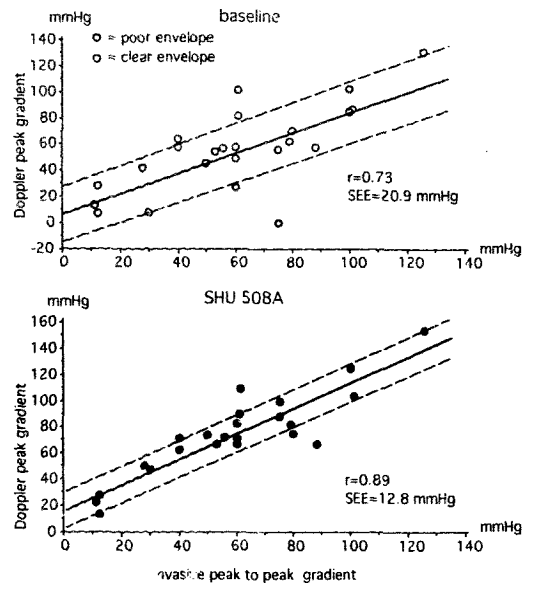


**Figure 3.** Correlation between invasive peak gradient **(horizontal)** and Doppler peak gradient **(vertical)** at baseline study was moderate **(top panel)** and improved with contrast enhancement **(bottom panel)**. **Dotted lines** = SEE.

of image after contrast enhancement, four had a mitral valve prothesis. Reversed systolic flow, indicating severe mitral regurgitation (four patients), could be recorded in one patient at baseline study and in four of four after contrast enhancement. Peak systolic and diastolic pulmonary flow velocities after contrast enhancement were in accordance with transesophageal Doppler measurements ($r \geq 0.91$) (Fig. 5).

**Mitral regurgitation.** In color Doppler, maximal jet area of mitral regurgitation (Fig. 6) increased from 3.1 ± 3.4 cm$^2$ at baseline to 9.5 ± 9.2 cm$^2$ with contrast enhancement ($p < 0.001$). There was a high degree of variability in the increase of jet area in individual patients ranging between 0% and 1,400% of the baseline jet area (mean 276%). The correlation between transesophageal measurements of maximal jet area and transthoracic measurements was moderate for the baseline images ($r = 0.71$), demonstrating underestimation for the unenhanced transthoracic Doppler images, and was excellent after contrast enhancement ($r = 0.97$), with the individual values close to the line of identity (Fig. 7). The individual jet areas expressed as a percent of left atrial area were compared with the angiographic grading. After contrast enhancement, discrimination of severity grades improved ($p < 0.005$), and the correlation coefficient was $r = 0.90$ compared with $r = 0.76$ at baseline.

The unenhanced continuous wave Doppler recording of regurgitant jet velocity had ambiguous envelopes in 23 patients. After contrast enhancement (Fig. 8), signal-to-noise ratio improved so that peak velocity could be confidently measured in 17 (4.3 ± 1.0 vs. 3.2 ± 1.0 m/s at baseline, $p < 0.01$). In the remaining patients with good quality baseline studies, the regurgitant jet velocities were also enhanced, but without significant change of peak velocity (5.3 ± 0.4 vs. 5.0 ± 0.3 m/s at baseline).

## Discussion

**Patient tolerance.** SHU 508A is composed of a combination of galactose (99.9%) and palmitic acid (0.1%). Previous studies in 1,500 patients on the safety of this contrast agent have reported a low incidence of adverse events and no serious adverse reactions (8,10). The reactions noted in the present multicenter study are most probably attributable to local effects caused by the hyperosmolarity of the galactose suspension. They were brief and resolved spontaneously. No clinically relevant changes in laboratory variables or hemodynamic and physical signs were detected. On the basis of these data, it would appear that the intravenous administration of SHU 508A is safe and well tolerated by patients.

**Dose.** In normal subjects, there is high interindividual variation in the echogenicity of the flowing blood and in the amount of ultrasound absorption by precordial tissue. Thus, it is not surprising that the concentrations of SHU 508A required for good quality Doppler enhancement varied between 200 and 400 mg/ml in the present study. The present data indicate that the initial dose of SHU 508A should be 16 ml (200 mg/ml). If there is still insufficient color coding of normal anterograde atrial flow (<70% of the left atrial area), an increase in the concentration of subsequent injections is warranted to 300 mg/ml and then to 400 mg/ml. If artifacts are noted, a reduction in dosage to 10 ml of 200 mg/ml coupled with a slower injection rate is advisable. The duration of increased Doppler signal intensity by the contrast agent was long (range 30 to 300 s) and allowed optimal placement of the sample volume in each patient. In contrast, sonicated serum albumin has been reported to provide 10 to 90 s of Doppler signal

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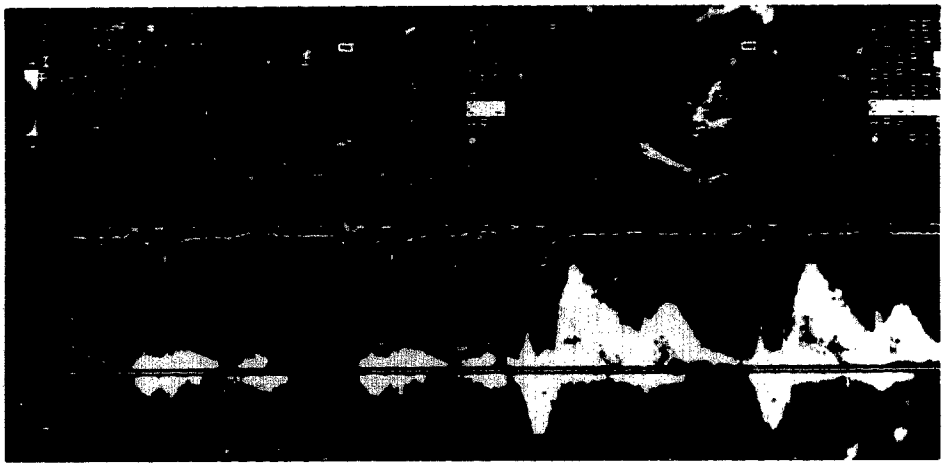


**Figure 4.** Original pulsed Doppler recording of pulmonary venous flow from an apical transducer position. **Left,** Note the signal-to-noise ratio preventing any quantitative analysis. **Right,** With contrast enhancement the signal-to-noise ratio improves, and flow traces have clear envelopes.

increase (6,7). The duration of the contrast effect in two-dimensional echocardiography of SHU 508A has been reported to be shorter than that for color Doppler enhancement (11), indicating the high sensitivity of Doppler for contrast enhancement at even low concentrations of the microbubbles, which may hardly be perceived in two-dimensional echocardiography.

**Aortic stenosis.** Recently, a study in a small group of patients selected for poor quality Doppler images reported (6) that injection of sonicated albumin microbubbles was useful for the noninvasive assessment of severity of aortic stenosis. Our study group included 51 unselected patients with aortic stenosis as a component of their cardiac lesions. After intravenous injection of SHU 508A, the envelope of aortic flow velocity was enhanced in 95% of the patients, enabling the calculation of the pressure gradient with certainty, as confirmed by good agreement between Doppler and catheterization data in a subset of patients. Low Doppler signal intensity of the aortic velocity curve caused poor quality recording in 29 of 51 patients at basal conditions, so that pressure gradient could not be measured confidently. In 15 of these patients, marked Doppler underestimation of actual pressure gradient occurred in the absence of contrast enhancement. Now, it must be emphasized that the apparent increase in peak flow velocity after intravenous injection of SHU 508A is solely a result of an increase in the signal-to-noise ratio and of the fact that low-intensity Doppler signals of any velocity were misinterpreted as noise and therefore were not displayed as velocity by the ultrasound machine. This is confirmed by our data in the 22 patients with good quality Doppler recordings at baseline study, in whom peak velocity did not change after injection of the contrast agent.

**Pulmonary venous flow.** Transthoracic recording of pulmonary venous flow is limited, particularly in patients with cardiomegaly or large atria. Our success rate of recording adequate pulmonary venous flow patterns from at least one pulmonary vein was only 27% in unselected patients with valvular and left ventricular diseases undergoing baseline echocardiography. There are few published reports about the success rate with which pulmonary venous flow can be recorded from the precordium. Only two reports (12,13) exist in which a higher percent of pulmonary vein flow was recordable. These were related either to patient selection or to the investigators having extensive experience in the field of Doppler. Contrast enhancement improved the signal-to-noise ratio

**Table 2.** Comparison of Unenhanced and Contrast-Enhanced Transthoracic Doppler Indexes of Pulmonary Venous Flow in the Subgroup of 23 Patients in Whom Unenhanced Pulsed Doppler Recordings Could Be Analyzed

| | All (n = 23) | | | B Signal Intensity ≥3 (n = 8) | | | B Signal Intensity <3 (n = 15) | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | C | p Value | B | C | p Value | B | C | p Value |
| Signal intensity (score 0–5) | 2.5 ± 0.6 | 3.6 ± 0.7 | < 0.001 | 3.0 ± 0 | 4.0 ± 0.5 | < 0.001 | 2.0 ± 0.6 | 3.4 ± 0.7 | < 0.001 |
| Max systolic velocity (cm/s) | 61 ± 14 | 53 ± 36 | NS | 68 ± 13 | 71 ± 13 | NS | 46 ± 32 | 50 ± 38 | < 0.05 |
| Systolic velocity time integral (cm) | 15.1 ± 5.9 | 15.4 ± 9.9 | NS | 19.2 ± 3.8 | 20.9 ± 5.4 | NS | 12.1 ± 5.7 | 13.4 ± 10.1 | NS |
| Max diastolic velocity (cm/s) | 56 ± 11 | 62 ± 12 | < 0.05 | 57 ± 10 | 57 ± 11 | NS | 55 ± 15 | 63 ± 11 | < 0.01 |
| Diastolic velocity time integral (cm) | 12.6 ± 4.5 | 14.9 ± 4.4 | < 0.05 | 14.6 ± 3.9 | 14.8 ± 5.5 | NS | 10.4 ± 4.6 | 15.1 ± 3.3 | < 0.01 |
| Max velocity atrial reversal (cm/s) | 28 ± 8 | 31 ± 9 | NS | 31 ± 9 | 32 ± 8 | NS | 14 ± 26 | 18 ± 29 | < 0.05 |
| Duration atrial reversal (ms) | 147 ± 50 | 152 ± 50 | NS | 172 ± 46 | 179 ± 50 | NS | 135 ± 49 | 140 ± 51 | NS |

Data presented are mean value ± SD. B = unenhanced baseline; C = contrast enhanced; max = maximal.

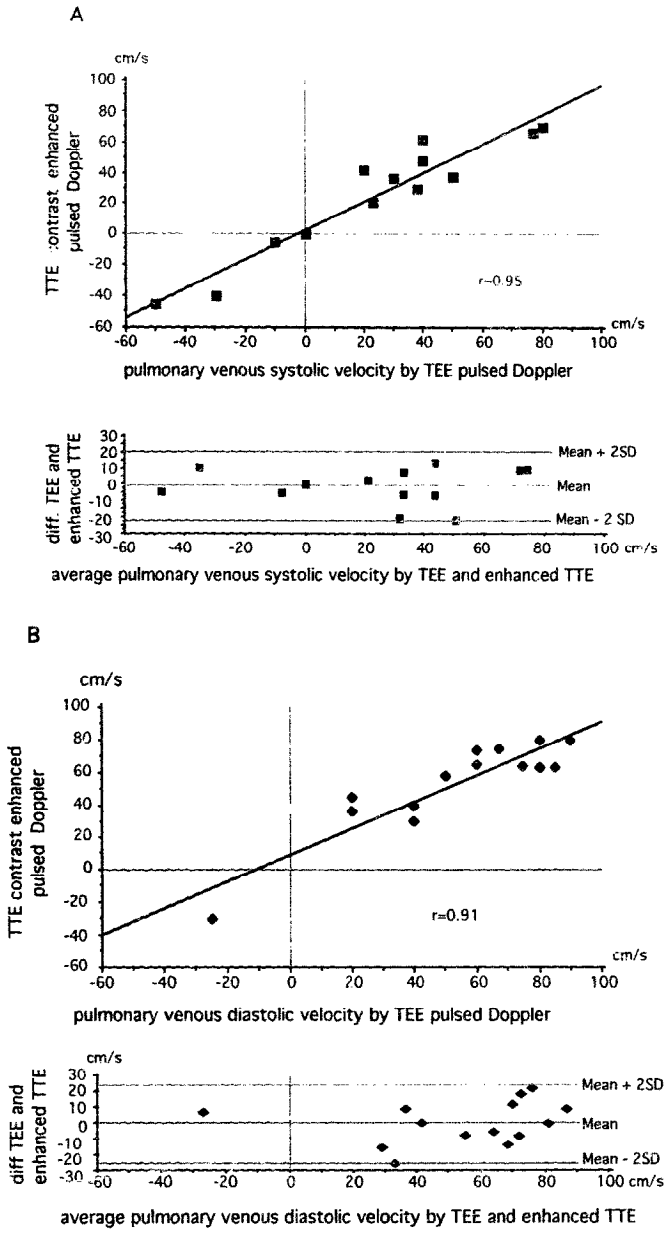



**Figure 5. Top panels,** Peak systolic (**A**) and diastolic (**B**) pulmonary flow velocities by contrast-enhanced transthoracic (TTE) pulsed Doppler (**vertical**) plotted against the corresponding peak velocities obtained with unenhanced transesophageal (TEE) Doppler. **Bottom panels,** Agreement between the two techniques for measuring peak pulmonary flow velocity. diff. = difference.

and thus the Doppler envelopes in almost all patients, with the possible exception of these with mitral valve prostheses. Contrast enhancement allowed quantitative analysis of pulmonary venous flow in 92% of our patients. The indexes derived from the enhanced recordings were confirmed by the data derived from high quality baseline studies (Table 2). It must be emphasized that analyzable but weak signals with complete envelope resulted in underestimation of the most frequently measured indexes, such as maximal velocities and time-velocity integrals. Evaluation of pulmonary venous flow patterns with regard to their diagnostic and hemodynamic relevance has mainly been performed with transesophageal echocardiography (14,15). We therefore compared measurements of peak flow velocities as obtained from transesophageal echocardiography with contrast-enhanced transthoracic velocities and found good agreement (Fig. 5). Our results indicate that contrast-enhanced Doppler provides similar information, thus obviating the need for transesophageal echocardiography in the majority of patients.

**Mitral regurgitation.** The mean increase in mitral regurgitation jet area as displayed by color Doppler was 276% with high interindividual variation. These results are similar to those of a recent two-center study (8). It is our opinion that there is persistent reluctance among cardiologists to accept the contrast-enhanced display as a clinical tool simply because many years of low signal intensity transthoracic imaging have made the image of a mainly black-coded left atrium so familiar. We therefore compared transthoracic jet areas before and

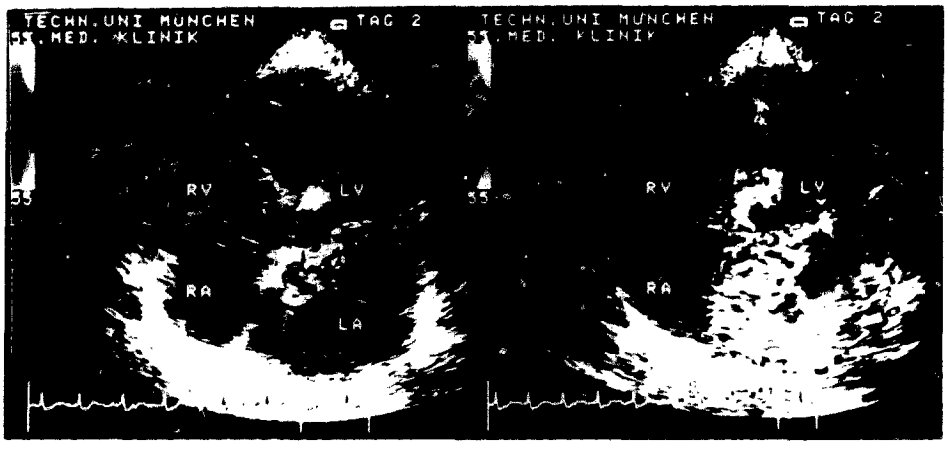
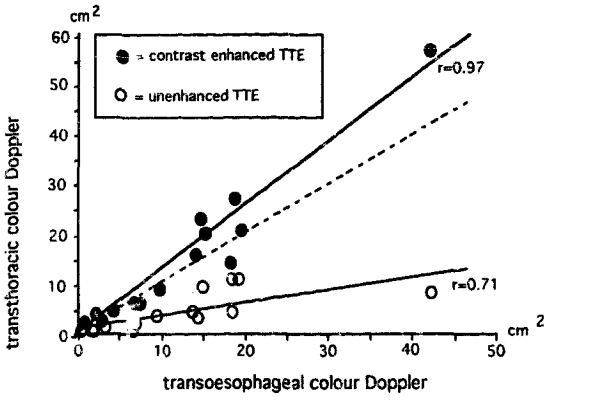



**Figure 6.** Original color Doppler recording in a patient with severe mitral regurgitation as a result of prolapse of the posterior leaflet. Note the complete display of the eccentric jet only on the **right tracing** with contrast enhancement. LA (RA) = left (right) atrium; LV (RV) = left (right) ventricle; TAG = day.



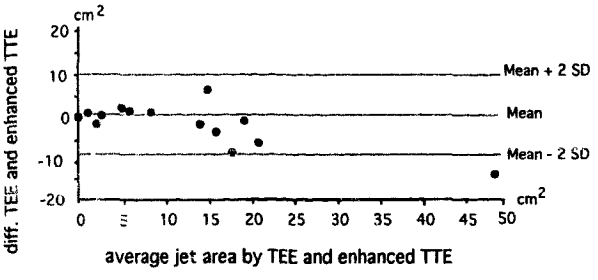




**Figure 7. Top,** Maximal jet area of mitral regurgitation as obtained with transthoracic color Doppler (TTE) **(vertical)** before **(open circles)** and after **(closed circles)** contrast enhancement plotted against maximal jet area obtained at transesophageal color Doppler (TEE) **(horizontal). Dashed line** = curve of equality. There is obvious underestimation by the unenhanced transthoracic method. **Bottom,** Agreement between contrast-enhanced transthoracic and unenhanced transesophageal measurements is demonstrated.

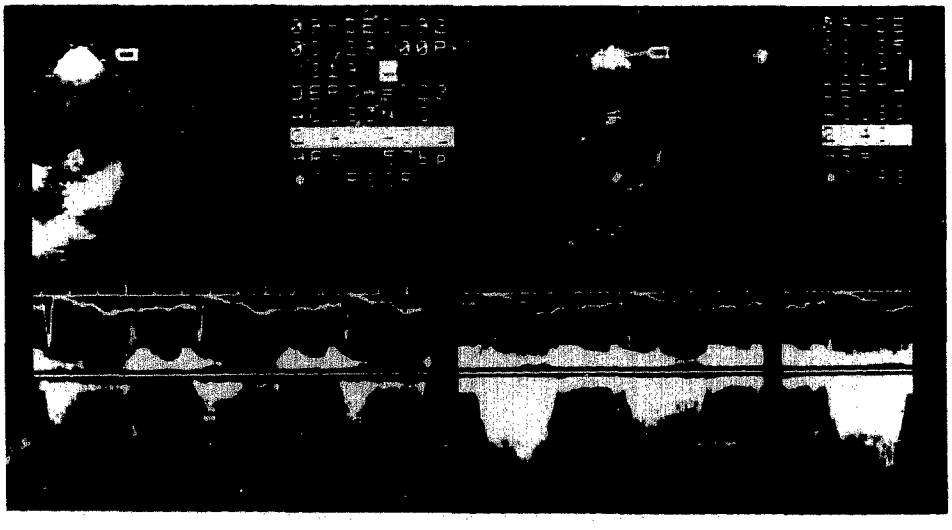


**Figure 8.** Original continuous wave Doppler recording of the regurgitant velocities in mitral regurgitation is too indistinct to determine peak velocity at the baseline study **(left)**. After contrast enhancement **(right)**, the increased intensity of Doppler signal provided clear envelopes and therefore quantitative analysis.

**Table 3.** Comparison Between Patients With and Without Transesophageal Echocardiography or Left Ventricular Angiography

| | Mitral Regurgitation | | | Aortic Stenosis | | |
|---|---|---|---|---|---|---|
| | No. of Pts | Jet Area (%LA) | | No. of Pts | Peak Gradient (mm Hg) | |
| | | B | C | | B | C |
| LV angiography | | | | | | |
| With | 23 | 13 ± 10 | 37 ± 23 | 24 | 55 ± 32 | 74 ± 29 |
| | | NS | NS | | NS | NS |
| Without | 37 | 12 ± 16 | 35 ± 27 | 27 | 44 ± 37 | 60 ± 45 |
| TEE | | | | | | |
| With | 14 | 12 ± 12 | 39 ± 27 | | | |
| | | NS | NS | | | |
| Without | 46 | 13 ± 17 | 36 ± 24 | | | |

Data presented are mean value ± SD. LA = left atrium; LV = left ventricular; Pts = patients; TEE = transesophageal echocardiography; other abbreviations as in Table 2.

after contrast enhancement with the better accepted images from the transesophageal approach (which is well known for its higher sensitivity in the detection of flow). Recent studies have shown that jet areas displayed transesophageally are considerably larger than those shown transthoracically (16,17), and semiquantification has been proposed using transesophageal imaging (18). The data in this study confirmed gross underestimation of jet areas displayed by the transthoracic approach compared with the transesophageal approach (Fig. 7). However, contrast-enhanced jet areas were virtually the same size as those displayed with transesophageal imaging. This is surprising because the two imaging modalities differ with respect to the most important factors that influence the sensitivity of flow detection by color Doppler flow imaging. These are attenuation due to ultrasound penetration depth and absorption from precordial tissues, both of which are severe handicaps in transthoracic color Doppler display, whereas the higher ultrasound frequency used with the transesophageal approach is known to reduce jet area in the presence of low Doppler signal intensity (19). It appears from our data that ultrasound penetration depth and precordial absorption are dominant limitations of unpredictable extent for the transthoracic display of regurgitant jet velocities in the unenhanced setting with low Doppler signal intensities. Doppler signals too low in intensity are obviously misinterpreted as noise by the ultrasound machine and are cut off by the wall filter. However, this limitation can be overcome by using contrast agents to increase the echogenicity of blood, and hence Doppler signal intensity, thus allowing all Doppler flow information to be displayed. It therefore follows that using this compensation technique improves the correlation between jet area and angiographic grading of severity in mitral regurgitation to the level we have hitherto attributed solely to the transesophageal technique, as we have shown in the present study.

**Clinical implications.** Contrast-enhanced Doppler allows confident evaluation of severity of aortic stenosis and mitral regurgitation even in technically difficult cases. This technique further facilitates assessment of pulmonary venous flow pattern and thus the semiquantification of mitral regurgitation, which has heretofore been the domain of transesophageal echocardiography. Because of patient discomfort associated with the transesophageal technique, Doppler contrast enhancement now appears to be an important new alternative in the sequence of diagnostic tools used to assess mitral regurgitation. Furthermore, contrast enhancement facilitates improved recordings of the maximal mitral regurgitant jet velocity by continuous wave Doppler. This may have potential with regard to calculation of maximal instantaneous first derivative of left ventricular pressure for additional evaluation of left ventricular function (20).

In our opinion patients should receive an ultrasound contrast agent if the spectral Doppler recordings essential for quantification of the individual lesion are suboptimal for analysis. For evaluation of regurgitant lesions it is essential that flow detection be sensitive enough in the receiving chamber. This may easily be assessed by using normal anterograde flow as an indicator of color Doppler sensitivity. If the color-coded area of normal flow is <70% of this particular cavity, Doppler signal enhancement is recommended.

**Study limitations.** We did not perform simultaneous Doppler and catheterization studies. Simultaneous transesophageal and precordial contrast studies were not performed either but were performed one after the other during stable hemodynamic conditions. The subgroups of patients with either angiographic or transesophageal evaluation were not different with regard to severity of cardiac lesion (Table 3). The duration of contrast enhancement was assessed by inspection of the video recording and was therefore a subjective judgment. This method appeared to be acceptable because of the length of the time intervals observed. Similarly, the scoring of Doppler signal intensity for the assessment of image quality is subjective but has been shown to have acceptable interobserver and intraobserver variability (21).

**Summary.** Peripheral venous injection of the galactose-based contrast agent SHU 508A enhances spectral and color Doppler in the left heart chambers, thus increasing the sensitivity of the Doppler system for displaying all flow information available from the patient. This has been shown to be particularly useful in the evaluation of aortic stenosis and mitral regurgitation. This technique also allows better assessment of indexes of left ventricular function derived from pulmonary venous flow pattern and mitral regurgitant velocity envelopes. Thus, it can improve evaluation of valve lesions and their functional hemodynamic consequences and may obviate the use of transesophageal echocardiography in a significant number of cases.

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