DETECTION OF RIGHT-TO-LEFT ATRIAL COMMUNICATION USING AGITATED SALINE CONTRAST IMAGING: EXPERIENCE WITH 1162 PATIENTS AND RECOMMENDATIONS FOR ECHOCARDIOGRAPHY

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Background – Right-to-left shunting via a patent foramen ovale (PFO) has a recognized association with embolic events in younger patients. The use of agitated saline contrast imaging (ASCi) for detecting atrial shunting is well documented, however optimal technique is not well described. The purpose of this study is to assess the efficacy and safety of ASCi via TTE for assessment of right-to-left atrial communication in a large cohort of patients.

Method - A retrospective review was undertaken of 1162 consecutive transthoracic (TTE) ASCi studies, of which 195 had also undergone clinically indicated transesophageal (TEE) echo. ASCi shunt results were compared with color flow imaging (CFI) and the role of provocative maneuvers (PM) assessed.

Results - 403 TTE studies (35%) had paradoxical shunting seen during ASCi. Of these, 48% were positive with PM only. There was strong agreement between TTE ASCi and reported TEE findings (99% sensitivity, 85% specificity), with six false positive and two false negative results. In hindsight, the latter were likely due to suboptimal right atrial opacification, and the former due to transpulmonary shunting. TTE CFI was found to be insensitive (22%) for the detection of a PFO compared with TTE ASCi.

Conclusions - TTE ASCi is minimally invasive and highly accurate for the detection of right-to-left atrial communication when PM are used. TTE CFI was found to be insensitive for PFO screening. It is recommended that TTE ASCi should be considered the initial diagnostic tool for the detection of PFO in clinical practice. A dedicated protocol should be followed to ensure adequate agitated saline contrast delivery and performance of provocative maneuvers.

The foramen ovale is an important component of the fetal circulation, allowing oxygenated blood to pass from the right atrium (RA) to the left atrium (LA), thus ensuring oxygen-rich blood reaches the foetal brain. At birth, aeration of the neonatal lungs markedly reduces pulmonary vascular resistance so RA pressure falls below LA pressure, effectively closing the foramen ovale. Subsequently, any transient increase in RA pressure above LA pressure will result in right-to-left shunting. Permanent fusion of the foramen ovale occurs by age two in approximately 75% of individuals with patency remaining in the other 25% (1-4).

The presence of a patent foramen ovale (PFO) has been linked with many illnesses including cryptogenic stroke, transient ischemic attacks (TIA), migraines, platypnoea-orthodeoxia syndrome (POS), and even decompression sickness amongst SCUBA divers(5). The presumed mechanism for cryptogenic stroke is the migration of a thrombus, air bubble or fat embolus from the venous system into the LA via a PFO, with subsequent systemic embolization(6). Implication of the PFO as the cause for paradoxical embolization (PDE) is strongest when the “PFO triad” is present. This triad consists of venous source of thrombosis, temporal association of transiently raised right atrial pressures with the neurologic event, and the presence of a PFO(7).

The detection of PFO by TTE is greatly improved by using agitated saline contrast injection (ASCi)(8). Intravenous injection of saline following agitation between two syringes enhances the backscatter of the ultrasound, thus highlighting venous blood flow. The “bubbles” generated by using agitated saline are too large to cross the pulmonary capillary bed (9, 10), thus visualization of contrast in the left heart chambers indicates either intracardiac or transpulmonary shunting. Provocative maneuvers such as Valsalva maneuver (VM), sniff and cough transiently increase right atrial (RA)

pressure above left atrial (LA) pressure. These maneuvers further enhance the sensitivity of ASCi for detection of atrial shunting (figure 1) and make evidence of right to left shunting more obvious (figure 2)(11-13).

Transesophageal echo (TEE) is the gold standard for visualization of atrial septal anatomy (5, 8). CFI during TEE is very effective at demonstrating left-to-right shunting when present. However, right-to-left shunting through a PFO is often absent at rest, and provocative maneuvers are required. There are technical challenges in eliciting an adequate increase in RA pressure during TEE. The presence of the TEE probe prevents closure of the glottis which is required for an effective VM (5). This can be further complicated by varying degree of patient sedation. The fasting state of TEE patients along with sedation induced hypotension can result in a lowered RA pressure leading to a reduced detection rate. These factors are eliminated with TTE, which if properly performed, can be a superior technique for demonstrating right-to-left shunting with ASCi.

The purpose of this study is to assess the efficacy and safety of ASCi via TTE for assessment of right-to-left atrial communication in a large cohort of patients.

Method

Study Population/Patient Selection

Over 18,000 consecutive, digitally stored TTE studies from the Hearts 1st echocardiography database (Greenslopes Private Hospital, Brisbane) performed between 01 December 2003 and 07 September 2009 were available for analysis. 1162 patients (559 male, 603 female, mean age 51 ± 16 years) were retrospectively identified having undergone a digitally stored comprehensive TTE study with ASCi.

A subgroup of 195 patients were identified to have also undergone TEE for further delineation of atrial septal anatomy. All studies were reported by experienced echocardiologists. Independent blinded review was performed by a study investigator for all of the CFI studies (Investigator - AF) and a subset (n = 50) of the ASCi studies (Investigator – KM) to ensure consistency of reporting.

Transthoracic Echocardiography

TTE examinations were carried out by experienced sonographers using either an Acuson Sequoia C512 or an Acuson Aspen (Siemens, Mountain View, CA, USA). Standard echocardiographic protocols were followed based on the recommendations of the American Society of Echocardiography (14-18).

CFI assessment for left-to-right shunting across the atrial septum, was performed in parasternal short axis, apical 4-chamber, and subcostal 4-chamber and short axis views, and were reported as positive, negative, indeterminate or technically inadequate. During assessment of the atrial septum, respiration was paused appropriately for image optimization. Provocative maneuvers were not specifically performed during CFI. The CFI was reported as positive if a discrete color jet was visualized passing through the atrial septum from at least one view. A study was deemed indeterminate if color flow could not be differentiated from caval flow or possible artifact. Studies that had inadequate imaging due to suboptimal acoustic windows or challenging color optimization were also coded as such.

Agitated saline contrast imaging

To ensure maximal diagnostic yield from ASCi, a standard imaging protocol for all ASCi studies was used as described below. ASCi studies were undertaken with 18 or 22

gauge cannula in an antecubital vein (rarely in a dorsal hand vein) using 8.5mL normal saline, 0.5mL of air, and 1mL blood aspirated from the cannula. Blood was used in the injection due to it's enhanced contrast appearance (19).This solution was then agitated forcefully between two syringes connected to extension tubing with a three-way stopcock, and rapidly injected once a suitable TTE image was obtained. Most commonly, an A4C view was used, however on occasion, the parasternal short axis view at the level of the atrial septum (aortic valve level), or subcostal four chamber view were utilised. On first visualization of contrast entering the RA, a 4 or 6 second digital loop was acquired. Dense opacification of the RA was imperative for accuracy in performance of ASCi. Competitive flow arising from the IVC, can result in localized loss of contrast along the RA side of the atrial septum, thereby resulting in a false negative result. In these cases, external manual compression of the liver was utilised as a tool to reduce IVC flow and help differentiate between competitive IVC flow and negative contrast from an ASD.

In addition to normal respiration, images were also obtained during provocative maneuvers to elicit right-to-left atrial shunting; these maneuvers included VM, sniff, +/- cough. Satisfactory performance of a provocative maneuver was defined as complete opacification of the RA adjacent to the atrial septum at the time of leftward bowing of the atrial septum. Failure to demonstrate at least transient leftward bowing of contrast opacified atrial septum on 2D imaging indicated insufficient performance of this maneuver, and the attempt was repeated. Where this was not achieved despite repeated efforts the ASCi study was deemed indeterminate. A minimum of five (5) injections with a combination of normal respiration, sniff and Valsalva were performed in all studies, as previously recognized by Johansson et al (20) to achieve maximum diagnostic yield. When both leftward bulging of IAS and dense contrast filling of RA

were present, the sensitivity for PFO detection after a single injection has been reported as high as 95% (21).

An ASCi study was coded as negative if there was no left heart contrast seen within 5 beats of entrance of contrast into the right atrium following provocative maneuvers or at rest. Micro bubbles visualized in the left heart chambers following 5 cardiac cycles were presumed to represent transpulmonary transit and were thus considered negative. Studies were coded as positive if there was any contrast seen in either of the left heart chambers within 5 beats of entrance of contrast into the right atrium. In addition, it was noted which maneuver was associated with contrast visualization. Studies were considered indeterminate if the image quality was suboptimal for visualization of contrast, when adequate maneuvers could not be performed, or when opacification of the right atrial septum could not be achieved.

Transesophageal Echocardiography

Of the 1162 patients who underwent TTE with ASCi, 195 also underwent TEE; considered the gold standard for anatomical assessment of the atrial septum. All examinations were performed under sedation (Fentanyl/Midazolam, +/- Propofol) or general anaesthetic. All examinations were performed by echocardiologists using the standard imaging protocol in our practice and an Acuson Sequoia C256 or C512 ultrasound system (Siemens, MountainView, CA) with a TE-V5M multiplane transesophageal probe. A comparison of detection of right-to-left atrial communication by TTE with ASCi and TEE was performed in this sub-group.

Statistical analysis

Statistical analyses were performed using commercially available statistical software (SPSS version 15.0, SPSS Inc, Chicago, IL). Levine's test for homogeneity as quantitative analysis and a bell curve for qualitative demonstration of equal distribution of variance demonstrated normal distribution of variables. Continuous and categorical variables were expressed as mean ± standard deviation (SD) and percentage respectively. One-way analysis of variance (ANOVA) was used for comparison of means for continuous variables between the groups of patients. Post-hoc analysis was performed using the Scheffé method when the ANOVA demonstrated a significant difference. Significance between categorical variables was assessed using a chi-squared test for goodness of fit. A P-value of <0.05 was considered statistically significant. Sensitivity and specificity tests were used to compare TTE ASCi, TTE CFI and the TEE subgroup.

Results

Clinical indications for ASCi

The clinical indications for performing ASCi in all patients are demonstrated in Table 1. The most common indications for ASCi were TIA/CVA (25.6%), assessment of right ventricular function (17.6%) and episodes of visual loss (12.7%). Some form of neurologic symptom or sign was basis for referral in 70.8% of the indications. The clinical indication for performing ASCi was not documented on the report or referral in 5.2% of studies.

Patient demographics and clinical characteristics

The patient demographics and clinical characteristics are summarized in Table 2. There was a small but significant difference ($p<0.01$) in the mean age, heart rate and both

systolic and diastolic blood pressure of the negative group when compared with the positive group. There was also a significant difference ($p<0.01$) in both systolic and diastolic blood pressures of the indeterminate group compared with the positive group.

Transthoracic CFI and ASCi

Table 3 summarizes the relationship between TTE CFI and shunting with ASCi. Assessment of the atrial septum for PFO using CFI demonstrated high specificity but low sensitivity for detection of shunting with ASCi. Left-to-right atrial shunting visualized by CFI was found to have a positive predictive value of 77%, and a negative predictive value of 68%.

Right-to-left atrial shunting was observed in 34.7% (n=403) of the sample population undergoing TTE echo with ASCi. No shunting was observed in 61.5% (n=715) of cases and the remainder were categorized as indeterminate or non-diagnostic for atrial shunting (n=44). The techniques required to provoke right-to-left shunting are displayed in Table 4. In patients with positive ASCi, shunting was present at rest in half of the cases (51.6%). A provocative maneuver was required to provoke shunting in the remaining cases, which did not demonstrate shunting at rest (48.4%).

Comparison of TTE and TEE

Of the overall cohort, 195 underwent TEE, thereby providing a definitive assessment of the atrial septal anatomy, in particular whether a PFO was present or not. There were no significant differences between the TEE subgroup and the remainder of the study population with regard to standard demographic and echo parameters. Of these, 128 patients were found to have a PFO, 15 patients an atrial septal defect (ASD), and 3 patients with both. There was good agreement between right-to-left shunting seen on

TTE ASCi when compared with the reported TEE findings (99% sensitivity, 85% specificity – Table 5). There were 6 false positive and 2 false negative ASCi studies. CFI by TTE was shown to be an insensitive (28%) but highly specific (100%) technique for detection of right-to-left atrial shunting. The addition of ASCi without provocative maneuvers increased the sensitivity of TTE to 58% (specificity 98%). There was a further improvement in the sensitivity of using ASCi with the addition of provocative maneuvers (99%) however there was a subsequent decrease in specificity (85%).

Safety

Throughout the 1162 TTE ASCi and 195 TEE studies, there were no reported deaths or adverse cardiac or neurological events attributed to the procedure.

Discussion

To our knowledge, this is the largest retrospective observational study that has examined the use of ASCi with TTE for detection of PFO. The purpose of this study was to assess the efficacy and safety of ASCi for assessment of PFO in a large cohort of patients. There were no adverse events reported from TTE ASCi, in keeping with the expectation that TTE ASCi is a very low morbidity procedure when performed by experienced operators.

CFI Findings

CFI by TTE was found to have low sensitivity (22%) but a high specificity (96%) compared with TTE ASCi results for the detection of PFO. This was consistent with the TEE subgroup findings with sensitivity and specificity of 28% and 100% respectively. The low sensitivity of CFI to detect PFO is expected given the small pressure gradient between the atria (hence low velocities to map by CFI), and the jet is in the far field in all

TTE imaging planes(22). The negative predictive value (68%) suggests the absence of TTE CFI does little to rule out atrial shunting via a PFO.

A limitation of these findings is that PM were not used during CFI, thus the sensitivity of this technique may be under-reported. However, as only 72 studies were positive by CFI at rest compared to 208 by ASCi at rest, the incremental benefit of TTE ASCi for detection of right-to-left atrial shunting is evident. The high specificity of TTE CFI in this study and the high frequency of indeterminate classifications by color are due to the frequent difficulty in differentiating caval blood flow (reflecting off atrial septum) from a true left-to-right shunt. Positive CFI findings were only made in situations when flow was clearly seen passing directly across the atrial septum.

Provocative Maneuvers Findings

Of the 403 positive TTE ASCi studies, right-to-left shunting was present at rest in half of the group (N=208, 51.6%). A provocative maneuver was required to demonstrate shunting in the remaining cases. The goal of provocation is to transiently increase RAP above LAP, opening the flap-like foramen ovale, and facilitate passage of contrast into the LA. The change in pressure induced by the VM needs to be sufficient to reduce venous return and consequently cause an inversion of the inter-atrial pressure gradient. A rudimentary measure of increased right atrial pressure is visualization of leftward bowing of the atrial septum, indicative of adequate VM performance (20). The findings of the current study support this and highlight the need for effective provocative maneuvers as part of the standard ASCi protocol. The false negative studies (n=2) were reviewed and can be attributed to inadequate opacification of the RA against the atrial septum or insufficient elevation in RA pressure following Valsalva. This highlights the importance of close adherence to proper ASCi imaging technique.

Previous research has described a relationship between elevated left atrial pressure (LAP) and reduced ability to visualize atrial shunting (8, 23, 24). If the LAP is chronically elevated, there may be no time in the cardiac cycle when RAP exceeds the LAP, which prevents contrast crossing across the atrial septum. In the current study there was no significant difference in mean LAP compared with TTE shunt result. Moreover, none of the false negative results of ASCi TTE compared to TEE had elevated LAP values.

Criteria for diagnosis of shunting by ASCi

There are a range of opinions in the literature regarding what constitutes a positive study in regards to both timing of shunting and the amount of bubbles visualized (8, 12, 22, 25-29). In the current study, an ASCi study was considered positive if any number of micro bubbles were visualized in the left heart within five cardiac cycles following initial entrance of contrast into the RA. There were six false positive ASCi results when compared with TEE. Subsequent review of the images concluded the trivial degrees of shunting seen in three of the false positives, was confirmed to be due to transpulmonary transit. In the remaining false positive studies, whilst fulfilling the criteria for right-to-left shunting, the precise timing of the shunt by TTE ASCi could not be determined due to imaging constraints. The current study opted for a higher sensitivity by using five beats as the cutoff criteria for the presence of an intra-cardiac shunt and the resulting reduction in specificity reflects this.

While the assessment of the number/volume of micro bubbles seen in the left heart is theoretically a quantitative measure, in practice qualitative descriptive terms were more commonly used (e.g trivial, significant, marked, LV opacification). There is evidence that the size of the shunt correlates to risk of recurrent paradoxical thromboembolic events (30) however there are no validated cut-offs for such in published literature. As such, a

descriptive approach (trivial, mild, large shunting etc) has been adopted in our laboratory.

Limitations

This was a retrospective observational study from a single centre based in a private hospital. There are a number of limitations from this situation which could potentially affect the findings of this study, and these can be largely related to patient selection, retrospective data error or reporting bias. The authors recognize that only a small subset of the study population went on to have a TEE. This could be a source of error in the data, resulting in underestimation of the false negative TTE ASCi results. A prospective study comparing TEE to TTE ASCi is currently being undertaken to address this. Whilst the protocol for ASCi has essentially remained unchanged over the past five years (accounting for the majority of patients in this study), there was some variability in technique in the earlier years. This was minimized by the inclusion of a blinded review of all of the CFI studies and a subset of ASCi studies.

Conclusions

Although PFO is a common finding in the normal population, a link between PFO and cardio-embolic neurological events is well established. With the advent of percutaneous PFO closure, there is an increasing demand for PFO screening in these patients. While TEE is considered the gold standard for defining atrial septal anatomy, screening with TEE is not appropriate or feasible due to a lack of widespread availability, additional associated costs, and the small but defined procedural risk. TTE is widely available and is not associated with procedural risks identified with TEE; however CFI by TTE alone is too insensitive to be an effective screening tool for PFO. Following our experience of

1162 ASCi studies, the improved accuracy of TTE using ASCi in addition to well performed provocative maneuvers justifies its use as a screening tool for detecting PFO.

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