Can J Anesth/J Can Anesth (2020) 67:1824–1838
https://doi.org/10.1007/s12630-020-01813-2

REVIEW ARTICLE/BRIEF REVIEW

Point-of-care echocardiography for the evaluation of right-to-left cardiopulmonary shunts: a narrative review

L'échocardiographie au chevet pour évaluer les shunts cardiopulmonaires de droite à-gauche : un compte rendu narratif

Tim Montrief, MD, MPH · Stephen Alerhand, MD · André Denault, MD, PhD · Jeffrey Scott, DO

Received: 26 February 2020 / Revised: 10 June 2020 / Accepted: 10 June 2020 / Published online: 17 September 2020

Abstract *Right-to-left pulmonary and cardiac shunts (RLS) are important causes of refractory hypoxia in the critically-ill perioperative patient. Using a point-of-care ultrasound (POCUS) agitated saline bubble study for an early diagnosis allows patients with clinically significant RLSs to receive expedited therapy. This narrative review discusses the principles of agitated saline ultrasonography as well as the role of POCUS in detecting the most common RLS types seen in the intensive care unit, including patent foramen ovale, atrial septal defects, and pulmonary arterio-venous malformations. An illustrated discussion of the procedure, as well as shunt-enhancing maneuvers (Valsalva or lung recruitment maneuver with subsequent rapid release) is provided. With the wide dissemination of bedside ultrasound within the perioperative and critical care arena, POCUS practitioners should be knowledgeable of the potential pitfalls leading to both false-positive and false-negative studies. False-positive studies may be due to congenital abnormalities, mischaracterization of intrapulmonary shunts as intracardiac shunts (and vice versa), or evidence of the Valsalva effect. False negatives are typically due to respiratory-phasic variation, performing an inadequate shunt-enhancing maneuver, inadequate injection of agitated saline, or pathophysiologic states of elevated left atrial pressure. Finally, alternative POCUS methods for determining presence of an RLS in patients with poor echocardiographic windows are discussed, with a focus on pulsed-wave Doppler interrogation of arterial signals.*

Résumé *Les shunts pulmonaires et cardiaques de droite à-gauche sont d'importantes causes d'hypoxie réfractaire chez le patient périopératoire en état critique. En réalisant un test aux bulles sous échographie au chevet, un diagnostic rapide de shunt de droite à-gauche peut être posé, favorisant le traitement rapide des patients présentant un shunt de droite à-gauche significatif d'un point de vue clinique. Ce compte rendu narratif présente les principes de l'échographie avec test aux bulles ainsi que le rôle de l'échographie au chevet pour détecter les types les plus répandus de shunts de droite à-gauche à l'unité de soins intensifs, notamment les communications interauriculaires, les foramens ovales perméables et les malformations artérioveineuses pulmonaires. Nous présentons également une discussion illustrée de l'intervention, ainsi que des manœuvres augmentant le shunt (manœuvre de Valsalva ou de recrutement pulmonaire avec cessation rapide subséquente). Étant donné l'utilisation répandue de l'échographie dans le domaine des soins périopératoires et critiques, les praticiens de l'échographie au chevet devraient être conscients des écueils potentiels menant à des résultats faux positifs ou faux négatifs. Les résultats faux positifs peuvent être dus à des anomalies congénitales, à la*

T. Montrief, MD, MPH
Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

S. Alerhand, MD
Department of Emergency Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA

A. Denault, MD, PhD (✉)
Department of Anesthesiology and Critical Care Division, Montreal Heart Institute, Université de Montréal, 5000 Belanger Street, Montreal, QC H1T 1C8, Canada
e-mail: andre.denault@umontreal.ca

J. Scott, DO
Division of Cardiothoracic and Transplant Critical Care, Jackson Health System, Miami Transplant Institute, Miami, FL, USA

caractérisation erronée de shunts intrapulmonaires en tant que shunts intracardiaques (et vice versa) ou à l'efficacité de l'effet Valsalva. Les résultats faux négatifs sont fréquemment dus à des variations des phases respiratoires, à la réalisation d'une manœuvre inadéquate d'amélioration du shunt, à l'injection inadéquate de solution saline agitée, ou à des états physiopathologiques de pression auriculaire gauche élevée. Enfin, les méthodes alternatives d'échographie au chevet visant à déterminer la présence d'un shunt de droite à-gauche chez les patients présentant des fenêtres échocardiographiques sous-optimales sont discutées, avec une emphase sur l'interrogation des signaux artériels par Doppler pulsé.

Keywords echocardiography · point-of-care ultrasound · bubble study · pulmonary arterio-venous malformation · patent foramen ovale

Right-to-left intrapulmonary and intracardiac shunts (RLS) are important causes of profound hypoxia as they permit passage of deoxygenated venous blood into the systemic circulation.[1] A patent foramen ovale (PFO) can be found in up to 20–25% of healthy individuals, although the presence of an acute RLS is relatively rare.[2–4] These RLSs are an underappreciated cause of significant hypoxia, necessitating an early and accurate diagnosis to optimize management. A clue in the suspicion and/or identification of an intracardiac shunt occurs when the patient's changes in blood pressure and oxygen saturation are proportional (Fig. 1). In patients with intracardiac shunts, desaturation will occur when the right atrial pressure exceeds the left atrial pressure.[1] Increasing the left atrial pressure with the use of a vasopressor such as noradrenaline or phenylephrine, as shown in Fig. 1, will reduce the RLS and proportionately increase the oxygen saturation.

Venous thromboemboli can pass through to the systemic circulation by bypassing the lungs through either a PFO, atrial septal defect (ASD), or a pulmonary arterio-venous malformation (PAVMs).[1,5–7] An intracardiac defect with RLS has been detected in about 10% of patients with ischemic stroke,[8] although other studies have reported an incidence up to 46% in those with cryptogenic stroke.[9,10] Left-to-right cardiopulmonary shunts (LRS), including ventricular septal defect and ASD, may lead to severe pulmonary hypertension secondary to right heart volume overload.[1]

Ultrasound-enhancing agents (UEAs) have become a useful tool for cardiovascular imaging, particularly for the diagnosis and assessment of cardiopulmonary shunts. Agitated saline (AS) is the agent used primarily and comprises large bubbles (approximately 30 µm) that cannot flow through the pulmonary circulation.[1] In patients without RLSs, no bubbles are present in the left side of the heart during a bubble study.[11] Because AS does not routinely pass to the left side of the heart, it cannot evaluate the left heart, but does allow RLSs to be visualized.[1,12] If bubbles appear in the left heart on the ultrasound monitor, a cardiopulmonary shunt must be present. This is colloquially known as a "bubble study."

Right-to-left pulmonary and cardiac shunts may be found in patients with various lung diseases that cause the veno-capillary tree to dilate. There are a variety of modalities available to evaluate these shunts, including transesophageal echocardiography (TEE) and transcranial

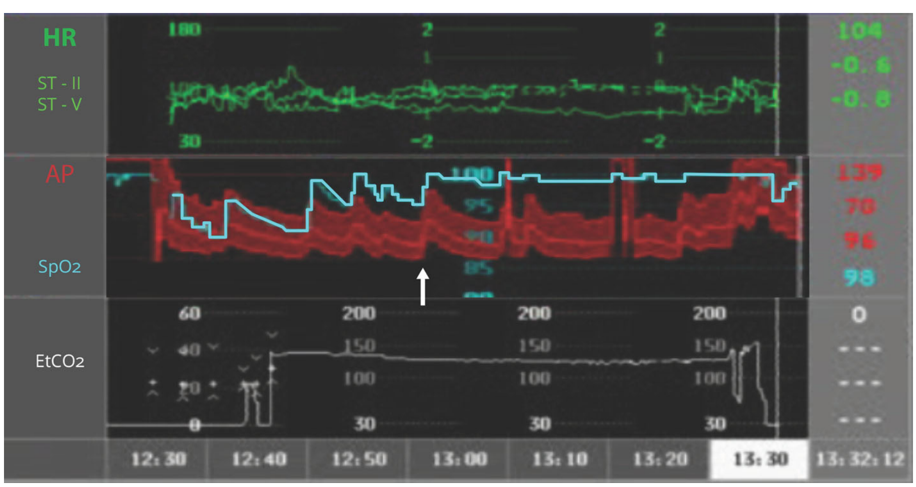

Fig. 1 Perioperative monitoring during percutaneous interatrial septal defect closure in a 37-yr-old woman. The changes in arterial pressure (AP) and pulse oximetry saturation (SpO_2) before and after closure at 13:00 (white arrow) are illustrated. Note that before closure there were parallel changes in AP and SpO_2 but once the septal defect was closed the relationship between AP and SpO_2 was lost. Parallel changes in AP and in SpO_2 should always raise the possibility of an intracardiac shunt. $EtCO_2$ = end-tidal carbon dioxide; HR = heart rate.

Doppler ultrasonography (TCD).[12] While TEE is the clinically accepted standard for diagnosing RLSs, it is an invasive procedure requiring sedation, a skilled operator, and specialized equipment.[12,13] Furthermore, evidence suggests that contrast-enhanced transthoracic echocardiography (TTE) can detect the majority of RLSs with better sensitivity than TEE examinations (100% *vs* 85%),[11,14,15] and with better specificity than contrast-enhanced TCD.[16]

Point-of-care ultrasound in the anesthesiologist's or intensivist's hands assists in the evaluation of clinically important RLSs, such as in severe refractory hypoxemia or paradoxical embolism.[17] Early POCUS evaluation for patients with end-stage heart failure is important to assess for left ventricular assist device (LVAD) candidacy.[18] The physiology associated with an LVAD includes reduced left heart filling pressures and may precipitate RLS and hypoxemia in patients with a PFO.[19] Using POCUS for an early diagnosis allows patients with clinically significant RLSs to receive expedited therapy.

Article selection methods

In this review, the role of AS-enhanced POCUS for detecting RLSs with emphasis on the proper application of shunt-enhancing maneuvers is illustrated. Focus is placed on the most prevalent RLS types seen in the intensive care unit (ICU), including PFO, ASD, and PAVMs. The authors searched PubMed and Google Scholar for articles with the keywords "bubble study" OR "agitated saline contrast injection" OR "right to left shunts" AND "echocardiography", AND "intensive care". Authors included randomized-controlled trials, narrative reviews, systematic reviews and meta-analyses, book chapters, case reports and series, and clinical guidelines, as well as prospective and retrospective cohort studies. Only articles published in English were included in this review. The initial literature search revealed over 600 articles. Authors reviewed all the relevant articles and decided which studies to include in the review by consensus. A total of 105 resources were selected for inclusion in this narrative review.

Principles of AS echocardiography

As part of the piezoelectric effect, an ultrasound device's mechanical energy deforms the crystals at the end of the transducer and emits inaudible sound waves (1–5 MHz). These sound waves propagate and reflect through tissues of varying acoustic impedance (resistance to sound waves), then these signals return to the transducer. Once again, the crystals are deformed, and this mechanical energy is converted to electrical energy, which is then amplified to produce a pixelated image on the ultrasound display screen

As sound waves travel from one tissue to another, the change in acoustic impedance at the interface also reflects sound waves. The ability of a sound wave to propagate from one tissue to another depends on the difference between their respective impedance.[20] The larger the difference in acoustic impedance, the more the ultrasound waves reflect, and the more echogenic the surface will appear.[20]

Red blood cells, despite generally appearing anechoic, actually produce a very weak echogenic signal because of the differing densities of red blood cells and the surrounding blood plasma.[21] This can present as "spontaneous echo contrast", an echogenic swirling pattern seen in settings of low-velocity blood flow or stasis.[22] Gas is approximately 100,000 times less dense than blood.[1] Thus, the gas bubbles of AS enhance this difference in acoustic impedance at the blood-saline-air interface to generate a greater reflection of sound waves compared with between red blood cells and plasma alone.[23]

It is important to differentiate between AS and other UEAs. Because of their broad applicability and advantageous safety profile, many different types of UEAs have been developed, and guidelines on their use have been recently updated.[24] They consist of varying sized bubbles, shell material, and gas cores. Initial ultrasound enhancement employed non-encapsulated nitrogen and oxygen from ambient air. These bubbles are incapable of crossing the pulmonary vascular capillary bed and were primarily used for right heart evaluation. Nevertheless, in the case of RLS, these bubbles were noted in the left heart. The first-generation UEAs are manufactured air bubbles that are encapsulated or attached to one of a variety of microparticles.[11,25] These agents are injected intravenously and appear in the left heart.[25] Second-generation agents (i.e., activated perfluorocarbon and stabilized sulfur hexafluoride microbubbles surrounded by a phospholipid shell) replace air with a fluorocarbon gas that increases stability as well as the duration of its ultrasonic effect.[25,26] More recent agents include a polymer shell, leading to more consistent enhancement.[11,26] Regardless, all UEAs have a long track record of safety, even in patients with known cardiac shunts.[27,28] Nevertheless, AS is the preferred method for evaluating RLSs using POCUS in the acute care setting because of its ease of availability and low cost, although several variations of UEAs have the potential to be used as well (Table 1).

Table 1 Common ultrasound-enhancing agents and recommended dosing

Agent	Recommended dose
Saline with air	9.0–9.5 mL 0.9% saline with 0.5–1.0 mL air
Saline with blood and air	8.5 mL 0.9% saline with 1 mL blood and 0.5 mL air
Perflutren lipid microsphere (Definity®)	10 $\mu L \cdot kg^{-1}$ followed by 10 mL 0.9% saline
Albumin shell with perflutren (Optison®)	0.5 mL
D-galactose microparticle solution (Echovist®)	5–10 mL
Urea-linked gelatin (Haemaccel®)	10 mL
Oxypolygelatine (Gelifundol®)	10 mL
Dextrose 5% water	10 mL

Adapted from Soliman *et al.*[12]

Fig. 2 Materials necessary for point-of-care bubble study: 18-G peripheral intravenous catheter, 9.5 mL of normal saline with 0.5 mL ambient air, two 10 mL Luer Lock syringes, and a three-way stopcock with extension tubing. Note: positioning the stopcock "off" to the patient allows saline agitation between the two syringes.

Equipment, instrumentation, and technique

Vascular access and contrast preparation

Performing and optimizing a bubble study relies on consistent preparation and injection of AS, which is best performed with an assistant performing the injection while the sonographer obtains the images.[11] To begin with, the bubbles require thorough agitation immediately prior to injection.[11] When using AS for RLS detection, the technique relies on utilizing two 10-mL syringes connected to a three-way stopcock to agitate the saline (Fig. 2).[11] As AS separates into its component parts quickly, the saline should be re-agitated before each injection.[11] It is recommended to use a Luer Lock syringe to avoid accidentally spraying saline during agitation.[11] It is recommended that the AS be composed of 9.0–9.5 mL of normal saline and 0.5–1.0 mL of room air.[11] The American Society of Echocardiography guidelines recommend a mixture of 8 mL of normal saline, 1 mL of the patient's own blood, and 0.5–1.0 mL of room air as an alternative.[4] This may increase the intensity of the microbubbles visualized by echocardiography.[29] Additionally, some authors have reported using AS with added benzyl alcohol (9 $mg \cdot mL^{-1}$ as a preservative in saline) as opposed to AS alone.[30] The alcohol acts as a surfactant, leading to smaller bubbles and better overall intravenous contrast effect.[31] This saline-air mixture should be forcefully injected between two syringes until the bubbles appear uniform, without visibly large air bubbles.[11,32] When this is achieved, the entire syringe's contents should be injected, as the AS mixture quickly separates into its composite parts.[11] This AS injection should be followed by a second syringe of "flush" solution to ensure that the AS reaches its destination faster and in a more complete manner.

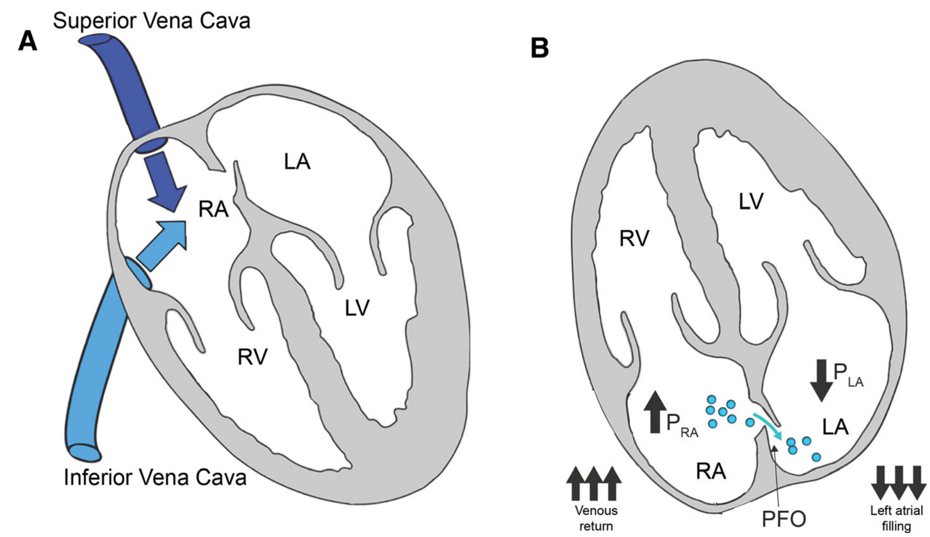

Fig. 3 **A**. Venous flow patterns in the superior vena cava and inferior vena cava. The inferior vena cava flow is directed towards the atrial septum, while superior vena cava flow is pointed towards the tricuspid valve. This allows the agitated saline to preferentially pass through an intracardiac right-to-left shunt. **B.** Mechanism of right-to-left shunt augmented by Valsalva. An arrow facing upward indicates increase in pressure and facing downward indicates decrease in pressure. LA = left atrium; LV = left ventricle; PFO = patent foramen ovale; P_{LA} = left atrial pressure; P_{RA} = right atrial pressure; RA = right atrium; RV = right ventricle.

Injection of UEAs through a small-bore catheter destructs the thin-walled external capsule; however, this is not the case for unencapsulated AS, which may be used with any size of intravenous catheter.[33] Nevertheless, AS should be administered through a 20-G or larger cannula, most commonly in the antecubital veins, although using femoral and dorsal hand veins has been reported.[34,35] As the patient may be placed in left lateral decubitus to enhance imaging windows, venous access should be preferentially gained on the patient's right side.

Compared with an antecubital vein, utilization of a femoral vein for AS injection increases the sensitivity for PFO detection during bubble studies.[34,36–38] This is because inferior vena cava blood flow is directed towards the atrial septum, while superior vena caval flow is pointed towards the tricuspid valve (Fig. 3).[39] There are some practical disadvantages to using the femoral vein, notably an increased rate of vascular complications, including inadvertent arterial puncture, thrombosis, bleeding, and, in rare cases, arterio-venous fistula formation.[40] Nevertheless, femoral vein access remains a valuable option in cases of incomplete right atrial opacification or if there is a high index of suspicion for an RLS despite a negative bubble study using an upper limb vein.

Imaging technique

Before administration of AS, an apical four-chamber view of the heart should be acquired. Alternatively, one may obtain a subcostal view or a parasternal short axis view in which the atrial septum is visualized (Fig. 4).[35,41] The parasternal long axis view does not adequately evaluate the right atrium next to the atrial septum.[1] When possible, the patient should lie in the left lateral decubitus position, which brings the heart anterior and lateral, improving image acquisition.[1] Nevertheless, this may not be feasible in the critically-ill perioperative patient, in which case supine positioning is appropriate. If necessary, the patient's ribcage may be expanded by placing their left arm behind their head, thereby increasing space (acoustic window) for the phased array transducer in between the ribs.[1] The equipment settings should be configured to acquire a 20-sec duration clip. The ultrasound's depth and gain functions should be set to achieve the highest image resolution, with the screen's focal zone near the base of the heart. Retrospective capture is preferred and allows the operator to record the previous 20-sec loop when saving a clip. Prospective capture, conversely, records the upcoming 20-sec loop and may not allow adequate recording of the RLS. In particular, this may occur in those with very low cardiac output who require more time for AS to fully opacify the right atrium. This may be mitigated by starting prospective capture at, or just before, injection of the AS.

Shunt-enhancing maneuvers and their associated physiology

Although right atrial pressure is typically lower than the left atrial pressure, this is not always the case. During the patient's normal respiration, transient reversal of the interatrial pressure gradient (right atrial pressure > left atrial pressure) may be sufficient to allow a short-lived

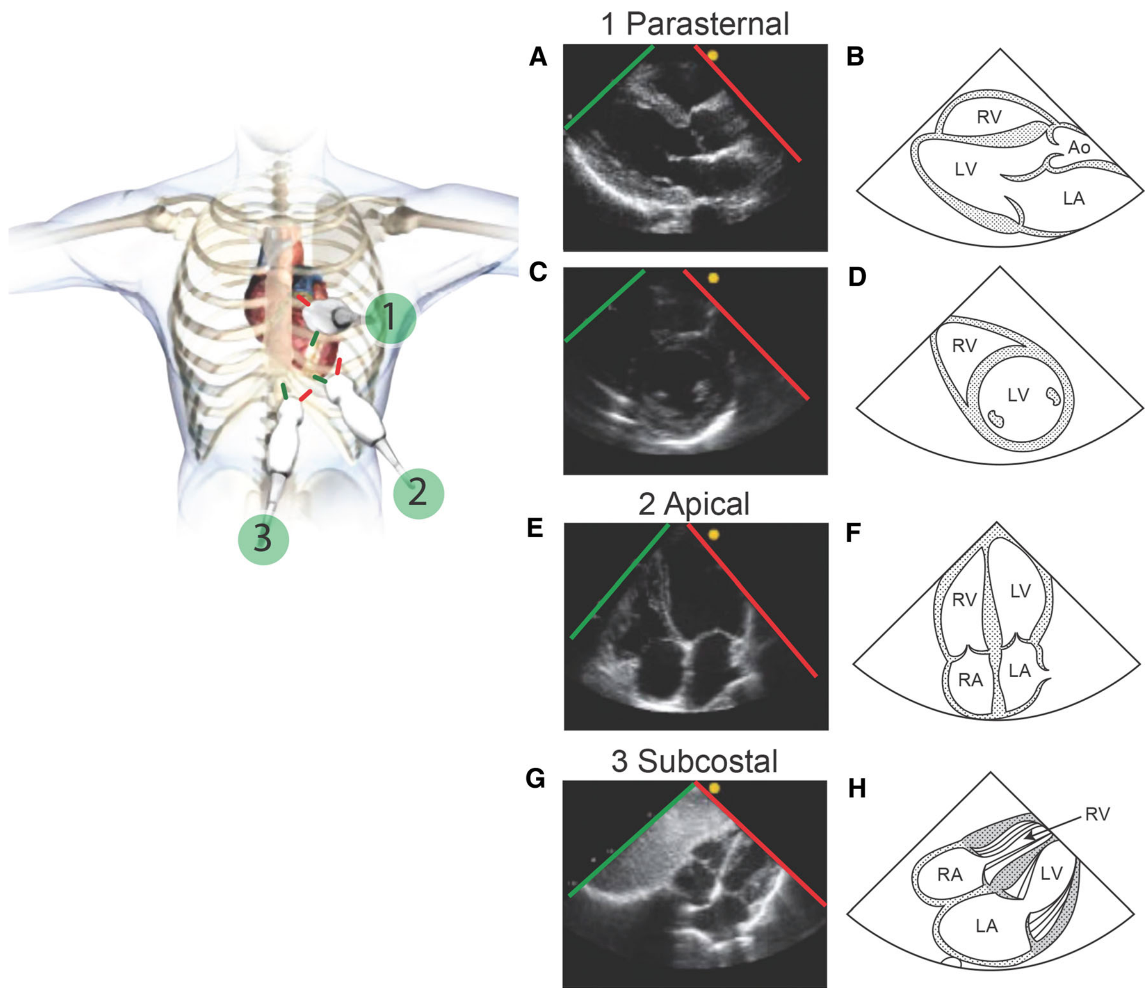

Fig. 4 The focused cardiac ultrasound study (FOCUS) exam. This includes these important transthoracic echocardiographic views. Scanning should be performed in a systematic, clockwise fashion, from three main areas: 1) parasternal (A,D), 2) apical (E,F), and 3) subcostal (G,H). Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. (Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc. from Denault *et al.*).[105]

period of right-to-left shunting, particularly if a large defect is present. Nevertheless, this finding is not clinically reliable, and RLSs are difficult to assess on echocardiography without the aid of shunt-enhancing maneuvers such as Valsalva or lung recruitment maneuvers with subsequent rapid release.[42] In the critically-ill perioperative patient unable to participate in a Valsalva maneuver, a lung recruitment maneuver can mimic the physiologic effects of Valsalva.[43] Lung recruitment maneuvers aim to quickly apply increased airway pressures for a short period of time, which increases intrathoracic pressure and decrease venous return. Release of this maneuver (and release of Valsalva) increases venous return to the right heart and augments right atrial filling, precipitating a transient right-to-left atrial pressure gradient, exposing an RLS. Nevertheless, successful use of the Valsalva maneuver or the release of a lung recruitment maneuver requires precise timing and adequate technique to accomplish.[1] It is often beneficial to practice these maneuvers prior to injection of AS.

For a proper Valsalva maneuver, the patient must pause their breathing after inhalation and bear down for approximately ten seconds.[1] Many patients cannot produce an adequate Valsalva even with coaching. In these patients, pressing on the abdomen with one hand and asking the patient to push out against the sonographer's hand, and then "relax", may be more successful.

These augmentation maneuvers change the position of the heart upon release. Upon inspiration or upon application of the recruitment maneuver, the heart moves caudad towards the abdomen, whereas upon release of the Valsalva or lung recruitment, it moves cephalad. The sonographer must adjust the imaging plane and continue to visualize the heart after release of these maneuvers as it

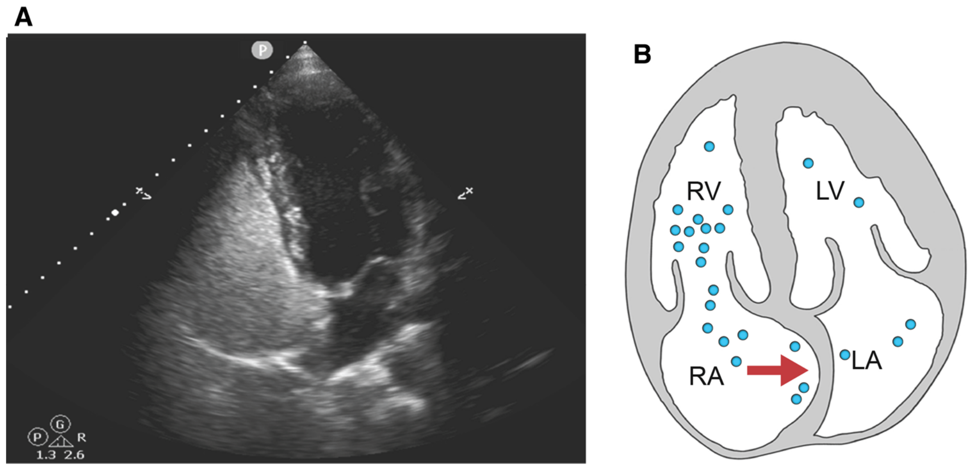

Fig. 5 **A**. Apical four-chamber view during Valsalva. **B.** Note the atrial septum shifting toward the left atrium (red arrow) as well as the full opacification of the right atrium. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

returns to its original position.[1] Additionally, the septum is normally convex toward the right atrium, as the pressure in the right atrium is less than that of the left atrium.[39] During these shunt-enhancing maneuvers, the atrial septum shifts toward the left (Fig. 5). With release, this pressure differential transiently changes and allows the septal curvature to alter, as the atrial septum shifts towards the right. Release of a Valsalva or lung recruitment maneuver is the optimal time to have a fully opacified right atrium, providing the highest sensitivity for detection of RLS.[13]

During the Valsalva maneuver, the saline mixture is agitated as described above and injected just prior to release of the Valsalva breath.[1] Clip acquisition should begin at the time of AS injection. Immediately after AS administration, the patient should begin to breathe normally.[1] At this time, AS should completely opacify the right heart. Agitated saline bubbles are incapable of passing the pulmonary circulation.[11] Therefore, any evidence of bubble effect in the left-sided circulation is likely due to the presence of a cardiopulmonary shunt.[11,23,44]

Colour flow Doppler is used frequently in sonography to semi quantitate general velocity and direction of blood flow within the heart, which may aid in identifying intracardiac shunts. Nevertheless, the interatrial pressure gradient is small without the aid of shunt-enhancing maneuvers, which leads to low velocities on colour Doppler and poor visualization of RLS.[35] Furthermore, the PFO jet is typically found in the far field of the ultrasound, impairing image resolution.[35] These both contribute to the low sensitivity (22%) of colour flow imaging to detect a PFO.[35,45] Colour Doppler echocardiography is useful for visualizing high-velocity flow signals present in LRS but performs poorly when evaluating for low-velocity flow signals in transient RLSs.[12,46]

Furthermore, any decrease in left heart diastolic compliance or elevation of left atrial pressure will make an RLS more difficult to evaluate.[47] This may be seen in a variety of conditions, including hypertension, restrictive or infiltrative cardiomyopathies, and valvular disease.[47] This has been borne out in the literature, including one study showing that 5% of patients with evidence of left heart disease have an RLS, compared with 29% in patients with no evidence of left heart disease.[48,49] Alternatively, patients with reduced right ventricular compliance and those with tricuspid valve disorders have increased right atrial pressure, aiding in the evaluation of RLSs, as well as increasing the potential for clinical hypoxia.[47] Theoretically, any conditions elevating right heart pressures can be associated with an RLS.[47]

Maneuvers that increase venous return to the right heart are often required to accurately diagnose RLSs (Fig. 3).[12,50–52] Techniques that directly alter venous return, such as abdominal compression or placing the patient in the Trendelenburg position may also be employed for this purpose, but they are not nearly as sensitive as techniques that indirectly increase venous return such as a well-executed Valsalva or release of lung recruitment maneuver.[53,54] The presence of positive end-expiratory pressure increases the intrathoracic pressure, right ventricular afterload, and right atrial pressure while decreasing the left ventricular preload; together, these improve RLS detection.[55–57] When determining the efficacy of a shunt-enhancing maneuver on echocardiography, one should see opacification of the right atrium when the atrial septum bows toward the left heart (Fig. 5).[35,58,59] The maneuvers are deemed inadequate if there is no evidence of septal bowing, which should prompt a repeat attempt.[35] Similarly, a repeat bubble study is necessary if a minimal amount of AS appears in the left heart, which may indicate an inadequate shunt-enhancing maneuver.

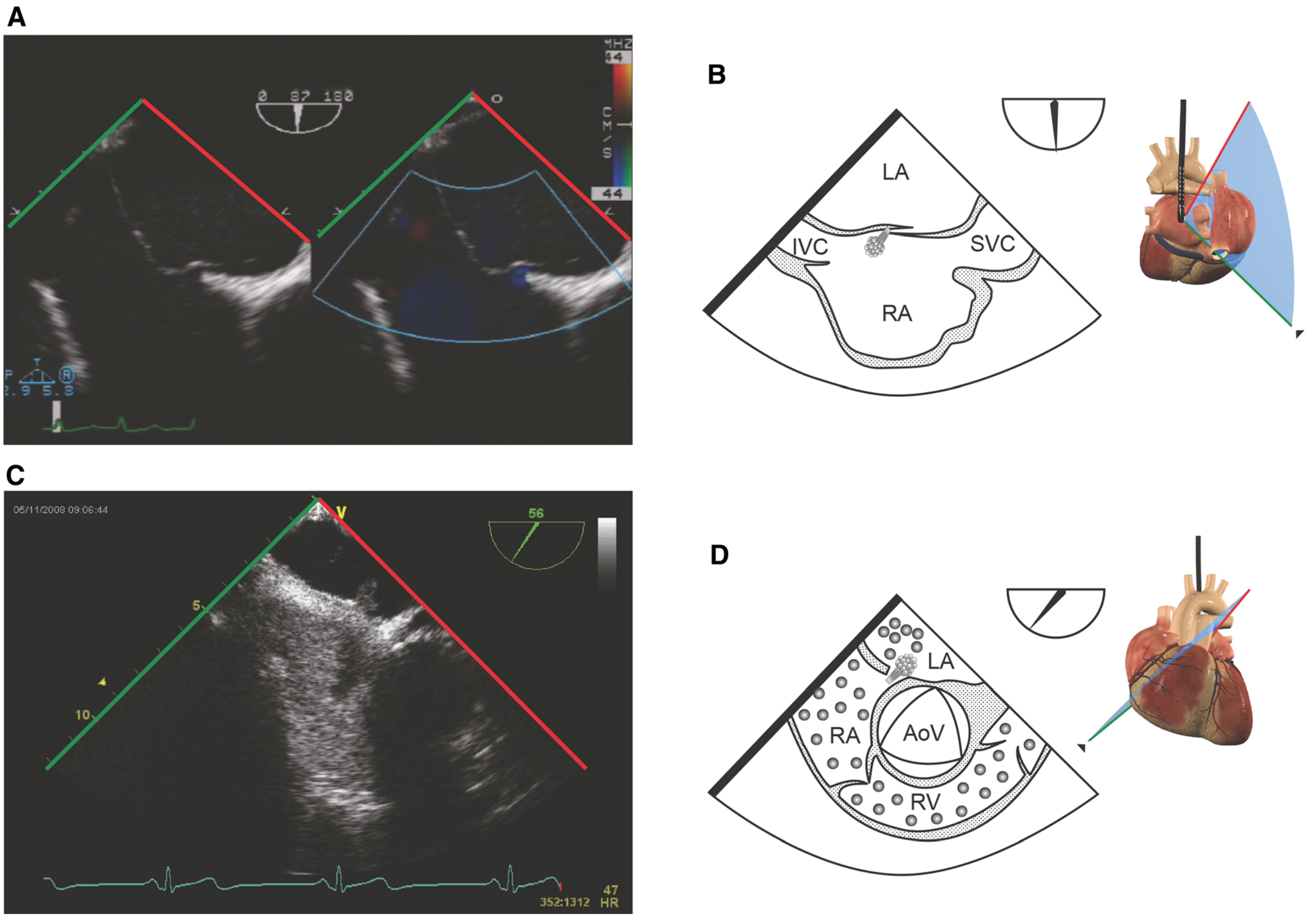

Fig. 6 Patent foramen ovale (PFO). (A,B) A PFO is shown by colour Doppler (Nyquist 44 cm·sec^{-1}) in a mid-esophageal (ME) bicaval view. (C,D) ME right ventricular inflow/outflow view shows opacification of the right-sided cardiac chambers during intravenous injection of agitated normal saline. At the release phase of a Valsalva maneuver, microbubbles are seen crossing from the right atrium (RA) to the left atrium (LA) through a PFO. AoV = aortic valve; IVC = inferior vena cava; RV = right ventricle; SVC = superior vena cava. (Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc. from Denault *et al*.).[105]

Echocardiography for the detection of anatomic cardiopulmonary shunts

Intracardiac shunts

There are many etiologies of an intracardiac RLS, including a variety of ASD subtypes and coronary sinus defects. Nevertheless, this review is limited to the two most common intracardiac shunt pathways—PFOs and secundum ASDs. Compared with ASDs, a PFO is a natural part of cardiac embryology.[1] Commonly, the foramen ovale closes before adulthood; however, up to 25% of the population has evidence of a PFO.[1,3] On conventional echocardiography without AS, a PFO typically appears as piece of myocardial tissue adjacent to the foramen ovale attached to the atrial septum (Fig. 6).[1] The PFO opens intermittently whenever the pressure in the right atrium exceeds the left atrial pressure, for example, during normal respiratory-phasic variation.[60] Nevertheless, whenever the pressure in the left atrium exceeds the right atrial pressure, the PFO remains closed, with a small LRS visible on colour flow Doppler (Fig. 6). An ASD may also be associated with an RLS, most commonly via a secundum ASD.[1] A secundum ASD is most commonly located in the middle of the interatrial septum. Secundum ASDs appear as an aperture on echocardiography, which are typically difficult to visualize without the aid of AS.[1]

Compared with PFOs, ASDs confer an increased risk of right heart volume overload.[1] A persistent interatrial communication is more likely to develop an LRS compared with the PFO intermittently communicating flap, as the PFO flap is typically pushed against the septum secundum because of elevated left atrial pressure.[61,62] When evaluating for the presence of an RLS, the AS injection must be precisely timed to the release of the shunt-enhancing maneuver.[1,63] Nevertheless, it should be noted that it may not be possible with POCUS alone to differentiate between a secundum ASD (small) and a large PFO. Because of atrial dilatation, severe stretching of the PFO may occur, making it indistinguishable from an ASD.

When using POCUS, an apical four-chamber view is the preferred image to detect AS in the right atrium.[49] After opacification of the right atrium, the septum is visualized to determine appropriate bowing, and cardiac cycles are counted.[49] Any appearance of AS in the left atrium or ventricle is diagnostic of an RLS, sometimes referred to as a "positive contrast effect".[51] The definition of a positive bubble study result, based on either the timing of AS appearance or number of bubbles visualized, remains under debate.[12] The absolute number of AS bubbles necessary to define a positive test result varies; most commonly between one, three, or five bubbles visualized in the left heart.[6,64–66] Nevertheless, a generally accepted definition of an RLS is any evidence of AS passing from the right to left heart after complete right atrial opacification.[11] Some have postulated that shunt size may be approximated by counting the number of bubbles visualized in the left heart in the three cardiac beats after right atrial septal opacification.[64,67] Right-to-left pulmonary and cardiac shunt size is categorized as small (< ten bubbles), moderate (> ten bubbles), and large (full opacification of the left atrium).[1,51,68] The amount of AS passing through the RLS is dependent on the atrial pressure gradient, which is augmented by shunt-enhancing maneuvers. The largest number of bubbles seen at any one time after shunt-enhancing maneuvers determines the size of the shunt.[51]

Left-to-right cardiopulmonary shunts, most commonly ASDs, can cause irreversible pulmonary hypertension due to right heart volume overload.[1] Any patient with echocardiographic evidence of right heart volume overload may warrant further investigation for an ASD and accompanying LRS.[1] Nevertheless, AS bubble studies should not be used to evaluate for patients with small ASDs.[1] Septal defects are primarily LRS because the left heart pressure is typically higher than the right heart pressure.[1] These ASDs may be best visualized with colour flow Doppler as a colour jet on the right side of the heart when left atrial pressure is higher than right atrial pressure.[1] If this jet is not visualized, and there is no evidence of increased right heart pressure, then an ASD is not likely to be present.[1]

Intrapulmonary shunts

Intrapulmonary RLS pathways include both macroscopic and microscopic PAVMs as well as intrapulmonary arteriovenous anastomoses. Recent literature suggests that intrapulmonary RLSs are present in up to 20% of the general population.[69–71] Pulmonary arterio-venous malformations represent a direct pathway between the pulmonary arteries and veins.[71,72] These are most commonly secondary to Osler-Weber-Rendu syndrome and are a well-described RLS pathway of thrombotic particles, occurring in up to one half of untreated patients.[12,73–75] Intrapulmonary shunts may be suggested by the presence of AS in the left atrium or ventricle 3–6 beats after atrial opacification, termed the "3–6 beat rule".[12,76] This is due to the increased "transit time" through the lungs as opposed to immediately through an intracardiac shunt.

Differentiating between intrapulmonary and intracardiac shunts

Clinicians attempt to differentiate between extracardiac and intracardiac RLSs by examining the time it takes for AS to appear in the left heart.[76] This is commonly referred to as the "3 beat rule".[76] If an RLS is present within 3–6 cardiac cycles after AS injection, the culprit lesion is likely to be intracardiac. Nevertheless, the clinical utility of this rule has recently been called into question.[45,77,78] Microbubbles appearing earlier than within 3–6 beats may be caused by a combination of intracardiac and extracardiac RLSs.[4,12,79] In the presence of a PFO, intrapulmonary shunts cannot be reliably detected because the AS may cross the interatrial septum while simultaneously crossing an extracardiac shunt.[1] Furthermore, poor atrial septal shifting may lead to late-appearing bubbles from a PFO, as has been reported numerous times in the literature.[79–81] Until more data are available to determine the clinical significance of the "3 beat rule", the clinician must be vigilant when employing AS to evaluate intracardiac and extracardiac RLSs.

Pitfalls in bubble study interpretation

False positives

There are multiple false-positive and false-negative interpretations when evaluating for an RLS with POCUS (Table 2). For instance, a prolonged Valsalva maneuver causes blood to stagnate in the pulmonary veins. These red blood cells aggregate into a rouleaux formation and may mimic AS when Valsalva is released.[82–85] Nevertheless, it should be noted that the only reported cases have occurred during TEE. Nonetheless, if this is suspected, the shunt-enhancing maneuver should be performed again without using AS. Appearance of bubbles during the attempt without AS would indicate that pseudo-bubbles are present.[49]

When performing a bubble study, rapid appearance of AS in the left atrium or ventricle should prompt

Table 2 Common pitfalls of interpreting echocardiography bubble study results, along with associated underlying mechanisms and potential solutions

False positive	Underlying mechanism	Potential solution
ASD incorrectly identified as a PFO	Presence of ASD and transient right-to-left shunt	Evaluate for ASD using colour Doppler imaging
Valsalva effect	Stagnation of red blood cells in the pulmonary veins during Valsalva, causing a rouleaux formation from stagnant blood flowing into left atrium during release phase	Repeat Valsalva maneuver without contrast, evaluating for Valsalva effect or for absence of pulsed-wave high-intensity transient signals detected by transcranial Doppler ultrasound
Large eustachian valve	An embryologic remnant of the valve of the inferior vena cava mistaken for inter-atrial septum	Inject agent through a femoral vein
Intrapulmonary shunt incorrectly identified as an intracardiac shunt	Intrapulmonary shunt connecting to a lower pulmonary vein, or coexisting with an intracardiac shunt	Recognize the limitations of the "3 beat rule" in clinical practice. The presence of an intracardiac shunt does not rule out the presence of a coexisting intrapulmonary shunt
False-negative	**Underlying mechanism**	**Potential solution**
Inadequate injection	Poor opacification of interatrial septum	Increase contrast dosing or optimize ultrasound settings
Inadequate Valsalva or shunt-enhancing maneuver	Failure to elevate the right atrial pressure above left atrial pressure due to inadequate shunt-enhancing maneuver	If inadequate effort by patient, repeat Valsalva with coaching. If inadequate release of recruitment maneuver, ensure adequate timing and/or increase intrathoracic pressure during recruitment
Large eustachian valve	Injected contrast into antecubital vein is streamed along the valve directly to the right ventricle	Inject agent through a femoral vein
Increased left atrial pressure	Failure to elevate the right atrial pressure above left atrial pressure due to increased left atrial pressure	Evaluate for left-sided cardiac pathology and increased left atrial pressure. Cannot exclude concomitant right-to-left shunt.
Respiratory-phasic variation	Transiently elevated right-to-left shunt during normal respiratory cycle	Use Valsalva maneuver

ASD = atrial septal defect; PFO = patent foramen ovale. Adapted from Soliman *et al*.[12]

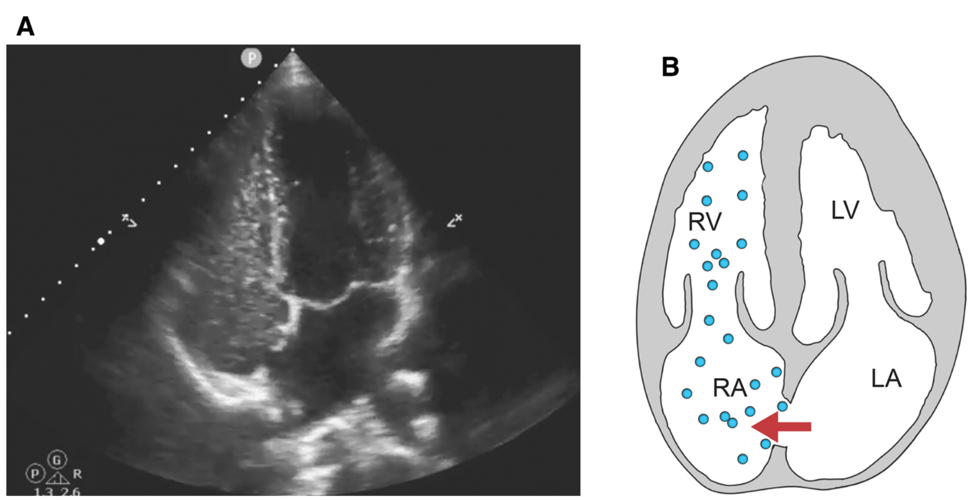

Fig. 7 (A,B) Negative contrast effect suggestive of an atrial septal defect. Note the absence of agitated saline on the right side of the heart immediately adjacent to the inter-arterial septum (red arrow) and no evidence of bubbles in the left atrium. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

consideration for the presence of an ASD.[49] Investigation of the interatrial septum with colour flow Doppler may identify an ASD. An interatrial LRS may present with a "negative contrast effect" during a bubble study.[12,86] This is seen as "a sharply delineated washout phenomenon appearing on the right atrial side of the interatrial septum in continuity with the contrast-free left atrium" (Fig. 7).[12,86] While the "negative contrast effect" may indicate the presence of an ASD, sensitivity ranges between 37% and 58% in the published literature.[87–89] Other findings indicative of an ASD and LRS include the presence of AS bubbles in the inferior vena cava after right atrial opacification, as well as characteristic flow patterns on colour Doppler imaging.[61,88] Finally, the presence of an

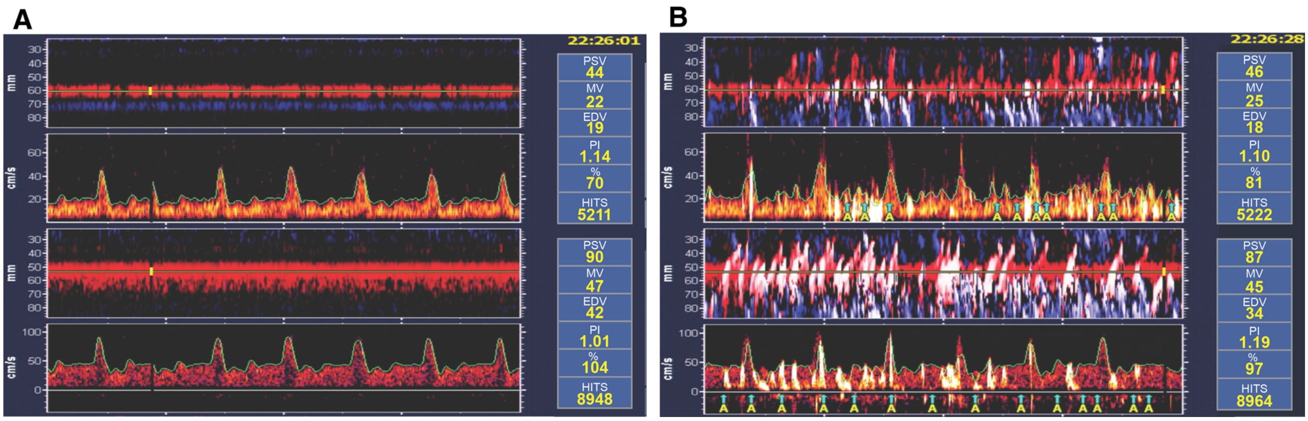

Fig. 8 **A**. Transcranial Doppler monitoring in a patient under extracorporeal membrane oxygenation (ECMO). **B.** Note the appearance of several high-intensity transient signals (HITS) during 10 mL saline injection through a central venous catheter. Air-trapping devices are not as efficacious as cardiopulmonary bypass with the use of ECMO. EDV = end-diastolic velocity; MV = mean velocity; PI = pulsatility index; PSV = peak systolic velocity.

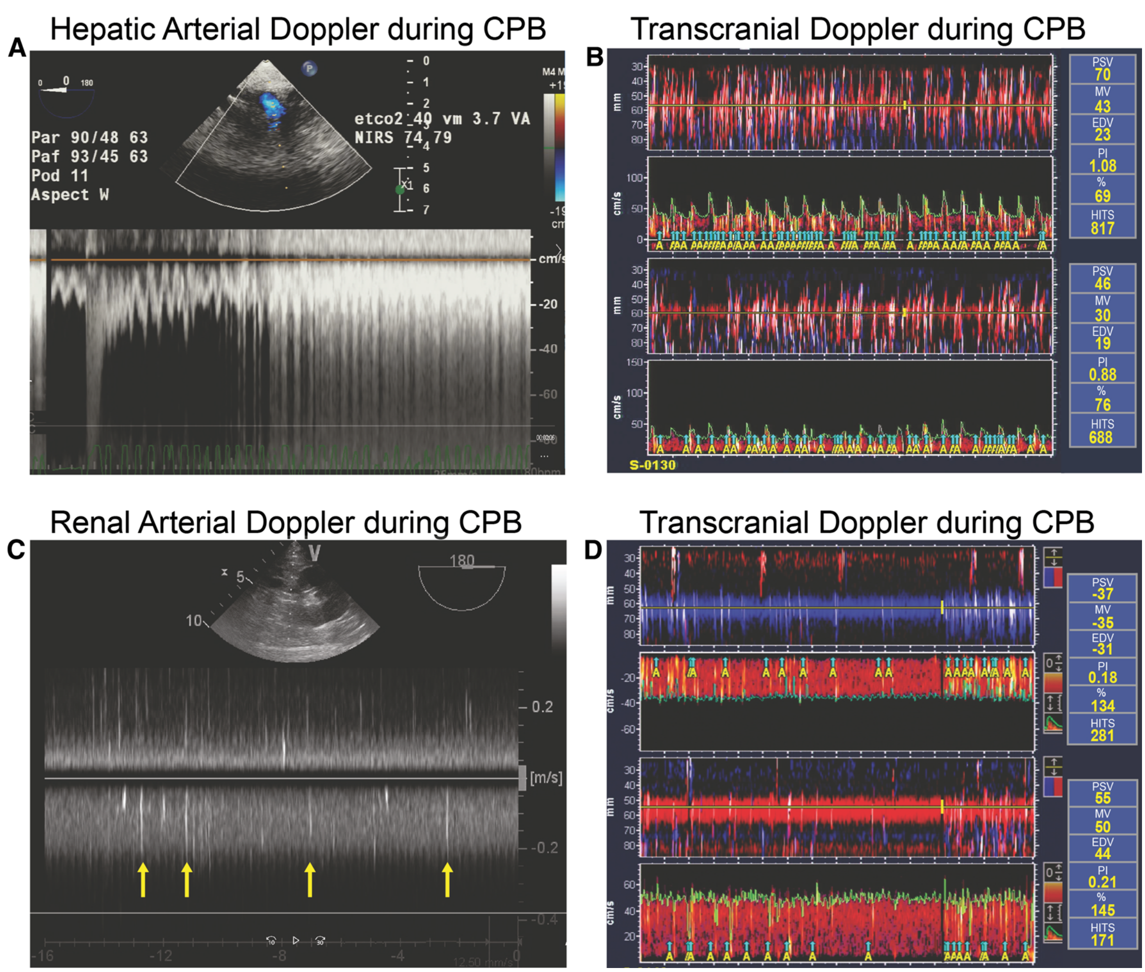

Fig. 9 Two patients undergoing cardiac surgery with simultaneous linear hair-like artefacts in the hepatic artery (A) and with several high-intensity transient signals (HITS) in the brain. In another patient, the artefacts are seen simultaneously in the renal artery (C) and in the brain (D). CPB = cardiopulmonary bypass; EDV = end-diastolic velocity; HITS = high-intensity transient signals; MV = mean velocity; PI = pulsatility index; PSV = peak systolic velocity. (Fig. 9A with permission of Denault *et al.*).[104]

enlarged right heart should prompt consideration for an ASD and LRS.

False negatives

One cause of a false-negative study is a large eustachian valve, an embryologic remnant of the valve of the inferior vena cava".[90] During fetal circulation, the eustachian valve preferentially facilitates blood flow toward the foramen ovale, left heart, and systemic circulation.[49] While the eustachian valve reabsorbs after birth in most people, there are multiple reports of persistent eustachian valves in adults.[49,90,91] The eustachian valve is a part of the Chiari network, which is described as a "fenestrated, net-like embryonic remnants of valves of sinus venosus, lying closely in relation to the inferior vena cava and coronary sinus".[92] The eustachian valve may be mistaken for the right atrial septum on ultrasound, potentially causing a false positive if injected AS is seen on either side of the valve.[1] Agitated saline delivered via the antecubital vein may stream directly along this valve into the right ventricle, resulting in incomplete opacification of the right atrium and a false-negative result.[93,94] In contrast, AS delivered via the femoral vein is preferentially directed towards the atrial septum in patients with a persistent eustachian valve.[94]

Chronically elevated left heart pressures predispose to a false-negative bubble result. This is because right atrial pressures may never exceed left atrial pressures, even in the presence of Valsalva augmentation.[48,95] Increased inferior vena cava flow may disrupt right atrial opacification, resulting in a false-negative bubble result.[35] In this scenario, blood flow through the inferior vena cava may be diminished by pressing firmly on the liver.[35] This maneuver may assist in differentiating between a "negative contrast effect" from an ASD and a bubble study disrupted by increased blood flow through the inferior vena cava.[35,59]

Normal variation in right heart pressures during respiration play an important role in false-negative bubble study results.[49] It is known that respiratory-phasic increases in right atrial pressure during end-inspiration may reveal a transient RLS across a PFO.[49] Nevertheless, this RLS may occur more than 3–6 beats after injection of AS, resulting in misclassification of an intracardiac shunt as an intrapulmonary shunt due to the timing of the phases of ventilation.[49] This pitfall can be overcome by evaluating the patient's respirations during the AS bubble study, or preferably, interpreting AS injection with Valsalva.[49]

An atrial septal aneurysm is a congenital deformity consisting of redundant and mobile interatrial septal tissue, which bulges into the right or left atrium.[96] If a patient has an atrial septal aneurysm, intracardiac shunts should be suspected, as these have strong associations with both PFOs and ASDs.[49,97,98] The atrial septal aneurysm can be used to evaluate the effectiveness of a patient's Valsalva, as the septum will deviate towards the side of the heart with the lowest pressure at all times.[49] When an effective Valsalva maneuver is released, the septum should transiently deviate towards the left atrium, the lower pressure chamber.[49]

Other alternative methods in the diagnosis of right-to-left pulmonary and cardiac shunts

The use of pulsed-wave Doppler on any arterial vessel is a simple way to diagnose the presence of air in the arterial circulation, particularly if no adequate cardiac windows are available. Transcranial Doppler monitoring modalities used in the operating room or in the ICU can detect and even measure the number of emboli that can occur (Fig. 8). Using this technique to obtain TCD signals using two-dimensional ultrasonography of the brain has been reported.[99] These embolic signals are called "high-intensity transient signals" (HITS) and are commonly observed during extracorporeal membrane oxygenation.[100] A simple saline injection can be associated with the appearance of those HITS even without contrast stressing the importance of bubble filters in those patients. When a standard TTE probe is used to perform brain ultrasound with a transcranial profile, high-intensity linear hair-like artefacts can also be seen in any artery such as the cerebral, hepatic, or renal arteries (Fig. 9). Techniques to obtain those signals have been reported previously.[99,101–104] Indeed, TCD is currently used as a diagnostic modality to exclude RLS in patients with unexplained stroke resulting from a PFO and performs as well as TEE.[16]

Conclusions

Point-of-care ultrasound echocardiography with AS is a quick, efficient method for investigating cardiopulmonary shunts and a useful clinical tool for the intensivist. This imaging modality is helpful for cases of acute RLS presenting with severe, refractory hypoxemia.[2] The paradigm for interpreting bubble study results is built on the tenet that AS does not cross into the left heart in patients without a RLS. Although bubble studies are the clinical standard for RLS identification, POCUS practitioners should be knowledgeable of the potential pitfalls leading to both false-positive and false-negative results. Pulsed-wave Doppler interrogation of any arterial signal can also be used to detect abnormal RLS but requires further investigation to determine the exact etiology and mechanism.

Author contributions All authors contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article.

Acknowledgements We thank Drs Jonathan Auerbach and John Combs for useful discussion. We thank Denault and colleagues for permission to reproduce their figures in our manuscript.

Disclosures Dr. Denault is speaker and consultant for CAE Healthcare; speaker for Masimo; and speaker for Edwards; he also received a research grant from Edwards.

Funding statement The study was supported by the Richard I. Kaufman Endowment Fund in Anesthesia and Critical Care and the Montreal Heart Institute Foundation.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia.*

References

1. *Lovering A, Goodman R.* Applied aspects of ultrasonography in humans. IntechOpen 2012; 159-74.
2. *Marples IL, Heap MJ, Suvarna SK, Mills GH.* Acute right-to-left inter-atrial shunt; an important cause of profound hypoxia. Br J Anaesth 2000; 85: 921-5.
3. *Sacco RL, Adams R, Albers G, et al.* Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation 2006; 113: e409-49.
4. *Silvestry FE, Cohen MS, Armsby LB, et al.* Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: from the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiogr 2015; 28: 910-58.
5. *Lechat P, Mas JL, Lascault G, et al.* Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988; 318: 1148-52.
6. *Mas JL, Arquizan C, Lamy C, et al.* Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001; 345: 1740-6.
7. *Petty GW, Khandheria BK, Meissner I, et al.* Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. Mayo Clin Proc 2006; 81: 602-8.
8. *de Belder MA, Tourikis L, Leech G, Camm AJ.* Risk of patent foramen ovale for thromboembolic events in all age groups. Am J Cardiol 1992; 69: 1316-20.
9. *Serena J, Segura T, Perez-Ayuso MJ, et al.* The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. Stroke 1998; 29: 1322-8.
10. *Miranda B, Fonseca AC, Ferro JM.* Patent foramen ovale and stroke. J Neurol 2018; 265: 1943-9.
11. *Stewart MJ.* Contrast echocardiography. Heart 2003; 89: 342-8.
12. *Soliman OI, Geleijnse ML, Meijboom FJ, et al.* The use of contrast echocardiography for the detection of cardiac shunts. Eur J Echocardiogr 2007; 8: S2-12.
13. *Pinto FJ.* When and how to diagnose patent foramen ovale. Heart 2005; 91: 438-40.
14. *Kerut EK, Norfleet WT, Plotnick GD, Giles TD.* Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol 2001; 38: 613-23.
15. *Gonzalez-Alujas T, Evangelista A, Santamarina E, et al.* Diagnosis and quantification of patent foramen ovale. Which is the reference technique? Simultaneous study with transcranial Doppler, transthoracic and transesophageal echocardiography. Rev Esp Cardiol 2011; 64: 133-9.
16. *Zito C, Dattilo G, Oreto G, et al.* Patent foramen ovale: comparison among diagnostic strategies in cryptogenic stroke and migraine. Echocardiography 2009; 26: 495-503.
17. *Gai N, Lavi R, Jones PM, et al.* The use of point-of-care ultrasound to diagnose patent foramen ovale in elective hip and knee arthroplasty patients and its association with postoperative delirium. Can J Anesth 2018; 65: 619-26.
18. *Han JJ, Acker MA, Atluri P.* Left ventricular assist devices. Circulation 2018; 138: 2841-51.
19. *Khazanie P, Rogers JG.* Patient selection for left ventricular assist devices. Congest Heart Fail 2011; 17: 227-34.
20. *Wong P.* Science of ultrasound and echocardiography. In: Wong P, Miller-Hance W, editors. Transesophageal Echocardiography for Congenital Heart Disease. London: Springer; 2014 .
21. *Abu-Zidan FM, Hefny AF, Corr P.* Clinical ultrasound physics. J Emerg Trauma Shock 2011; 4: 501-3.
22. *Siddiqui MA, Holmberg MJ, Khan IA.* Spontaneous echo contrast in left atrial appendage during sinus rhythm. Tex Heart Inst J 2001; 28: 322-3.
23. *Forsberg F, Basude R, Liu JB, et al.* Effect of filling gases on the backscatter from contrast microbubbles: theory and in vivo measurements. Ultrasound Med Biol 1999; 25: 1203-11.
24. *Porter TR, Mulvagh SL, Abdelmoneim SS, et al.* Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography Guidelines Update. J Am Soc Echocardiogr 2018; 31: 241-74.
25. *Ignee A, Atkinson NS, Schuessler G, Dietrich CF.* Ultrasound contrast agents. Endosc. Ultrasound 2016; 5: 355-62.
26. *Paefgen V, Doleschel D, Kiessling F.* Evolution of contrast agents for ultrasound imaging and ultrasound-mediated drug delivery. Front Pharmacol 2015; . https://doi.org/10.3389/fphar.2015.00197.
27. *Bommer WJ, Shah PM, Allen H, Meltzer R, Kisslo J.* The safety of contrast echocardiography: report of the Committee on Contrast Echocardiography for the American Society of Echocardiography. J Am Coll Cardiol 1984; 3: 6-13.
28. *Muskula PR, Main ML.* Safety with echocardiographic contrast agents. Circ Cardiovasc Imaging 2017; . https://doi.org/10.1161/CIRCIMAGING.116.005459.
29. *Fan S, Nagai T, Luo H, et al.* Superiority of the combination of blood and agitated saline for routine contrast enhancement. J Am Soc Echocardiography 1999; 12: 94-8.
30. *Garduno C, Chew S, Grocott HP.* Microbubble intravenous contrast during transesophageal echocardiography: agitated 0.9% saline versus agitated 0.9% saline with benzyl alcohol. J Cardiothorac Vasc Anesth 1999; https://doi.org/10.1016/s1053-0770(99)90251-3.
31. *Cardozo S, Gunasekaran P, Patel H, et al.* Is bacteriostatic saline superior to normal saline as an echocardiographic contrast agent? Int J Cardiovasc Imaging 2014; 30: 1483-9.
32. *Porter TR, Abdelmoneim S, Belcik JT, et al.* Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. J Am Soc Echocardiogr 2014; 27: 797-810.

33. *Eisenbrey JR*, *Daecher A*, *Kramer MR*, *Forsberg F*. Effects of needle and catheter size on commercially available ultrasound contrast agents. J Ultrasound Med 2015; 34: 1961-8.
34. *Hamann GF*, *Schatzer-Klotz D*, *Frohlig G*, *et al*. Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. Neurology 1998; 50: 1423-8.
35. *Marriott K*, *Manins V*, *Forshaw A*, *Wright J*, *Pascoe R*. Detection of right-to-left atrial communication using agitated saline contrast imaging: experience with 1162 patients and recommendations for echocardiography. J Am Soc Echocardiogr 2013; 26: 96-102.
36. *Gin KG*, *Huckell VF*, *Pollick C*. Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale. J Am Coll Cardiol 1993; 22: 1994-2000.
37. *Lindeboom JE*, *van Deudekom MJ*, *Visser CA*. Traditional contrast echocardiography may fail to demonstrate a patent foramen ovale: negative contrast in the right atrium may be a clue. Eur J Echocardiogr 2005; 6: 75-8.
38. *Saura D*, *Garcia-Alberola A*, *Florenciano R*, *et al*. Comparison of the degree of right atrial opacification seen on intracardiac echocardiography following femoral or antecubital injection of saline contrast. Rev Esp Cardiol 2007; 60: 660-3.
39. *Johansson MC*, *Eriksson P*, *Peker Y*, *et al*. The influence of patent foramen ovale on oxygen desaturation in obstructive sleep apnoea. Eur Respir J 2007; 29: 149-55.
40. *Kornbau C*, *Lee KC*, *Hughes GD*, *Firstenberg MS*. Central line complications. Int J Crit Illn Inj Sci 2015; 5: 170-8.
41. *Denault AY*, *Couture P*, *Vegas A*, *Buithieu J*, *Tardif JC*. Transesophageal Echocardiography Multimedia Manual, Second edition: A Perioperative Transdisciplinary Approach. NY: Informa Healthcare; 2011 .
42. *Kronik G*, *Mosslacher H*. Positive contrast echocardiography in patients with patent foramen ovale and normal right heart hemodynamics. Am J Cardiol 1982; 49: 1806-9.
43. *Lovas A*, *Szakmány T*. Haemodynamic effects of lung recruitment manoeuvres. BioMed Res Int 2015. https://doi.org/10.1155/2015/478970.
44. *Seol SH*, *Lindner JR*. A primer on the methods and applications for contrast echocardiography in clinical imaging. J Cardiovasc Ultrasound 2014; 22: 101-10.
45. *Thanigaraj S*, *Valika A*, *Zajarias A*, *Lasala JM*, *Perez JE*. Comparison of transthoracic versus transesophageal echocardiography for detection of right-to-left atrial shunting using agitated saline contrast. Am J Cardiol 2005; 96: 1007-10.
46. *Awasthy N*, *Radhakrishnan S*. Stepwise evaluation of left to right shunts by echocardiography. Indian Heart J 2013; 65: 201-18.
47. *Le Gloan L*, *Legendre A*, *Iserin L*, *Ladouceur M*. Pathophysiology and natural history of atrial septal defect. J Thorac Dis 2018; 10: S2854-63.
48. *Siostrzonek P*, *Lang W*, *Zangeneh M*, *et al*. Significance of left-sided heart disease for the detection of patent foramen ovale by transesophageal contrast echocardiography. J Am Coll Cardiol 1992; 19: 1192-6.
49. *Woods TD*, *Patel A*. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. J Am Soc Echocardiogr 2006; 19: 215-22.
50. *Kronik G*, *Slany J*, *Moesslacher H*. Contrast M-mode echocardiography in diagnosis of atrial septal defect in acyanotic patients. Circulation 1979; 59: 372-8.
51. *Lynch JJ*, *Schuchard GH*, *Gross CM*, *Wann LS*. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. Am J Cardiol 1984; 53: 1478-80.
52. *Lam YY*, *Yu CM*, *Zhang Q*, *Yan BP*, *Yip GW*. Enhanced detection of patent foramen ovale by systematic transthoracic saline contrast echocardiography. Int J Cardiol 2011; 152: 24-7.
53. *Gorgulu S*, *Eksik A*, *Eren M*, *et al*. Assessment of the effects of various maneuvers on both atrial pressure changes. Int J Cardiol 2003; 92: 241-5.
54. *Beigel R*, *Goland S*, *Siegel RJ*. Comparison of the effect on right atrial pressure of abdominal compression versus the Valsalva maneuver. Am J Cardiol 2014; 113: 183-6.
55. *Vedrinne JM*, *Duperret S*, *Gratadour P*, *Barthelemy C*, *Motin J*. Effects of mechanical ventilation with PEEP on right to left intra-cardiac shunt caused by patent foramen ovale. Ann Fr Anesth Reanim 1995; 14: 387-92.
56. *Luecke T*, *Pelosi P*. Clinical review: positive end-expiratory pressure and cardiac output. Crit Care 2005; 9: 607-21.
57. *Granati GT*, *Teressa G*. Worsening hypoxemia in the face of increasing PEEP: a case of large pulmonary embolism in the setting of intracardiac shunt. Am J Case Rep 2016; 17: 454-8.
58. *Johansson MC*, *Eriksson P*, *Dellborg M*. The significance of patent foramen ovale: a current review of associated conditions and treatment. Int J Cardiol 2009; 134: 17-24.
59. *Johansson MC*, *Eriksson P*, *Guron CW*, *Dellborg M*. Pitfalls in diagnosing PFO: characteristics of false-negative contrast injections during transesophageal echocardiography in patients with patent foramen ovales. J Am Soc Echocardiogr 2010; 23: 1136-42.
60. *Wu LA*, *Malouf JF*, *Dearani JA*, *et al*. Patent foramen ovale in cryptogenic stroke: current understanding and management options. Arch Intern Med 2004; 164: 950-6.
61. *Martin SS*, *Shapiro EP*, *Mukherjee M*. Atrial septal defects - clinical manifestations, echo assessment, and intervention. Clin Med Insights Cardiol 2015; 8: 93-8.
62. *Rigatelli G*. Should we consider patent foramen ovale and secundum atrial septal defect as different steps of a single anatomo-clinical continuum? J Geriatr Cardiol 2014; 11: 177-9.
63. *Wei D*, *Ju Y*. Importance of an adequately performed Valsalva maneuver for detecting a right-to-left shunt indicating foramen ovale reopening. J Ultrasound Med 2015; 34: 879-83.
64. *Homma S*, *Di Tullio MR*, *Sacco RL*, *et al*. Characteristics of patent foramen ovale associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. Stroke 1994; 25: 582-6.
65. *Hausmann D*, *Mugge A*, *Daniel WG*. Identification of patent foramen ovale permitting paradoxic embolism. J Am Coll Cardiol 1995; 26: 1030-8.
66. *Martin F*, *Sanchez PL*, *Doherty E*, *et al*. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. Circulation 2002; 106: 1121-6.
67. *Stone DA*, *Godard J*, *Corretti MC*, *et al*. Patent foramen ovale: association between the degree of shunt by contrast transesophageal echocardiography and the risk of future ischemic neurologic events. Am Heart J 1996; 131: 158-61.
68. *Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators.* Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. Circulation 2002; 105: 2625-31.
69. *Gossage JR*. The role of echocardiography in screening for pulmonary arteriovenous malformations. Chest 2003; 123: 320-2.
70. *Giordano P*, *Nigro A*, *Lenato GM*, *et al*. Screening for children from families with Rendu-Osler-Weber disease: from geneticist to clinician. J Thromb Haemost 2006; 4: 1237-45.
71. *Gossage JR*. Role of contrast echocardiography in screening for pulmonary arteriovenous malformation in patients with hereditary hemorrhagic telangiectasia. Chest 2010; 138: 769-71.

72. *White RI Jr*, *Mitchell SE*, *Barth KH*, *et al*. Angioarchitecture of pulmonary arteriovenous malformations: an important consideration before embolotherapy. AJR Am J Roentgenol 1983; 140: 681-6.
73. *White RI Jr*, *Pollak JS*, *Wirth JA*. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. J Vasc Interv Radiol 1996; 7: 787-804.
74. *Gossage JR, Kanj G*. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998; 158: 643-61.
75. *Angriman F*, *Ferreyro BL*, *Wainstein EJ*, *Serra MM*. Pulmonary arteriovenous malformations and embolic complications in patients with hereditary hemorrhagic telangiectasia. Arch Bronconeumol 2014; 50: 301-4.
76. *Freeman JA*, *Woods TD*. Use of saline contrast echo timing to distinguish intracardiac and extracardiac shunts: failure of the 3- to 5-beat rule. Echocardiography 2008; 25: 1127-30.
77. *Shub C, Tajik AJ, Seward JB, Dines DE*. Detecting intrapulmonary right-to-left shunt with contrast echocardiography. Observations in a patient with diffuse pulmonary arteriovenous fistulas. Mayo Clin Proc 1976; 51: 81-4.
78. *Attaran RR*, *Ata I*, *Kudithipudi V*, *Foster L*, *Sorrell VL*. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. Echocardiography 2006; 23: 616-22.
79. *Ahmed S*, *Nanda NC*, *Nekkanti R*, *Yousif AM*. Contrast transesophageal echocardiographic detection of a pulmonary arteriovenous malformation draining into left lower pulmonary vein. Echocardiography 2003; 20: 391-4.
80. *Seward JB*, *Tajik AJ*, *Spangler JG*, *Ritter DG*. Echocardiographic contrast studies: initial experience. Mayo Clin Proc 1975; 50: 163-92.
81. *Fenster BE*, *Curran-Everett D*, *Freeman AM*, *et al*. Saline contrast echocardiography for the detection of patent foramen ovale in hypoxia: a validation study using intracardiac echocardiography. Echocardiography 2014; 31: 420-7.
82. *Van Camp G*, *Cosyns B*, *Vandenbossche JL*. Non-smoke spontaneous contrast in left atrium intensified by respiratory manoeuvres: a new transoesophageal echocardiographic observation. Br Heart J 1994; 72: 446-51.
83. *Kim HH*, *Tam JW*, *Chan KL*. A prospective transesophageal echocardiographic study to assess a new type of left atrial spontaneous contrast at rest and during respiratory manoeuvres. Can J Cardiol 1999; 15: 1217-22.
84. *Ogata T*, *Yasaka M*, *Nagatsuka K*, *Yamamura O*, *Minematsu K*. Factors associated with occurrence of the intraleft atrial nonsmoke spontaneous individual contrast phenomenon after a Valsalva maneuver during transesophageal echocardiography. Ultrasound Med Biol 2006; 32: 339-43.
85. *Lopez-Haldon J*, *Lopez-Pardo F*, *Rodriguez-Puras MJ*, *Martinez-Martinez A*. Patent foramen ovale not so patent. Echocardiography 2009; 26: 465-8.
86. *Konstantinides S*, *Kasper W*, *Geibel A*, *Hofmann T*, *Koster W*, *Just H*. Detection of left-to-right shunt in atrial septal defect by negative contrast echocardiography: a comparison of transthoracic and transesophageal approach. Am Heart J 1993; 126: 909-17.
87. *Weyman AE*, *Wann LS*, *Caldwell RL*, *et al*. Negative contrast echocardiography: a new method for detecting left-to-right shunts. Circulation 1979; 59: 498-505.
88. *Gullace G*, *Savoia MT*, *Ravizza P*, *Knippel M*, *Ranzi C*. Detection of atrial septal defect with left-to-right shunt by inferior vena cava contrast echocardiography. Br Heart J 1982; 47: 445-53.
89. *Hanrath P*, *Schluter M*, *Langenstein BA*, *et al*. Detection of ostium secundum atrial septal defects by transoesophageal cross-sectional echocardiography. Br Heart J 1983; 49: 350-8.
90. *Yavuz T*, *Nazli C*, *Kinay O*, *Kutsal A*. Giant eustachian valve with echocardiographic appearance of divided right atrium. Tex Heart Inst J 2002; 29: 336-8.
91. *Kim MJ*, *Jung HO*. Anatomic variants mimicking pathology on echocardiography: differential diagnosis. J Cardiovasc Ultrasound 2013; 21: 103-12.
92. *Islam AK*, *Sayami LA*, *Zaman S*. Chiari network: A case report and brief overview. J Saudi Heart Assoc 2013; 25: 225-9.
93. *Schuchlenz HW*, *Weihs W*, *Hackl E*, *Rehak P*. A large Eustachian valve is a confounder of contrast but not of color Doppler transesophageal echocardiography in detecting a right-to-left shunt across a patent foramen ovale. Int J Cardiol 2006; 109: 375-80.
94. *Koh TW*. When to use femoral vein injection for diagnosis of patent foramen ovale - effect of a persistent eustachian valve on right atrial flow patterns during contrast transesophageal echocardiography. Echocardiography 2017; 34: 768-72.
95. *Attaran RR*, *Baweja G*, *Foster L*, *Butman S*, *Sorrell VL*. Lower patent foramen ovale detection with transthoracic echocardiography in atrial fibrillation. Int J Cardiovasc Imaging 2008; 24: 819-24.
96. *Atak R*, *Ileri M*, *Ozturk S*, *Korkmaz A*, *Yetkin E*. Echocardiographic findings in patients with atrial septal aneurysm: a prospective case-control study. Cardiol Res Pract 2019. https://doi.org/10.1155/2019/3215765.
97. *Butterfield M*, *Riguzzi C*, *Frenkel O*, *Nagdev A*. From the heart: interatrial septal aneurysm identified on bedside ultrasound. West J Emerg Med 2014; 15: 719-20.
98. *Snijder RJ*, *Luermans JG*, *de Heij AH*, *et al*. Patent foramen ovale with atrial septal aneurysm is strongly associated with migraine with aura: a large observational study. J Am Heart Assoc 2016. https://doi.org/10.1161/JAHA.116.003771.
99. *Couture EJ*, *Desjardins G*, *Denault AY*. Transcranial Doppler monitoring guided by cranial two-dimensional ultrasonography. Can J Anesth 2017; 64: 885-7.
100. *Marinoni M*, *Migliaccio ML*, *Trapani S*, *et al*. Cerebral microemboli detected by transcranial doppler in patients treated with extracorporeal membrane oxygenation. Acta Anaesthesiol Scand 2016; 60: 934-44.
101. *Denault A, Liberman M, Paquin S*. Extra-Cardiac Transesophageal Ultrasonography. Basic Transesophageal and Critical Care Ultrasound. NY: Taylor and Francis, CRC Press; 2018: 41-61.
102. *Beaubien-Souligny W*, *Denault A*, *Robillard P*, *Desjardins G*. The role of point-of-care ultrasound monitoring in cardiac surgical patients with acute kidney injury. J Cardiothorac Vasc Anesth 2019; 33: 2781-96.
103. *Beaubien-Souligny W*, *Denault AY*. Real-time assessment of renal venous flow by transesophageal echography during cardiac surgery. A A Pract 2019; 12: 30-2.
104. *Denault A*, *Haddad F*, *Lamarche Y*, *Bouabdallaoui N*, *Deschamps A*, *Desjardins G*. Commentary: Postoperative right ventricular dysfunction - integrating right heart profiles beyond long-axis function. J Thorac Cardiovasc Surg 2020; 159: e315-7.
105. *Denault A*, *Vegas A*, *Lamarche Y*, *Tardif J*, *Couture P*. Basic Transesophageal and Critical Care Ultrasound. NY: Taylor and Francis, CRC Press; 2018.