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Doppler Contrast Echocardiography

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1. Introduction

The advent and evolution of 2D echocardiography with Doppler gave a new dimension to the evaluation of valvular heart disease (VHD) and noninvasive cardiovascular hemodynamics. Extending from basic M-mode evaluation to the more sophisticated Doppler techniques, the way one looks at the valve anatomy and physiology has changed significantly. Doppler echocardiography has become the everyday tool for diagnosing valve pathology and for the serial evaluation of VHD (van de Brink et al, 1991). Despite significant technical advancements in image quality, spatial and temporal resolution, suboptimal image quality has not been entirely eliminated. Often due to body habitus (both obesity and markedly underweight individuals), chronic obstructive lung diseases or mechanically ventilated patients, 2D echocardiography suffers from poor signal to noise ratio (SNR). In these circumstances, the spectral Doppler signals are also weak due to high acoustic impedance. Harmonic imaging, power Doppler, low mechanical index pulsing and contrast echocardiography (CE) are some of the methods to improve image quality (Allen MR et al, 1999; Kitzman DW et al, 2000).

Gramiak and Shah, often considered pioneers in the use of contrast agents, demonstrated the use of indocyanine dye to improve visualization of cardiac chambers (Gramiak & Shah, 1969). Several authors have compared the application of contrast use against second harmonic imaging in assessing endocardial definition and proven its superiority (Kornbluth M et al, 2000). The American Society of Echocardiography (ASE) has recommended the use of contrast for the purposes of improving endocardial visualization in all subjects with >2 suboptimal contiguous wall segments, to reduce interpreter's variability and augment accuracy (Mulvagh SL et al, 2008). They also recommend using contrast agents to diagnose pathologic conditions that occur predominantly in the left ventricular (LV) apex, since this near-field region is better visualized after CE. This would include diseases such as apical variant of hypertrophic cardiomyopathy, isolated left ventricular noncompaction, apical thrombus and left ventricular aneurysm or pseudoaneurysm.

Contrast agents have also been used for enhancing the spectral Doppler signals required for evaluation of LV diastolic function, cardiovascular hemodynamic assessment, and comprehensive valvular analysis. Despite these standard national guidelines and recommendations, it has been estimated that <1% of warranted patients ever receive contrast. These authors believe that CE is underutilized across the globe. In this chapter, we focus our attention to one particular use of contrast agents-the augmentation of continuous

and pulse wave spectral Doppler to assist in the evaluation of valvular function and the estimation of cardiovascular hemodynamics.

Evaluation of valve function rests on acquiring accurate spectral and color Doppler signals. Not infrequently, physicians are asked to interpret echo studies with inadequate Doppler signal jets which may result in either the underestimation (lack of signal) or overestimation (excess noise) of the true flow gradients. In such instances, one can effectively utilize contrast agents to better define the Doppler signal to increase SNR, translating into optimized assessment of VHD. Contrast agents have been used to increase the sensitivity of Doppler signals for the assessment of tricuspid regurgitation, pulmonary venous flow, aortic and mitral regurgitation and stenosis.

Contrast agents have evolved tremendously from their initial use by Gramiak and Shah. Initial agents used by these authors were Indocyanine green, normal saline, and 5% dextrose in water (Gramiak & Shah, 1969). Currently, 2nd generation contrast agents are routinely available for use. Prior to understanding the role of contrast agents in Doppler echocardiography; the reader should have some insight into the properties, behavior and evolution to the current generation of contrast agents. In the United States (US), the Federal Drug and Administration (FDA) agency has approved two contrast agents for the indications of left ventricular opacification (LVO) and endocardial border delineation (EBD). Definity (Lantheus Medical Imaging, North Bellerica, MA) has a phospholipid shell and Optison (GE Healthcare, Princeton, NJ) has a human albumin shell. Both of these agents were designed to allow relative diffusion and permeability and ultimate dissolution of the encapsulated gas, which is perflouropropane (PFC). There are several other agents, (Levovist, SonoVue, CARDIOSphere and Imagify) used all across the globe but haven't yet gained FDA approval. SonoVue has been approved and recommended by the European Society of Echocardiography (ESE) for similar LVO indications as recommended by the ASE. These agents are used primarily for LVO and EBD, but there is evidence to support their utility for other indications, including spectral Doppler augmentation. Unlike contrast for LVO, the use of contrast specifically for Doppler enhancement requires a smaller amount of contrast and care in decreasing the Doppler gain settings (sometimes to the zero baseline) to avoid excess noise ("blooming" effect). If one was to measure this noise, then the estimated velocity will be incorrect and the calculated pressure gradient inaccurate. To minimize this potential, these authors perform the Doppler analysis after the 2D LVO study so the contrast is less intense. Also, be certain to measure only along the normal Doppler spectral contour and avoid small irregularities or 'spikes' within the modal velocity display.

2. Right heart

Initial use of contrast agents was confined to right-sided pathology as the initial agents did not have the ability to cross the pulmonary circulation. The first attempt at using traditional contrast agents like agitated saline, dextrose and sonicated albumin was to improve tricuspid regurgitation (TR) spectral Doppler signals to establish the diagnosis of pulmonary hypertension (PH). Sonicated albumin (Albunex, Molecular Biosystems, Inc., San Diego, California) has the ability to traverse the pulmonary circulation. Noninvasive estimation of pulmonary arterial pressures is crucial to monitor patients with heart disease and to make screening diagnosis of PH. Besides, the relevance of exercise response to pulmonary pressures cannot be ignored as it adds prognostic importance. The ability to capture accurate tricuspid regurgitation Doppler signals in patients with or without pulmonary

hypertension, at rest or immediately after exercise, is highly variable even with optimum system gain, filters, compression and patient (multiple views, variable patient positions, breath holding) settings.

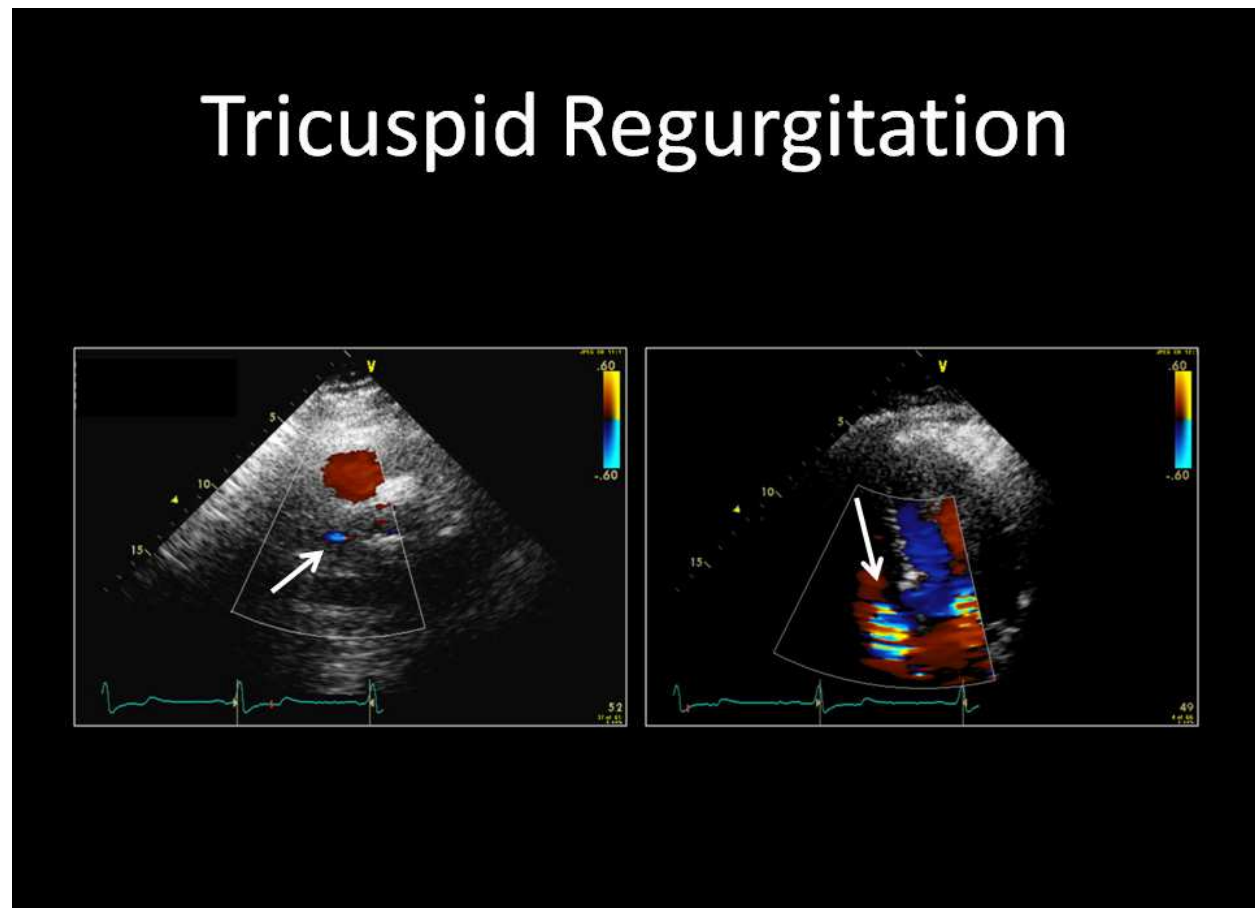


Fig. 1. Color flow Doppler display of tricuspid regurgitation (TR). Left. Unenhanced systolic image with very weak color flow demonstrating minimal TR (arrow). Right. Contrast enhanced image with gains set at zero to minimize noise artifact. Note the enhanced systolic color flow Doppler signal (arrow) allowing for an increased likelihood to measure the conventional spectral Doppler tracing

The idea to improve TR Doppler signal began with a simple experiment of intravenous injection of agitated normal saline. Beard and Byrd, analyzed 38 patients referred to their echocardiography laboratory (in addition to 7 normal subjects), looking for enhancement of the TR spectral Doppler signals (Beard and Byrd, 1988). They concluded that agitated saline significantly improved the TR jet if the jet was inadequately visualized before contrast enhancement. Importantly, it did not impact the results if there was no Doppler signal seen prior to saline enhancement. This is important, since in the absence of any TR, taking the time to perform a contrast-enhanced Doppler evaluation may not be warranted. However, it has been reported that TR is present in >50% of normal young individuals and this percentage is significantly greater in patients with cardiovascular pathology (Shah & Raney, 2008). In this study, many of patients had pulmonary artery catheters in place and the enhanced spectral Doppler TR gradient estimated PA pressures was able to be corroborated with the invasive PA pressure measurements.

Tricuspid Regurgitation

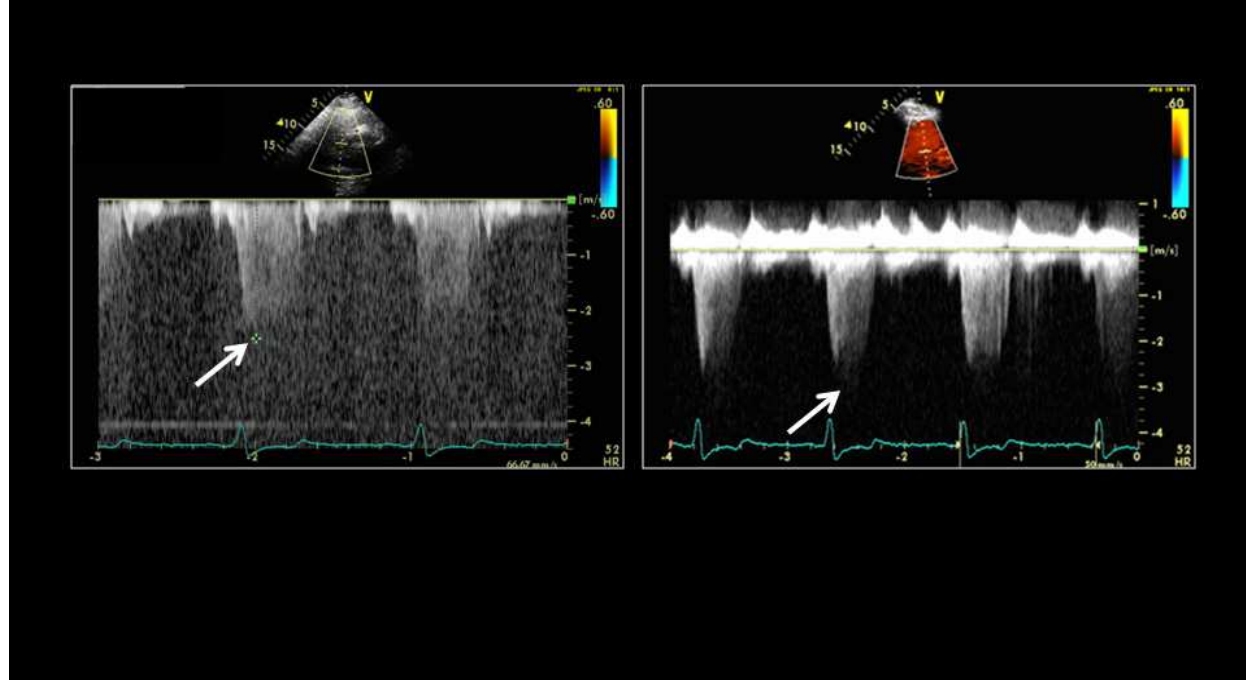


Fig. 2. Continuous wave spectral Doppler display of tricuspid regurgitation (TR). Left. Unenhanced systolic image with weak Doppler display demonstrating a maximal TR velocity of 2.5M/s or 25mmHg gradient (arrow). Right. Contrast enhanced image with increased signal to noise ratio able to confirm the maximal systolic velocity approaching 3.0M/s or 36mmHg (arrow)

Himelman et al reported similar findings in patients with chronic obstructive pulmonary disease and demonstrated similar results at rest and with exercise (Himelman et al, 1988). However, the criticism of agitated saline has been that the Doppler signal obtained tends to be noisy and rough ("fish bone like") and only marginally better than unenhanced spectral or color flow Doppler. Terasawa et al compared agitated saline with sonicated albumin in patients with invasive hemodynamic data to assess the right ventricular systolic pressure (RVSP) (Terasawa et al, 1993). The authors observed that both contrast agents enhanced the spectral Doppler signals, but possibly due to cursor angle errors, they both underestimated the invasively determined RVSP. Several other investigators also noted that the sonicated albumin findings were significantly more accurate relative to the agitated saline findings (Beppu et al, 1991). Despite these results, owing to its universal availability and ease of administration, agitated saline remains the contrast agent primarily used for enhancement of right sided spectral Doppler signals such as the maximal TR velocity. Modern contrast agents (Definity and Optison) have not been extensively studied for the purposes of right sided conditions including TR spectral Doppler signal optimization. Investigators at Mayo clinic conducted retrospective analysis of a large number of patients who received Definity

for the purposes of RVSP estimation and suggested its utility for this indication (Abdelmoneim et al, 2010). However, the intention of the study was to demonstrate the safety of this contrast agent in patients with pulmonary hypertension undergoing stress echocardiography. Second generation contrast agents improve the spectral Doppler envelope of TR by increasing the SNR and increasing the likelihood that the actual peak TR velocity is identified.

In addition to the estimation of the RVSP (as a surrogate of the pulmonary artery systolic pressure), Doppler echocardiography is also able to estimate the pulmonary artery diastolic pressure (PADP) using the spectral Doppler envelope of pulmonary regurgitation (PR). The pulmonary capillary wedge pressure (PCWP), also the PADP (a surrogate of the left atrial pressure), has shown to correlate well with the sum of PR end diastolic pressures gradients and the estimated right atrial (RA) pressure, also known as the central venous pressure. RA pressure can be estimated using inferior vena cava dimensions and phasic respiratory changes. To determine the PR end diastolic gradient, the spectral Doppler velocity profile of the PR jet must be accurately measured, but is often suboptimal due to a weak signal. This has been shown to improve with use of sonicated albumin by several authors (Masuyama T et al, 1986). Analyzing the overall evidence, it appears that use of modern contrast is safe and useful as a screening tool for the diagnosis of PH in suspected patients, particularly when there is a hint that the spectral Doppler is weak and an underestimation of the true maximal velocity. Contrast enhanced Doppler echocardiography appears to be a promising option for the serial follow up of patients with PH, thus obviating the need for frequent invasive testing. Furthermore, exercise Doppler echocardiography with contrast may help unmask the diagnosis of PH in asymptomatic individuals. To date, the routine use of contrast agents for the purposes of enhancing the Doppler signals on the right side is not recommended and should be considered an option on an individual patient basis.

3. Left heart

Development of transpulmonary agents has expanded the horizon and potential for use of contrast agents. These agents tend to be stable, have an excellent acoustic profile, and tend to be biologically inert. 5% sonicated albumin was the first to be FDA approved for LVO and EBD. Due to concerns with pressure sensitivity, resulting in a very short effective half life, it was not been a widely used agent. Newer 2nd generation agents, like Definity and Optison, have properties of ideal transpulmonary agents and hence gained FDA approval in US.

Left ventricular filling pressure, compliance and diastolic function is assessed by a composite of multiple measurements and each component has its own value. Contrast agents are very effective for augmenting the pulmonary venous (PV) Doppler flow pattern which adds value to the assessment of diastolic function of the heart. Due to the distance of left atrium and the PV from the transducer, the spectral Doppler display of the PV flow is often suboptimal. Even if one is able to acquire signals, these usually have low SNR causing challenges in accurate assessment. A normal PV inflow displays a systolic phase and diastolic phase. There is another short, low velocity reversal of flow coinciding with atrial contraction, called the AR-wave (atrial reversal). In normal individuals systolic phase dominates. In patients with abnormal diastolic function, as the left ventricle gets stiffer, majority of emptying of the PV occurs in diastole which results in blunting of the systolic

phase with relative augmentation of the diastolic phase. The width and the velocity of the AR wave is also exaggerated (Rossvoll O et al, 1993; Tabata T et al, 2003). The systolic and diastolic phases of the PV tend to be well displayed, using PV flows obtained with TEE as the reference standard (Castello R et al, 1991). However, the atrial reversal phase is the most often suboptimal, but importantly has the highest correlation with LA pressure. It has been demonstrated that with the use of contrast agents, the visualization of the PV flow Doppler spectrum can be improved, particularly, the atrial reversal phase, translating into improved diastolic performance assessment (William MJ et al, 1995). Contrast increases the likelihood of identifying the actual peak systolic, diastolic and the atrial velocities, although the ratios of the systolic/diastolic velocities may remain unchanged (Izumi C et al, 1996). There are other reported studies which suggest that the peak systolic and diastolic PV velocities are augmented, but the atrial reversal flow might not be as robust as expected (von Bibra H et al, 1994). However, majority of published reports do come to the agreement that contrast agents improve the overall sensitivity of accurately measuring the different phases of PV spectral Doppler flow pattern. Importantly, the PV flow pattern also aids in the assessment of the severity of mitral stenosis and regurgitation.

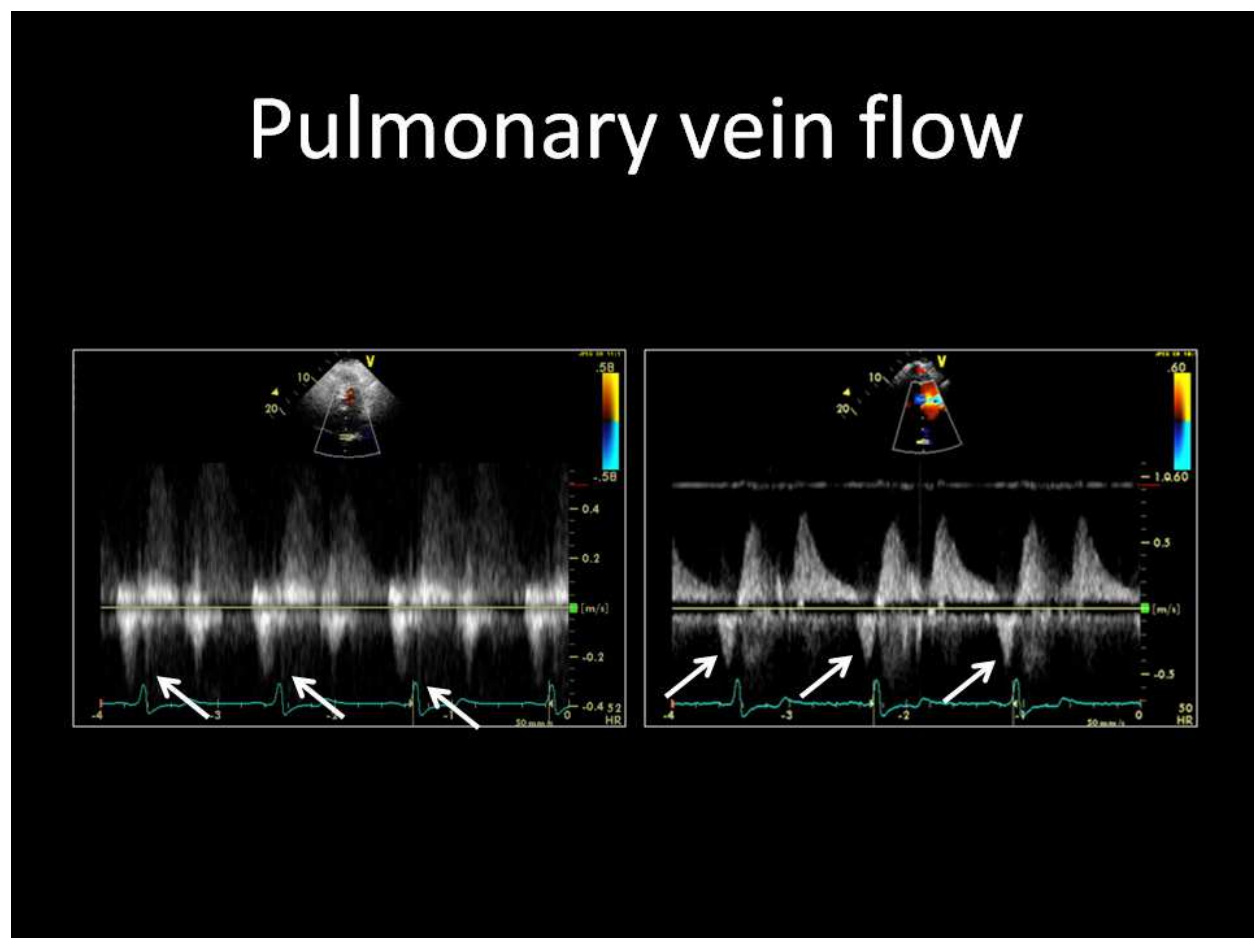


Fig. 3. Pulsed wave spectral Doppler display of pulmonary venous flow. Left. Unenhanced image with adequate tracing of the systolic (S) and diastolic (D) waves, but difficult to discern the atrial reversal (AR) velocity (arrow). Right. Contrast enhanced image with optimal spectral Doppler tracing confirming the AR maximal velocity is abnormally increased at $>40\text{cm/s}$ (arrow)

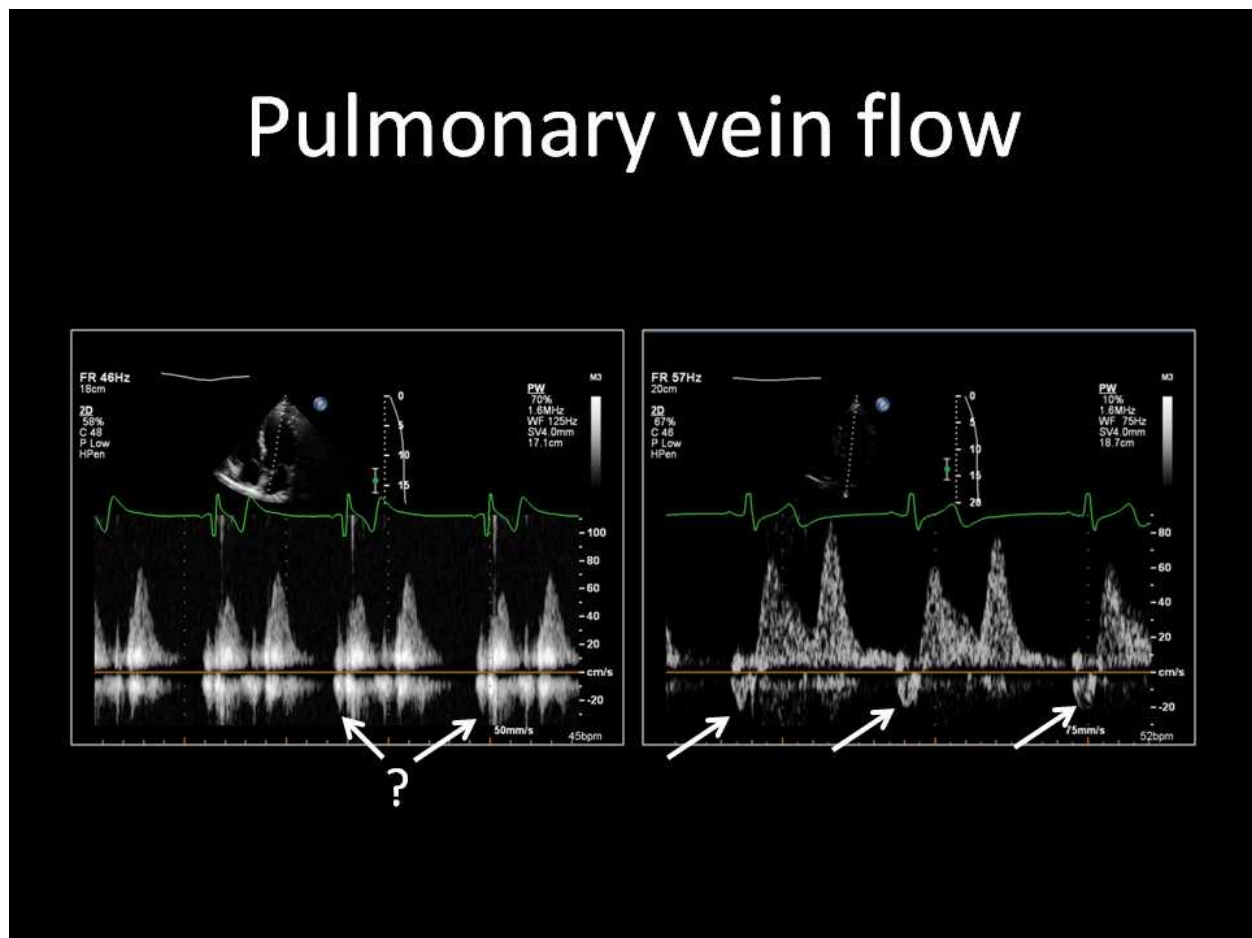


Fig. 4. This is a different patient demonstrating the ability to use contrast to improve pulmonary venous flow assessment. Pulsed wave spectral Doppler display of pulmonary venous flow. Left. Unenhanced image with adequate tracing of the systolic (S) and diastolic (D) waves, but difficulty in discerning the atrial reversal (AR) velocity (arrow). Right. Contrast enhanced image with optimal spectral Doppler tracing confirming the AR maximal velocity is normal and $<20\text{cm/s}$ (arrow)

Evaluation of severity of mitral regurgitation (MR) rests on obtaining adequate spectral and color flow Doppler across the mitral valve as well as observing the changes in pulmonary venous flow. In eccentric jets, where one can easily underestimate the severity of MR using the color flow Doppler pattern alone, additional parameters are vital. Contrast agents have previously been employed and have demonstrated their ability to assist in the evaluation of MR. Terasawa et al, demonstrated an improvement in the Doppler velocity profile in all study patients ($N=17$) with a good reproducibility (Terasawa A et al, 1993). These authors analyzed the velocity profile in detail to elucidate the mechanism for the noted augmentation of spectral Doppler display and suggested that the velocity in the centre of the jet remained unchanged before and after the contrast. However the marginal velocities along the edges of the spectral Doppler envelope were better seen due to improved signal-to-noise ratio. Unlike the effect of contrast which increases the identified peak velocity of the maximal TR spectral Doppler profiles, the peak mitral regurgitation spectral Doppler velocity was not significantly altered in this report. This finding should have important ramifications in the accurate determination of the spectral profile trace, which is used in

quantitative evaluation of the MR regurgitant volume (Enriquez-Sarano M et al, 1995; Hall SA et al, 1997; Pu M et al, 2001). This finding should add value and improve the ability to accurately measure other spectral Doppler parameters beyond the peak velocity. A number of spectral Doppler analyses have been reported as having significant clinical value and may benefit from contrast enhancement when the Doppler signal is weak (table 1).

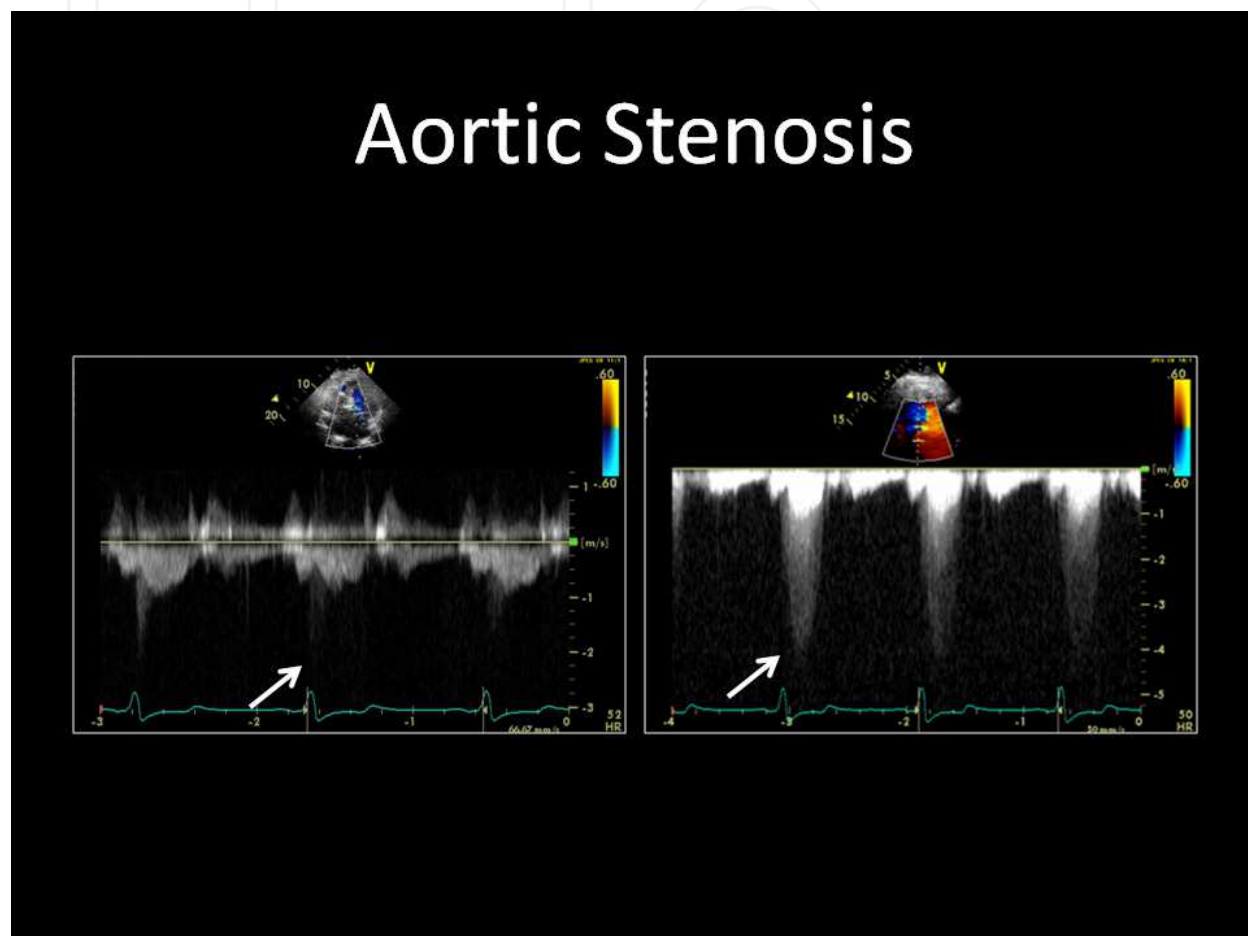


Fig. 5. Continuous wave spectral Doppler display of a patient with aortic stenosis. Left. Unenhanced image with weak tracing unable to confirm maximal gradient $>30\text{mmHg}$ (arrow). Right. Contrast enhanced image (same patient as shown on the left) with optimal Doppler tracing confirming a maximal gradient $>70\text{mmHg}$

Another interesting observation from this study, which these authors can confirm, was that the Doppler contrast augmentation effect lasted much longer than the LVO effect. This is a valuable property of contrast Doppler and by providing longer time window to capture the enhanced signals, the sonographer is able to complete the LVO portion of the 2D exam and then perform the enhanced Doppler exam afterwards. This phenomenon allows one to use a minimal amount of contrast for Doppler augmentation and does not require an additional contrast injection. In our experience, this latter spectral Doppler examination, performed after most of the contrast has 'washed out', retains the enhanced signal properties of the contrast agent while minimizing the potential for excess noise often created when the Doppler is used too soon.

Doppler parameter	Pathologic value	Clinical implication
Aortic Regurgitation PHT	< 200 ms	Elevated LVEDP
Aortic Stenosis	>4.0m/sec	Severe AS
Mitral Regurgitation (dP/dt)	<600mmHg/sec	Severe Systolic Dysfunction
PA Acceleration Time	< 90ms	Severely Elevated PASP
TR vti trace	> 25mmHg	Elevated PAMP

PHT, pressure half time; LVEDP, left ventricular end diastolic pressure; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; VTI, velocity time integral; PAMP, pulmonary artery mean pressure

Table 1.

Von Bibra et al used a saccharide based contrast agent and found a close correlation between the enhanced mitral spectral Doppler and TEE, thereby hinting an underestimation by the unenhanced TTE Doppler images. Their results echoed with findings of other investigators, emphasizing the role and utility of contrast in situations where the determination of MR severity is crucial (von Bibra H et al, 1995). Other investigators have demonstrated the role of contrast agents in patients with prosthetic mitral valves. In clinical situations of ambiguity or when discrepancies exist between different diagnostic modalities, adding contrast may be a simple technique to offer greater insight and clarification of valve pathophysiology (Donovan & Armstrong, 1996). Summarizing the limited published evidence, combined with our experiences, there is reasonable data to suggest that the use of contrast in cases where the spectral Doppler signals are low in intensity is warranted.

Aortic stenosis (AS) is a chronic progressive disease mainly affecting the elderly population. Assessment of the severity of AS is of crucial importance in the decision for timing of aortic valve replacement surgery. Evaluation of AS severity with TTE relies heavily on Doppler measurement of the transvalvular velocity, which in turn allows the estimation of the AV gradient and the calculation of aortic valve area (AVA) by use of the continuity equation (Otto CM, 2006). Alignment of the Doppler signal to the direction of blood flow is critical to obtain an accurate estimation of the jet velocity and gradients and hence the AVA. Underestimation is a valid concern when confronted with decision for surgery. Contrast has been shown to result in an improvement in the determination of the peak Doppler velocity AS profile, allowing a more accurate trans-aortic gradient estimation (Nakatani S et al, 1992). Importantly, in this study, the authors noted that patients with weak Doppler signals demonstrated improvements in their image profiles, but even those with adequate unenhanced Doppler signals were further improved by the use of contrast. As already demonstrated, contrast enhancement of the Doppler signal profile improves the ability to obtain the maximal velocity as well as the entire Doppler envelope trace. In AS, this portends to improvement in the estimation of the maximal and mean AV gradients. The normal protocol for obtaining maximal AS gradients requires the echo sonographer to utilize numerous ultrasound windows (usually > 3) in the hope of aligning the Doppler cursor with the actual AS flow. As the AV becomes diseased, the valve opening is altered and the blood flows in any number of directions from the LV to aorta. Therefore, it is uncommon that the optimal alignment can be predicted, as it is just as likely that the maximal velocity will be obtained in the right parasternal window as it will be in the apical

3, apical 5, subcostal, or suprasternal window. At times, there is a great variation in the maximal AS gradient from each of these windows. In our experience, the contrast enhanced Doppler signal is occasionally similar across multiple ultrasound windows. Whether this would portend to a quicker Doppler exam, by allowing the sonographer to limit the number of images acquired from multiple windows has yet to be proven.

4. Conclusion

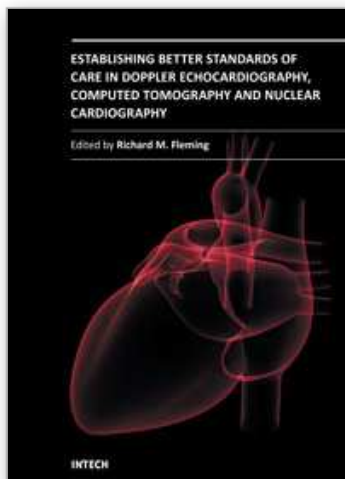
Contrast agents have now been in use for more than five decades from their initial application by Gramiak and Shah in 1960s. The 2nd generation agents used today, are safe, have the ability to cross the pulmonary circulation, are inert and have higher acoustic properties to aid in the evaluation of a vast spectrum of clinical dilemmas. Because of recent post-marketing concerns raised by the FDA, there have been several important, large studies reported that demonstrate and confirm the safety of these agents (Borges AC et al, 2002; Piscaglia F et al, 2006; Raisinghani A et al, 2003). In this chapter, the role of these contrast agents in augmenting the spectral Doppler profile for both right and left sides of the heart and including both regurgitant and stenotic valve diseases was highlighted.

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**Establishing Better Standards of Care in Doppler
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