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Contrast microsphere enhancement of the tricuspid regurgitant spectral Doppler signal - Is it still necessary with contemporary scanners?

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ABSTRACT

Background: Accurate evaluation of the tricuspid regurgitant (TR) spectral Doppler signal is important during transthoracic echocardiographic (TTE) evaluation for pulmonary hypertension (PHT). Contrast enhancement improves Doppler backscatter. However, its incremental benefit with contemporary scanners is less well established. The aim of this study was to assess whether the TR spectral Doppler signal using contemporary scanners was improved using a second generation contrast agent, Definity® (CE), compared to unenhanced TTE (UE).
Methods: Analysis of patients who underwent UE then CE TR interrogation was performed. TR signal was evaluated by an experienced reader and graded 1 (clear-high level of confidence of interpretation and complete spectral Doppler envelope), 2 (suboptimal with medium-low level of confidence of interpretation and incomplete envelope), 3 (poor-absent and no measurable spectral Doppler signal). Maximal TR velocity (TRV) was defined as peak velocity that could be clearly identified. An inexperienced sonographer read 30 randomly selected studies.
Results: 176 TTE were performed in 173 patients (mean age 57 ± 14.8 years). Wilcoxon signed rank test demonstrated significant improvement ($p < 0.0001$) in TR spectral Doppler signal quality with CE TTE. Mean score CE TTE vs. TTE = 2.32 ± 0.85 vs. 2.56 ± 0.75 respectively ($p < 0.0001$). Mean maximal TRV CE TTE vs. UE TTE = 2.61 ± 0.44 m/s vs. 2.54 ± 0.49 m/s respectively ($p < 0.0001$). The inexperienced reader had a greater improvement in scoring CE TTE signals vs. UE TTE ($p < 0.0001$).
Conclusion: In the era of contemporary scanners, CE improved the ability to detect and measure TRV, except in those with clear unenhanced TR spectral Doppler signals or greater than mild tricuspid regurgitation.

1. Introduction

Transthoracic echocardiography (TTE) is routinely used in clinical practice to non-invasively evaluate right heart haemodynamics, particularly as a technique to measure the right ventricular systolic pressure (RVSP). This application of TTE is recommended in both echocardiographic and pulmonary hypertension guidelines [1–3]. As TTE is a widely available, non-invasive investigation that is also safe and well tolerated, it is usually the first investigation requested when assessing for pulmonary hypertension. By incorporating the maximal tricuspid regurgitant (TR) velocity, as measured by spectral Doppler, into the modified Bernoulli equation, TTE can be used to non-invasively calculate RVSP, which is a surrogate of the pulmonary artery systolic pressure in the absence of pulmonary stenosis [1,4,5].

However, there are numerous well recognised limitations in using TTE to screen for pulmonary hypertension [6]. First, if there is no detectable TR spectral Doppler profile, the RVSP cannot be directly calculated. Consequently, other indirect measures are needed to assess pulmonary haemodynamics. Second, a clear spectral Doppler profile is required to enable both accurate and precise measurement of the peak velocity of the TR signal. Any inaccuracy or error in this measurement is only compounded by the multiplication of this value. The spectral Doppler

signal also has numerous inherent properties that may facilitate incorrect measurement. The signal may be incomplete with a poor spectral Doppler envelope. Additionally, the maximal velocity may be overestimated or underestimated with incorrect Doppler gain and filter settings.

In those patients with sub-optimal or no TR spectral Doppler signals, injection of agitated saline or echocardiographic contrast agents is recommended to enhance the Doppler signal [1,3–5,7]. However, the evidence base for this recommendation using second generation contrast agents and contemporary scanners is scant [8]. The aim of this study was to evaluate whether administration of a second generation contrast agent, Definity® (Lantheus Medical Imaging, North Billerica, MA, USA) whilst using contemporary scanners, would improve the derivation and measurement of the TR spectral Doppler envelope compared to conventional unenhanced imaging.

2. Methods

2.1. Study population

Approval to perform this study was obtained from The Prince Charles Hospital Human Research and Ethics Unit (HREC/16/QPCH/15). Patients (both stable out-patients and any in-patients) who were referred for a clinically indicated resting contrast enhanced TTE at our institution were included in this analysis. All patients gave informed consent prior to having the contrast echocardiogram.

2.2. Study protocol

The TR signal was initially assessed with conventional unenhanced TTE, using either a Philips iE33, EPIQ7 (Philips Medical Systems, Andover, MA, USA) or General Electric E9, E95 or Vivid Q scanner (GE Healthcare, Little Chalfont, Bucks, UK), prior to the administration of contrast. Images were acquired by experienced cardiac sonographers. Four conventional acoustic windows were used in all patients to evaluate the TR signal: the right ventricular inflow view from a modified parasternal long axis view, the parasternal short axis view, an apical four chamber view and a sub-costal view. Colour Doppler imaging was used initially to detect any TR signal in all four acoustic windows during unenhanced imaging. Evaluation of this TR jet using continuous wave Doppler was then performed, optimising alignment between jet direction and Doppler interrogation. This was performed in all four views.

Definity® contrast was then administered and the clinically indicated contrast enhanced TTE was performed. For each study, one ampoule of activated Definity® was diluted to either 10 mL or 50 mL with normal saline and administered as a bolus or continuous infusion, respectively. The contrast dose was adjusted to achieve optimal contrast imaging for each patient. Following completion of the clinically indicated contrast enhanced TTE, spectral Doppler analysis of the TR jet was re-evaluated in all four acoustic windows with the presence of circulating Definity® contrast. To avoid increasing contrast destruction, colour Doppler imaging was not reactivated when using contrast to evaluate the TR signal. Due to spectral blooming following contrast administration, modifications to the spectral Doppler settings were made with the contrast enhanced images; the spectral Doppler gain was decreased to 0–20% (from a baseline of 50%) and the "reject" or Doppler filters were increased. This was performed on all contrast signals to minimise the spectral "blooming". Fig. 1 is an example of a spectral Doppler TR signal with contrast, before and after image optimisation.

2.3. Image interpretation

For unenhanced and contrast enhanced TTE, in each of the four views, the TR severity, spectral Doppler signal quality and maximal velocity were measured. TR severity was graded as trivial, mild, moderate

or severe using the conventional American Society of echocardiography guidelines [1]. TR spectral Doppler signal quality was graded as class 1 (clear with a high level of confidence of interpretation and a complete spectral Doppler envelope), class 2 (sub-optimal with a medium - low level of confidence of interpretation and an incomplete envelope), or class 3 (poor-absent and no measurable spectral Doppler signal). Maximal velocity was defined as the peak velocity that could be clearly identified and measured in meters/s. For those patients in atrial fibrillation, with a measurable TR signal, the maximal velocity was averaged over 3–5 cardiac cycles. All images were interpreted independently by an experienced echocardiologist. To avoid possible bias induced by interpreting the contrast enhanced TTE data immediately after the corresponding unenhanced TTE, each data set was interpreted at different times. To assess whether contrast improved evaluation of the TR signal parameters by inexperienced sonographers, an inexperienced cardiology trainee read 30 randomly selected studies.

2.4. Statistical analysis

Categorical variables are displayed as absolutes and percentage. Continuous variables are displayed as mean ± one standard deviation. Comparison between unenhanced and contrast enhanced TR signal quality was performed using the Wilcoxon signed rank test. Comparison between the unenhanced and contrast enhanced TR signal maximal velocities was performed using the paired t-test. A p value of <0.05 was considered as statistically significant. Statistical analysis was performed using GraphPad Prism® (La Jolla, CA, USA).

3. Results

One hundred and seventy six TTE were performed in 173 patients who were referred for a clinically indicated contrast TTE. All patients had both unenhanced and then contrast enhanced TR spectral Doppler evaluation in all four acoustic windows. Table 1 describes the demographic data. There were no adverse events related to the contrast administration. Following administration of contrast, there was an improvement in the TR spectral Doppler signal quality in 178/704 (25.3%) of acquired views. Of these 178, there was an improvement in the spectral Doppler signal quality by two classes in 52 (7.4%) and by one class in 126 (17.9%). In 476/704 (67.6%) there was no change in TR spectral Doppler signal quality with contrast. In 50/704 (7.1%), there was a reduction in the TR spectral Doppler signal quality following contrast administration. Of these 50, there was a decrease in signal quality by two classes in 12 (1.7%) and by one class in 38 (5.4%). Fig. 2 displays the absolute signal quality classification grades for both unenhanced and contrast enhanced TTE. In a total of 140/704 views (19.9%), contrast administration resulted in the generation of a TR spectral Doppler profile which was non-existent with unenhanced TTE. The mean score for the spectral Doppler TR signal quality using unenhanced TTE was 2.56 ± 0.75 versus 2.32 ± 0.85 for contrast enhanced TTE (p = 0.001). Using the Wilcoxon signed rank test, there was a significant improvement in TR spectral Doppler signal quality with contrast enhanced versus conventional unenhanced TTE (z = 7.58, p < 0.0001). A significantly greater number of patients had a grade 1 TR spectral Doppler signal score (in any one of the four acquired acoustic windows) with contrast enhancement (97/173, 56.1%) compared to unenhanced imaging (56/173, 32.4%), p < 0.0001.

The maximal TR velocity could be confidently measured in 196/704 (27.8%) acoustic windows using unenhanced TTE and this improved to 296/704 (42%) using contrast enhanced TTE. Table 2 describes the maximal TR velocity measurement in each of the four acoustic windows, pre and post contrast administration. The mean maximal TR velocity was 2.54 ± 0.49 m/s with all measurable unenhanced TTE versus 2.61 ± 0.44 m/s with all measurable contrast enhanced TTE (p < 0.0001). The mean maximal TR velocity in those with a clear (class 1) spectral Doppler envelope quality was 2.67 ± 0.45 m/s using unenhanced TTE and
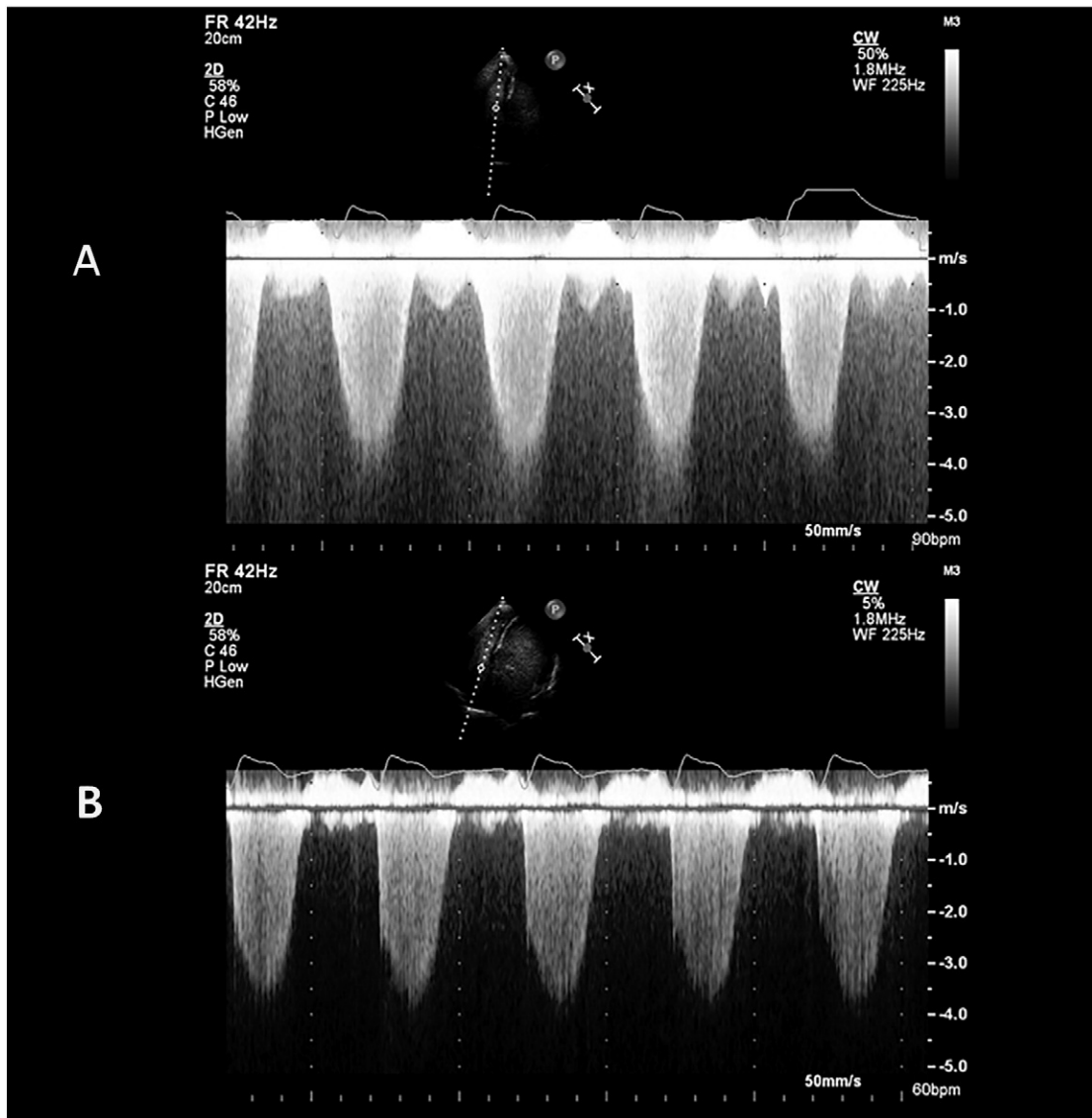
Fig. 1. Spectral Doppler TR signal with contrast, before (A) and after (B) image optimisation. Note the reduction in spectral gain from a baseline of 50% to 5% and an increase in the filtering.

2.69 ± 0.45 m/s with contrast enhanced TTE (p = 0.7). However, in those with a sub-optimal (class 2) spectral Doppler envelope, the mean maximal TR velocity was 2.36 ± 0.49 m/s with unenhanced TTE and 2.49 ± 0.39 m/s with contrast enhanced TTE (p = 0.09). With both the unenhanced and contrast enhanced TTE, the highest

mean maximal TR velocity was identified using the apical four chamber view (2.59 ± 0.43 m/s and 2.67 ± 0.42 m/s respectively). Table 3 displays the tricuspid regurgitation severity grading for all studies and the corresponding mean maximal velocities of the tricuspid regurgitant spectral Doppler signal with both unenhanced and contrast enhanced TTE. A total of 71 patients (40.3%) had a higher (>5 mm Hg) in estimated RVSP with the addition of contrast. Of note, there were 18 patients (10.2%) in which unenhanced TTE had a higher (>5 mm Hg) estimated RVSP than with contrast enhanced assessment.

Table 4 depicts the unenhanced and contrast enhanced TR spectral Doppler signal quality and mean maximal TR spectral Doppler velocity for the inexperienced reader. As for the experienced reader, the mean maximal TR velocity was significantly higher in the contrast enhanced versus unenhanced images (p = 0.03) for the inexperienced reader. The mean TR spectral Doppler signal image quality score by the inexperienced reader was lower for contrast enhanced versus unenhanced images, though this did not reach significance (p = 0.07). There was a significant difference in the grading between the experienced and inexperienced reader for tricuspid regurgitant spectral Doppler signal quality in the unenhanced images (z = 2.19, p = 0.02). However, there was no significant difference in the grading of the signal quality between the

Table 1
Patient demographics.

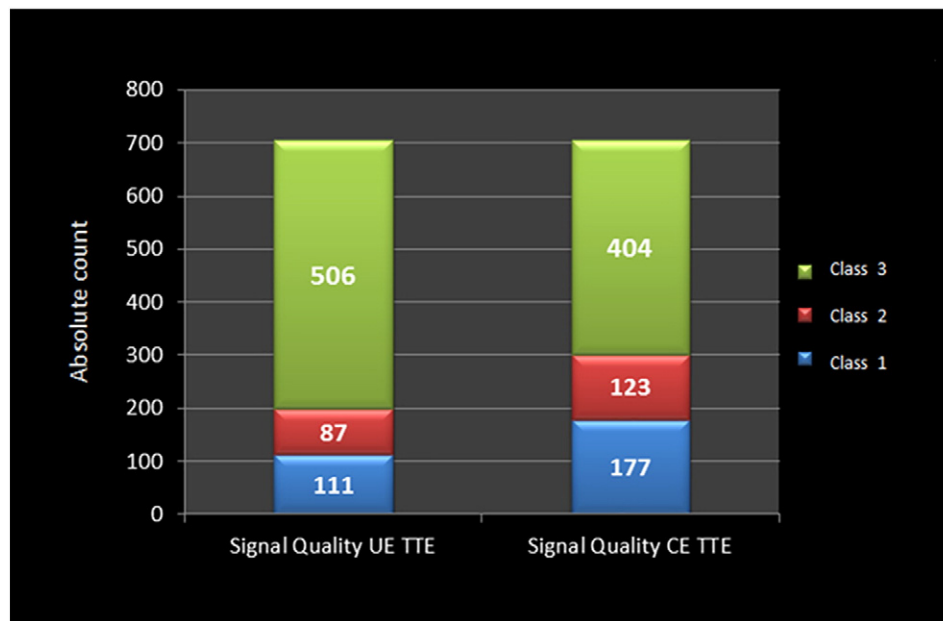| Age years (mean ± 1SD)		57 ± 14.8
Gender	Male	121 (69.9%)
	Female	52 (30.1%)
Rhythm	Sinus rhythm	153
	Atrial fibrillation	21
	Paced	2
Heart rate (mean ± 1SD)		76.2 ± 16.6
Contrast administration	Bolus	3
	Infusion	173
Echo scanner	Philips iE33	148
	Philips EPIQ	10
	GE E9	16
	GE E95	1
	GE Vivid Q	1

Fig. 2. Absolute scores for TR spectral Doppler signal quality for unenhanced and contrast enhanced TTE.

experienced and inexperienced reader in the contrast enhanced images ($z = -0.25$, $p = 0.8$).

4. Discussion

Measurement of the maximal TR velocity is an important component of a routine TTE examination, which has applicability and impact on a diverse group of disease processes and management algorithms. These range from conventional detection of pulmonary hypertension through to involvement in newer screening tools for the discrimination of pre-capillary from post-capillary pulmonary hypertension using TTE [9]. Non-invasive evaluation of pulmonary haemodynamics using the right ventricular systolic pressure derived from TTE has been routinely used for several decades. However, with closer scrutiny of the accuracy of techniques to calculate pulmonary haemodynamics, especially in the era of specific pulmonary vasodilator therapies, some questions have been raised on the accuracy of TTE for these parameters [10,11]. As such, there has been an increasing focus on the actual TR spectral Doppler signal quality when calculating the RVSP. In the late 1980's and the early 1990's, there were multiple studies which used either agitated saline or specific echocardiographic contrast agents to enhance the tricuspid regurgitant spectral Doppler signal. However, with the advent of significant advances in scanner technology and hence image quality over the last two decades, the issue of whether contrast agents still have a role to play in the optimisation of these spectral Doppler signal profiles has received little attention. Advances in scanning technology over the last 3 decades include improvements in both the beam forming elements within ultrasound transducers and the processing, analysis and display of the ultrasound signals. Signal generation and processing has progressed from fundamental to harmonic imaging and from an analogue to digital format [12]. Algorithms have been developed to improve the signal to noise ratio [13]. Automated gain settings along with two and three dimensional and spectral Doppler pattern recognition algorithms can enhance reproducibility and work flow [12,14,15]. It is possible that contemporary, more sophisticated imaging may render contrast agents redundant in the evaluation of the tricuspid regurgitant spectral Doppler signal.

Assessing this relationship, the results of our study are sixfold. Firstly, there was a significant increase in the number of patients who had a clear (grade 1) TR spectral Doppler signal with the addition of contrast. Secondly, in one fifth of acoustic windows without a TR spectral Doppler signal, contrast administration resulted in the generation of a spectral profile. Thirdly, in one quarter of acquired views, contrast improved the quality of a TR spectral envelope. Fourthly, in those cases of a clear (class 1) unenhanced TR spectral Doppler profile, contrast administration did not alter the measurement of the TR regurgitant velocity. Fifthly, if the TR regurgitation grade was more than mild, the addition of contrast did not result in a higher TR regurgitant velocity. Of note, in a small number of views (7.1%), contrast administration resulted in degradation of the quality of the TR spectral Doppler profile. Finally, the addition of contrast improved the TR signal quality scoring by an inexperienced reader.

The Doppler effect is generated by a change in sound frequency by a target moving toward or away from a reference point [16]. In conventional echocardiography, the target generating the signal is red blood cells and the reference point is the transducer. Variation in the backscattering properties of these moving structures directly affects the spectral Doppler envelope. Contrast agents are strong backscatters of ultrasound and consequently, they have application in enhancing spectral Doppler signals. Agitated saline contrast was the first method recommended to enhance the spectral Doppler regurgitant signal. There were multiple studies published in the 1980's and 1990's evaluating their utility [17–23]. One of the limitations of this technique is that the backscatter

Table 2
Mean TR maximal velocity in m/s for each acoustic window ± 1SD.

	Unenhanced TTE	Contrast enhanced TTE	p
RV inflow view	2.51 ± 0.57	2.57 ± 0.50	ns
Parasternal short axis	2.52 ± 0.49	2.57 ± 0.44	ns
Apical 4 chamber view	2.59 ± 0.43	2.67 ± 0.42	p < 0.0001
Subcostal view	2.45 ± 0.47	2.55 ± 0.40	p = 0.02

Table 3
Classification of TR severity and corresponding mean maximal TR spectral Doppler velocity for unenhanced and contrast enhanced TTE.

TR severity grade	Unenhanced TTE	Contrast enhanced TTE	p
No TR	0	2.53 ± 0.37	p < 0.0001
Trivial TR	2.40 ± 0.46	2.52 ± 0.48	p = 0.02
Mild TR	2.65 ± 0.49	2.83 ± 0.44	p = 0.0003
Moderate-severe TR	2.84 ± 0.42	2.79 ± 0.29	p = ns

Table 4

Classification of TR spectral Doppler signal quality and mean maximal TR spectral Doppler velocity for unenhanced (UE) and contrast enhanced (CE) TTE for inexperienced reader.

	Inexperienced UE TTE	Inexperienced CE TTE	p
TR signal	2.41 ± 0.74	2.29 ± 0.70	0.07
TR velocity	2.41 ± 0.50	2.58 ± 0.39	0.03

generated by this technique is a relatively course, heterogeneous and unstable reflector of ultrasound. Limitations of agitated saline, most likely due to the relatively large size, low number, short term and unstable nature of the bubble [24,25] include over-estimation of the velocity in patients with trivial tricuspid regurgitation and not having as good correlation with catheter derived RVSP compared to an air-blood-saline contrast mixture [22,26–28]. As such, it is not uncommon for agitated saline to produce course, incomplete spectral Doppler envelopes. These signals have been described as "fishbone" like in morphology [29]. Fig. 7A is an example of a tricuspid regurgitant spectral Doppler signal enhanced with agitated saline. Two studies have evaluated blood-air-saline mixes as a contrast agent for enhancement of the tricuspid regurgitant spectral Doppler signal and found that they were superior to an air-saline alone mixture in the calculation of RVSP [22,26].

However, we do not perform this technique due to the potential risk of equipment failure during the generation or injection of the mixture, which may result in exposure of personnel to the blood mixture.

Echocardiographic contrast microspheres have been used in routine clinical practice since the mid 1990's [7,30,31]. As a strong backscatterer of ultrasound, these agents can also be used to optimise a spectral Doppler signal, either on the left or right side of the heart [28,29,32–35]. However, all these studies have used a first generation contrast agent such as sonicated albumin or Levovist © (Bayer, Germany). The current evidence base for the utility of a second generation contrast agent in spectral Doppler signal enhancement coupled with contemporary scanners is almost non-existent, limited to just one abstract and a single case report [8,36]. Second generation contrast agents backscatter ultrasound at a rate 100 million times that of red blood cells [37]. These contrast agents potentially offer incremental benefit over agitated saline by being more stable and uniform, providing a stronger and more consistent reflective pattern as well as having significantly longer signal persistence.

In this study, the addition of contrast had numerous effects. Firstly, it resulted in the identification of a tricuspid regurgitant spectral Doppler signal when one was not identified using conventional unenhanced TTE in nearly one fifth (19.9%) of acquitted views. This was most likely a
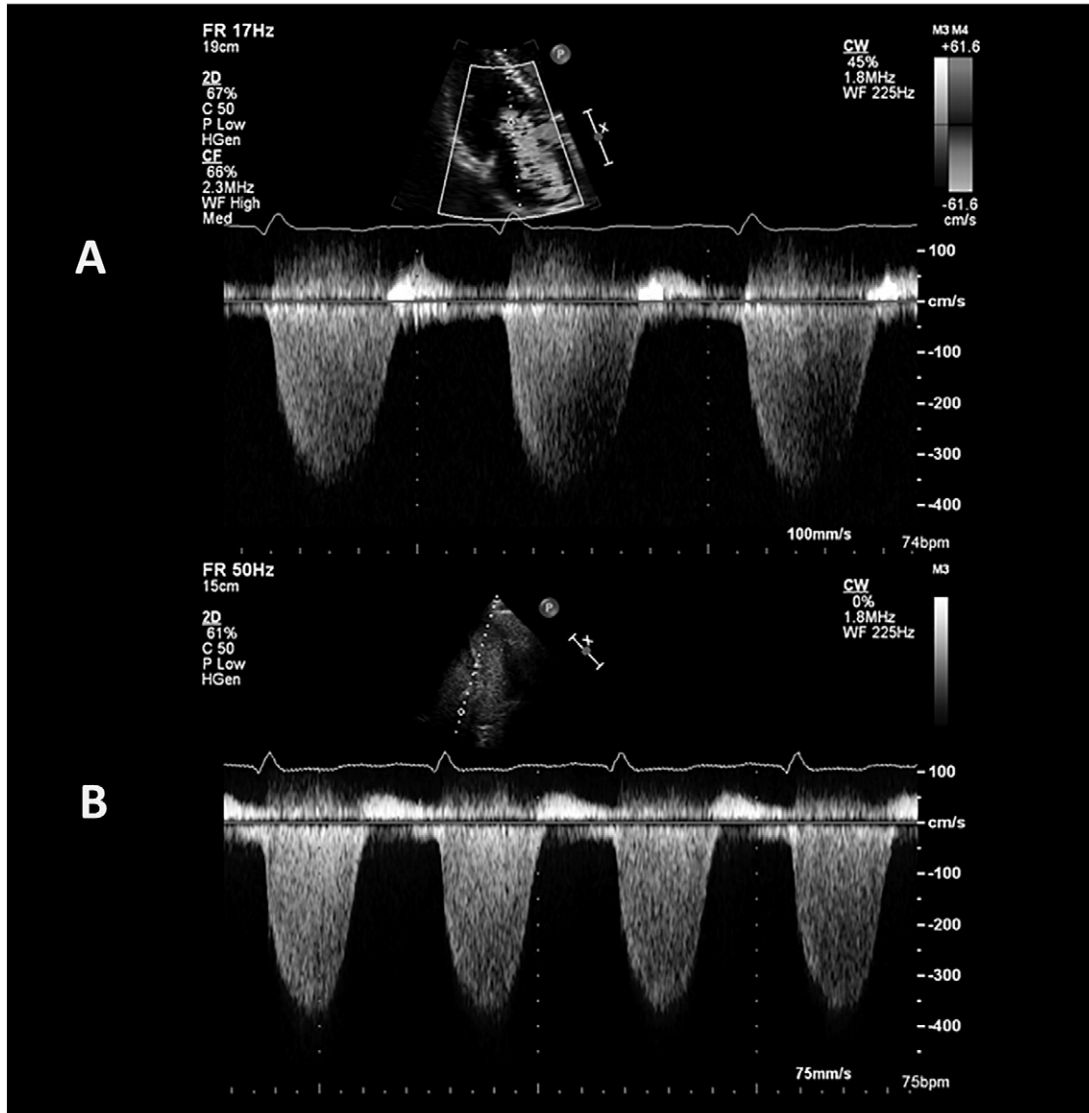

Fig. 3. Tricuspid regurgitant spectral Doppler signal profile with unenhanced (A) and contrast enhanced (B) TTE. Note the clear spectral envelope in both cases (but stronger with contrast) and the same maximal TR regurgitant velocities.
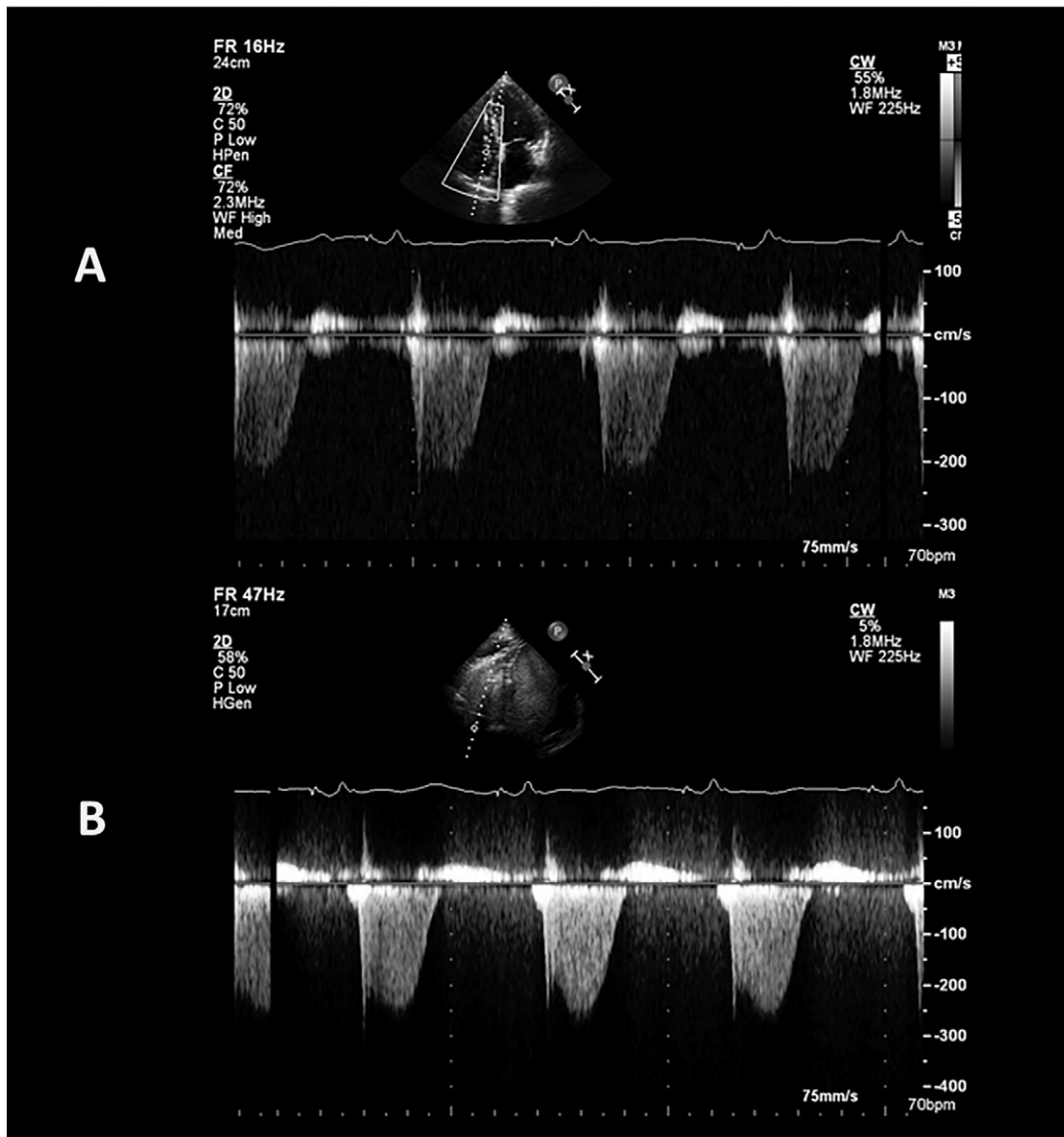
Fig. 4. Tricuspid regurgitant spectral Doppler signal profile with unenhanced (A) and contrast enhanced (B) TTE. Note the better defined spectral envelope and higher velocity with contrast enhancement.

function of the strong backscattering signal of the contrast, resulting in the sonographer being able to detect a small tricuspid regurgitant jet that could not be identified with conventional imaging. Overall, there was an improvement in the quality of the spectral Doppler envelope in one quarter of acquired views (25.3%). An inexperienced reader also had improved evaluation of the TR spectral Doppler signal quality following the addition of contrast. By improving the morphology of the TR Doppler envelope via it enhancing backscattering properties, contrast not only assisted experienced readers in Doppler evaluation but made it clearer for inexperienced readers in deciding how to grade a spectral Doppler envelope. Fig. 3 is an example where a relatively clear spectral Doppler envelope was achieved with unenhanced imaging and the addition of contrast did not significantly alter this measurement of the maximal TR velocity of this envelope. Note however the increased spectral Doppler waveform brightness due to the presence of the strong ultrasound reflectors.

The second effect of contrast was that it resulted in higher mean maximal regurgitant velocities in those views that had sub-optimal spectral Doppler profiles. Fig. 4 is an example of this phenomenon. In those views that had clear tricuspid regurgitant spectral profiles, there was no increase in the mean regurgitant velocities. Again, due to its strong backscattering properties, contrast would result in a clearer and more strongly demarcated peak velocity. As such, it is likely to generate higher velocities in patients with indistinct and hence incomplete spectral Doppler profiles with unenhanced TTE. Fig. 5 is an example where the addition of contrast significantly improved the quality of the spectral Doppler envelope, such that the maximal velocity could then be confidently measured.

Directly influencing the quality of the envelope is the grading of the tricuspid regurgitation severity. In our study, mild or less tricuspid regurgitation were found to have higher mean maximal regurgitant velocities with the addition of contrast. However, if the regurgitation was graded as more than mild, then there was no change in the mean maximal regurgitant velocities. This is mechanistically sound as a larger TR regurgitant jet would be more easily identified and hence likely to mitigate any incremental benefit that contrast enhancement may offer in that situation. Whilst not statistically significant, the unenhanced mean maximal regurgitant velocity was actually higher than that obtained with contrast in those with greater than mild tricuspid regurgitation. This may be due to the unenhanced signals being over-estimated
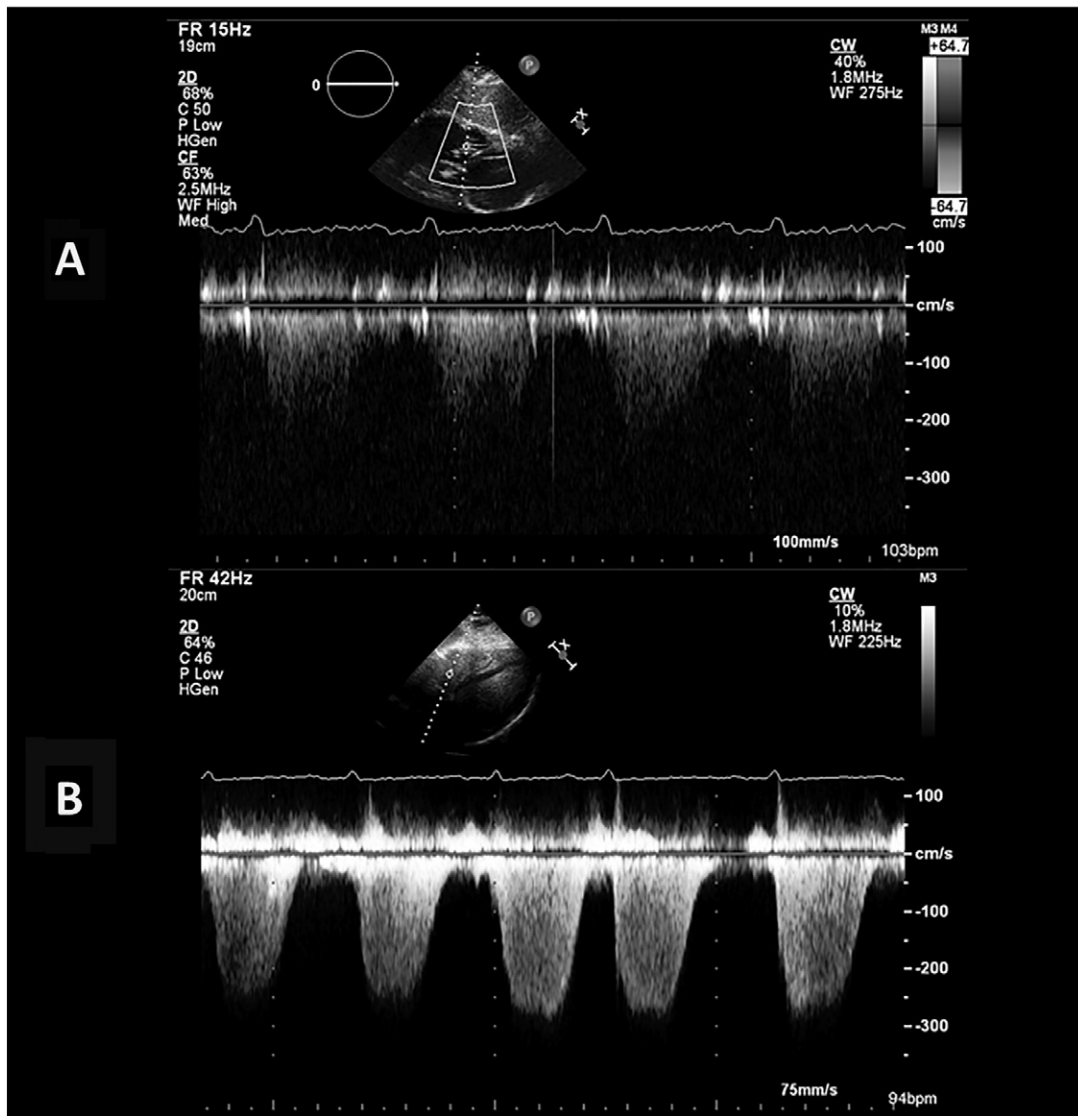
Fig. 5. Tricuspid regurgitant spectral Doppler signal profile with unenhanced (A) and contrast enhanced (B) TTE. Note the incomplete, unmeasurable spectral Doppler envelope with unenhanced imaging and the clearly defined spectral envelope with a measurable maximal velocity following contrast administration.

due to a "hazy" or indistinct peak of the Doppler envelope being measured in the clinical setting, rather than the true modal velocity. Fig. 6A is an example of an unenhanced spectral Doppler envelope where the gain and filters have remained unaltered. Fig. 6B demonstrates the impact of altering the gains and filter settings of the same spectral Doppler profile. Note the better defined envelope and the clearer and slightly lower maximal velocity. All contrast enhanced Doppler signals were optimised by adjusting the gain and filter settings to prevent spectral blooming. Again, the clinical implication of this finding is that contrast administration could be considered in those patients with incomplete spectral Doppler signals. It is unlikely to be of benefit if there is more than mild tricuspid regurgitation.

One unexpected finding of this study was that in 7.1% of acquired views, the administration of contrast resulted in the degradation of the tricuspid regurgitant spectral Doppler signal quality. There are several possible explanations for this finding. Having found a tricuspid regurgitant spectral Doppler signal with unenhanced TTE, the sonographer may not have spent the equivalent amount of time of attention to seeking out the contrast enhanced spectral Doppler signal. Alternatively, searching for a tricuspid regurgitant signal with unenhanced TTE has the advantage of using colour Doppler imaging to identify the regurgitant jet more clearly. Activation of colour Doppler imaging

during contrast enhanced TTE often does not provide a clear site for the regurgitant jet due to the broad spectrum of high intensity signals within the field of view. As such, it may have been more difficult to identify the site of the tricuspid regurgitant jets during the contrast enhanced TTE in some patients. As optimal alignment between the TR regurgitant jet an incident ultrasound beam is required to accurately measure the TR regurgitant jet using Doppler [1,5], the absence of being able to use colour Doppler imaging for this with contrast may have contributed to this source of variation.

Compounding possible variation in grading of the tricuspid regurgitant spectral Doppler signal envelope is the qualitative method in which they were graded. In our study, we deliberately used just three classes: clear, sub-optimal or absent/not measurable. This was used to help minimise misclassification of signal quality which may occur if a higher number of grading classes is used. Previously published work has used anywhere from 3 to 6 different classification grades for TR spectral Doppler signal quality [10,17,24,32].

4.1. Study limitations

The main limitation of this study was that it was purely a methodological study regarding generation and analysis of a spectral Doppler
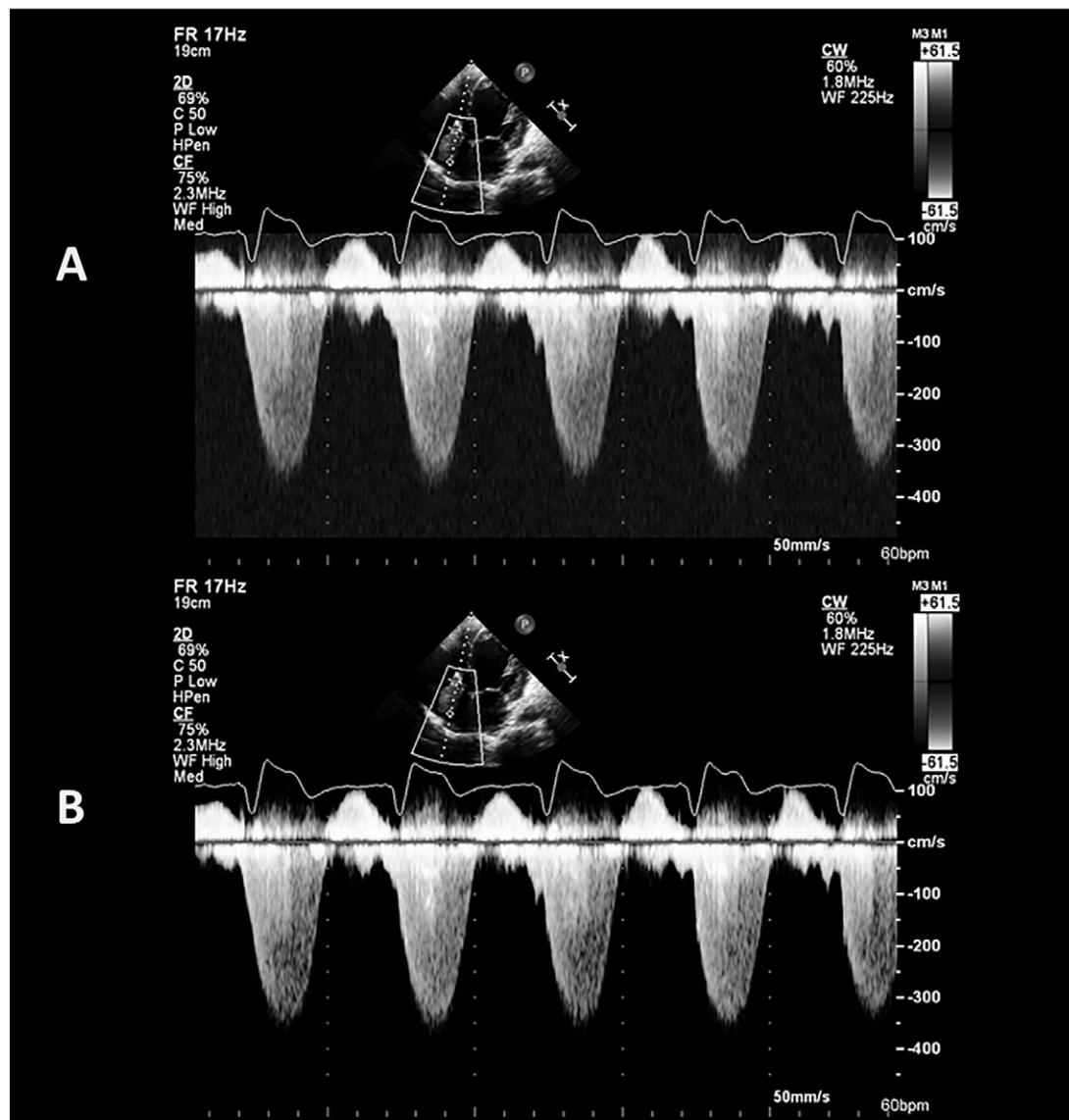
Fig. 6. Spectral Doppler signal with unenhanced TTE before (A) and after (B) optimisation of the envelope profile by altering the gain and filter settings. Note the better defined envelope and the clearer and slightly lower maximal velocity.

signal. It did not evaluate whether this signal was then translated into a more accurate measurement of the RVSP as derived from invasive right heart catheterisation. The unenhanced and contrast enhanced spectral Doppler data was collected in a near simultaneous manner. However, we did not have near simultaneous or contemporaneous invasive right heart catheter data to correlate with the non-invasive TTE data. As such, whilst incremental benefit was obtained with contrast enhanced signals, this cannot be confirmed as translation to a more accurate method to determine the RVSP. Additionally, the focus of this study was to assess whether contrast improves spectral Doppler profiles of the tricuspid regurgitant jet. Other components of the TTE examination to determine pulmonary haemodynamics, such as direct measurements (right atrial pressure) or indirect measurements (such as the right ventricular outflow tract acceleration time) were not evaluated. This study sought to assess if contrast agents were still required in the era of contemporary echocardiography scanners. To further evaluate this, an ideal study design would have been to also use a second scanner from 20 to 30 years ago to evaluate the tricuspid regurgitant spectral Doppler signal at the same time as the contemporary scanner.

One bias that was not controlled for in this study was the same sonographer acquired the contrast enhanced TTE images immediately following the unenhanced TTE images. As such, it is possible that knowing the unenhanced TTE spectral Doppler envelope, this potentially may have influenced the search for and the measurement of the contrast enhanced spectral Doppler signal. The most effective method to control for this bias would be to have separate sonographers acquire the unenhanced and contrast enhanced images, so they are blinded to the other images. Unfortunately, practical limitations of work flow precluded the ability to source two sonographers for a single TTE. Also, it was not feasible to randomise whether unenhanced or contrast enhanced signals were obtained first due to the long signal persistence of Definity® contrast. This would then have most likely partially infected the unenhanced spectral Doppler evaluation. Hence, contrast signals were always assessed following unenhanced TR estimation. Finally direct comparison between agitated saline and Definity® contrast was not performed in this study. Our experience is that agitated saline generates multiple course backscattering signals of high variation within a single cardiac cycle. This can make clear delineation of the spectral envelope difficult. Fig. 7 demonstrates a tricuspid regurgitant spectral Doppler profile with agitated saline (Fig. 7A) and then with contrast enhancement (Fig. 7B). Note the cleaner, better defined envelope with contrast over agitated saline. The primary focus of this study was to ascertain whether the more
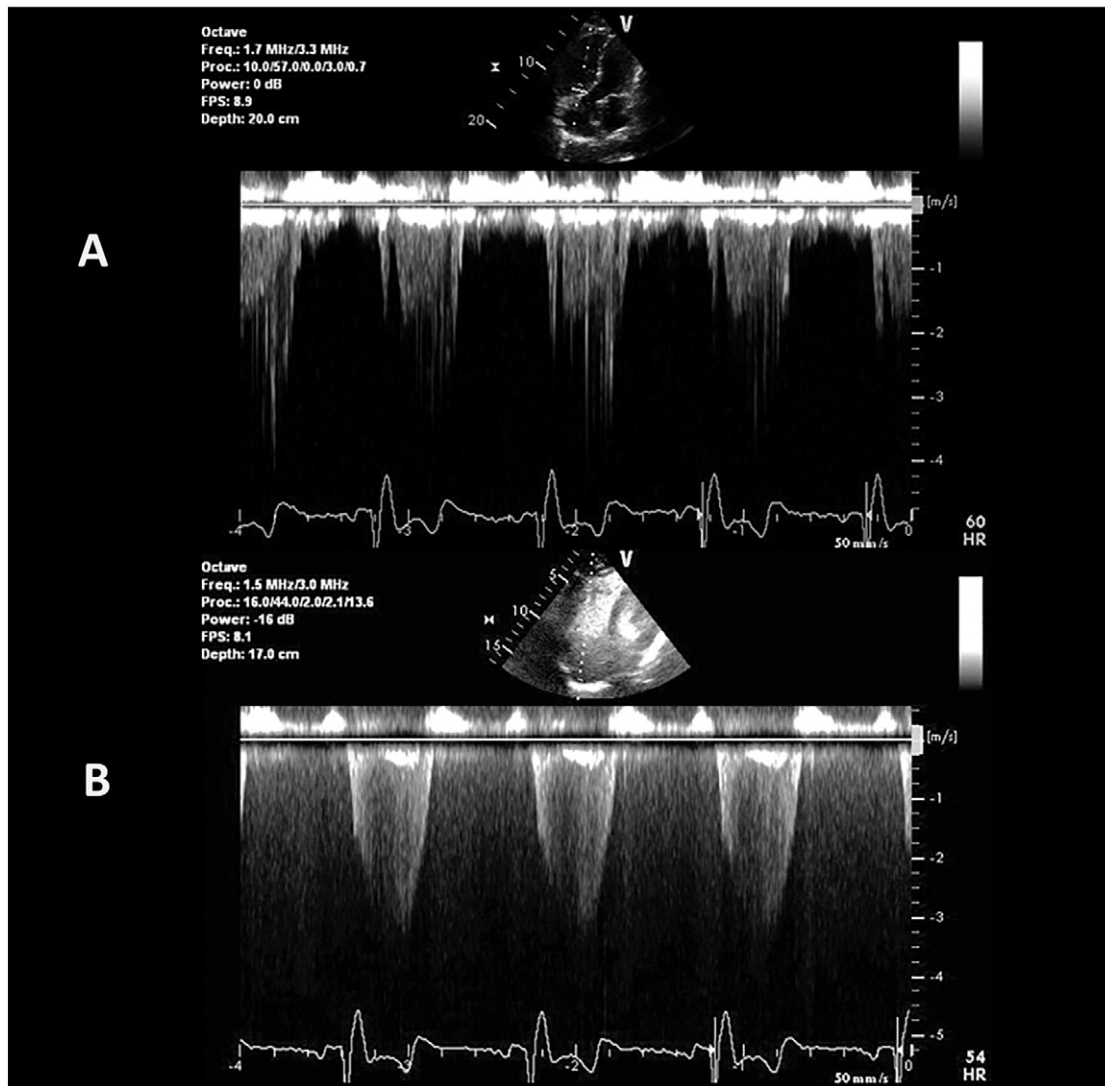
Fig. 7. Tricuspid regurgitant spectral Doppler profile with agitated saline (A) and then with contrast enhancement (B). Note the cleaner, better defined envelope with contrast over agitated saline.

expensive engineered contrast microspheres are still required with the advances in ultrasound technology, rather than comparing two different types of contrast agent. Our study only looked at one contrast agent (the only one approved and commercially available in our country) and its effect on the spectral Doppler profile. Whilst not evaluated in our study, all contrast agents would most likely have a similar effect.

5. Conclusion

In the era of contemporary echocardiographic scanners, the addition of a second generation echocardiographic contrast agent can still help optimise the tricuspid regurgitant spectral Doppler signal profile. These contrast microspheres add incremental value in a safe manner by identifying and optimising the spectral Doppler signal quality in a significant number of patients with non-existent or sub-optimal unenhanced tricuspid regurgitant signal profiles. However, in those with clear unenhanced TR spectral Doppler signal profiles or those with greater than mild TR, contrast administration is unlikely to be of incremental benefit. There may be a selective role for contrast microspheres in facilitating measurement of the RVSP in those patients with discordant results or in those with a normal TTE despite a high pre-test probability of pulmonary hypertension.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/

or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval to perform this study was obtained from The Prince Charles Hospital Human Research and Ethics Unit (HREC/16/QPCH/15).

Author contributions

DGP was involved with study conception, design, data analysis and drafting the article, MV was involved in data analysis and manuscript revision, DJB was involved in critical revision of the manuscript, CHC was involved in critical revision of the manuscript, JC was involved in critical revision of the manuscript, JLS was involved in critical revision of the manuscript, GMS was involved in critical revision of the manuscript. All authors approved the submitted manuscript.

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