Functional Echocardiography in the Neonatal Intensive Care Unit

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The role of functional echocardiography in neonatal intensive care unit is rapidly evolving, and increasingly neonatologists are using it in making clinical decisions in sick infants. Functional echocardiography can provide a direct assessment of hemodynamics on bedside, and may be considered as an extension of the clinical examination to evaluate cardiovascular wellbeing in the critically-ill infant. The physiological information may be used in targeting specific intervention based upon the underlying pathophysiology. Functional echocardiography is being used for diagnosis of pulmonary hypertension, patent ductus arteriosus, hemodynamic evaluation, assessment of cardiac function, and recognition of pericardial effusion and cardiac tamponade in the neonatal intensive care setting. Despite of its increasing popularity, there is a paucity of structured training programs for neonatologists to acquire skills in echocardiography. This review article discusses clinical applications of functional echocardiography in the neonatal intensive care unit.

Keywords: *Cardiac Doppler, Hemodynamic evaluation, Point-of-care ultrasound, Patent ductus arteriosus, Pulmonary hypertension.*

Echocardiography is the investigation of choice to diagnose congenital heart defects, and historically it has been performed by pediatric cardiologists. It is non-invasive, readily available, performed at the bedside, and provides information in real time, making it an ideal tool to evaluate hemodynamics and to acquire physiological and anatomical information in critically-ill patients [1-3]. This practice is well established in adults and pediatric cardiac intensive care units. Anecdotally, echocardiography is being used by the neonatologists in many neonatal intensive care units (NICU) across the world. A recent survey of clinical practice in the United Kingdom showed that it was being performed by neonatologists in most tertiary neonatal intensive care units. However, there remains a significant variation in the clinical practice of the neonatologists performing echocardiography [4].

Despite its increasing popularity and use in the neonatal clinical practice, there is no established structured training or accreditation process specifically designed for the neonatologists to acquire skills in targeted or functional echocardiography. Recently, three expert-consensus statements have been published recommending its use in the NICU and various terminologies have been used to describe the use of echocardiography by the neonatologists – targeted neonatal echocardiography (TNE), point-of-care ultrasound (POCUS), neonatologist performed echocardiography (NPE), and clinician performed ultrasound (CPU). All the expert consensus statements have emphasized on establishing a structured training program and accreditation process for the neonatologists [5-7].

Echocardiography can be used for structural assessment (performed to diagnose or rule out congenital heart defect) or functional assessment (focused evaluation of hemodynamics or cardiac function). Functional echocardiography can be used to address a specific clinical question or acquire additional physiological information helping the clinician in making decision bedside or in providing targeted therapy [3,5]. While the structural or comprehensive echocardiography provides cross-sectional assessment, functional echocardiography may be used serially to monitor change in hemodynamic status or response to intervention.

Ideally, access to functional echocardiography should be available round-the-clock in all NICUs providing care to critically sick infants, independent of the availability of the pediatric cardiologists or skilled neonatologists. When performed by an attending neonatologist, it may have added benefits in targeting the echocardiography to gain specific physiological or anatomical information, and it can be serially repeated to monitor the response by the clinical team. Therefore, recently emphasis has been on developing a structured training program specifically designed to train the neonatologists, neonatal trainees, fellows and residents.

The European and North American expert consensus statements [5-7] have recommended that the first scan should include a comprehensive structural assessment to rule out major congenital heart defects or at least define normality. The subsequent functional echocardiography scans can be focused or targeted to address specific question. This review article is an overview on the practical applications of functional echocardiography in the NICU and it is not aimed at detailed description of echocardiographic evaluation of any particular condition.

ASSESSMENT OF PULMONARY HYPERTENSION

Acute pulmonary hypertension in newborn, often referred as Persistent pulmonary hypertension of newborn (PPHN), continues to have high mortality in NICUs despite advances in neonatal care. Infants with acute pulmonary hypertension are often very sick and they need time-sensitive interventions to optimize cardiorespiratory support. The clinical presentation may mimic as critical cyanotic congenital heart defect. In clinical practice, a bedside point-of-care echocardio-graphy plays an important role to rule out underlying major congenital heart defect (CHD), diagnose pulmonary hypertension, assess its severity and target specific therapy [5,8-10].

The pulmonary artery systolic pressure (PASP) can be reliably estimated using echocardiography in the presence of tricuspid regurgitation (TR) as demonstrated in ***Web Fig.* 1**. The pressure gradient between right ventricle (RV) and right atrium (RA) are calculated by using modified Bernoulli's principle [3,11]. PASP is estimated by adding RA pressure, which are usually between 5-10 mmHg, to the peak pressure gradient between RV and RA obtained on continuous wave (CW) doppler, when there is no RV outflow tract obstruction. The pulmonary artery pressure may be underestimated in presence of impaired RV contractility.

The severity of pulmonary hypertension can also be estimated by the direction of shunts across ductus arteriosus or patent foramen ovale (PFO). A pure right-to left shunt across ductus arteriosus would suggest suprasystemic pulmonary artery pressure, while a bidirectional transductal is reflective of pulmonary pressure approximating systemic pressure. The shunt across PFO is generally bidirectional, even in presence of severe pulmonary hypertension. A cyanotic congenital heart defect should be ruled out in presence of a pure right-to-left shunt across PFO [3].

In absence of TR or transductal shunt, severity of pulmonary hypertension can be estimated by studying interventricular septum (IVS) and left ventricle (LV) shape in parasternal short axis view – normally LV is seen as circular. Rising pulmonary artery pressure flattens the IVS. In cases with severe pulmonary hypertension, RV becomes circular and paradoxical septal movements may be seen [3,9-11].

Persistent high pulmonary vascular resistance (RV afterload) in pulmonary hypertension may impair RV function, which can be quickly assessed on direct visualization ('eyeballing'). In pulmonary dysfunction, RV contractility appears impaired, and RV looks larger and stiffer with dilated RV outflow tract. LV dysfunction is common in presence of severe pulmonary hypertension – interventricular independence and paradoxical septal movement can impair LV contractility and loading conditions [3,9-11].

The Pulmonary artery acceleration time (PAAT) reflects the time taken to reach to the maximum velocity on pulmonary artery Doppler. PAAT is shortened in presence of pulmonary hypertension and PAAT value under 90 ms in neonates is highly suggestive of pulmonary hypertension [3,13]. PAAT/RVET (RV ejection time) ratio derived has been shown to negatively correlate with pulmonary pressures in premature infants. PAAT/RVET ratio has also been suggested a good predictor of late-onset chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) [3,9, 13].

The other parameters on echocardiography such as myocardial performance index, right ventricular systolic to diastolic (S/D) duration ratio and eccentricity index may be used for quantitative assessment of pulmonary hypertension [3,9-11,14]. A detailed description of these echocardiographic techniques is out of the scope of this article. The commonly used echocardiographic parameters to diagnose pulmonary hypertension in the clinical practice are summarised in ***Table* I**.

Early diagnosis of pulmonary hypertension on echocardiography may help in initiation of pulmonary vasodilator (such as inhaled nitric oxide) without any delay, and serial assessments may help in monitoring the response to treatment. In addition, early detection of cardiac dysfunction may help in rationalizing the choice of appropriate inotropic or vasopressor support based upon underlying pathophysiology [8-9,15].

DIAGNOSIS AND EVALUATION OF HEMODYNAMICS IN PATENT DUCTUS ARTERIOSUS

There is no consensus on the treatment of Patent ductus arteriosus (PDA) in preterm infants – when, how and who

TABLE I SUMMARY OF ECHOCARDIOGRAPHIC PARAMETERS COMMONLY USED IN EVALUATION OF ACUTE PULMONARY HYPERTENSION

Echocardiographic parameter	*Type of assessment*	*Echocardiographic view*
Right ventricular hypertrophy and or dilatation	'Eyeballing' visual assessment (qualitative); or RV/LV ratio (quantitative)	Apical 4-chamber view, parasternal long and short axis views
Estimation of PASP	Quantitative assessment by measuring TR	Apical 4-chamber view
Assessment of ductus arteriosus shunt	Qualitative assessment Right-to-left shunt suggests supra-systemic pulmonary artery pressure	High left parasternal 'ductal' view
Assessment of shunt *via* foramen ovale	Qualitative assessment Often bi-directional shunt in PPHN	Sub-costal view or apical 4 chamber view
Evaluation of IVS and LV shape	Qualitative assessment on visual inspection – flattening or bowing on IVS towards LV suggests pulmonary hyper-tension	Parasternal short axis view
Assessment of cardiac filling (preload)	Qualitative assessment on visual inspection	Apical 4-chamber view, parasternal long and short axis views
Assessment of cardiac functions (RV and LV functions)	Qualitative assessment on visual inspection or quantitative assessment;Tricuspid Annular Plane Systolic Excursion (TAPSE) Tissue Doppler imaging – S'wave Myocardial performance index of RV and LV function RV systolic to diastolic (S/D) duration Eccentricity index of LV	Apical 4-chamber view, parasternal long and short axis views

IVS: interventricular septum; LV: left ventricle; RV: right ventricle; PASP: pulmonary artery systolic pressure; PPHN: persistent pulmonary hypertension.

should be treated? Despite numerous studies published over five decades, the debate on the management of PDA continues [16]. Interestingly, even the definition of hemodynamically significant PDA (hsPDA) remains contentious, and there is no agreement on which echocardiographic parameters should be used to assess it in preterm infants [17,18].

The signs and symptoms of PDA depend not only on the size of ductus arteriosus, but also on the magnitude of the shunt and ability of premature myocardium to adapt to this excessive shunt [18]. Functional echocardiography can help in assessing the impact of transductal shunt on hemodynamic status – pulmonary hyperperfusion and systemic hypoperfusion (***Table* II** and ***Web Fig.* 2**). Hence, a detailed assessment of PDA and its hemodynamic significance has been suggested to rationalize the management of PDA in preterm infants [19].

Persistent PDA has been suggested as an independent risk factor for increased risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), acute pulmonary hemorrhage, and a 4-8 fold increase in mortality [20]. However, studies on PDA treatment have failed to demonstrate any benefit on the long-term outcomes [21]. Certainly there is a clear trend towards treating less number of infants with PDA [22]. However, safety of the conservative approach has not been established. In the authors' experience, large left-to-right shunt in hsPDA in extremely low birth (ELBW) infants may be associated with systemic hypotension, metabolic acidosis and increased risk of intraventricular hemorrhage or acute pulmonary hemorrhage, and these infants may benefit for early targeted treatment of PDA. Secondly, while some infants with an hsPDA may need intervention, others may need only careful observation [22]. While further trials on studying the long-term effects of persistent PDA and impact of its treatment are being carried out, a precise individualized approach based upon the clinical significance and careful hemodynamic assessment (impact on pulmonary hyper-perfusion and systemic hypo-perfusion) may be adopted while managing hsPDA in ELBW infants.

EVALUATION OF HEMODYNAMICS

Hemodynamic instability is very common in the sick

TABLE II SUMMARY OF COMMON ECHOCARDIOGRAPHIC PARAMETERS USED FOR EVALUATING HEMODYNAMIC SIGNIFICANCE OF PATENT DUCTUS ARTERIOSUS

Type of assessment	*Echocardiographic parameter*	*Features suggestive of hs-PDA*
Evaluation of ductus arteriosus characteristics	• Size of the duct • Direction of transductal blood flow • Doppler flow pattern (pulsatile or restrictive)	Ductal size >2mm Pulsatile flow pattern with no signs constriction
Assessment of pulmonary hyperperfusion	Visual assessment for volume overloading of left atrium / left ventricle • LA/Ao ratio • Increased pulmonary venous return	Significant volume overloading of "eyeballing" or LA/Ao ratio >1.6
Assessment of systemic hypoperfusion	• Retrograde flow in descending aorta • Retrograde flow in coeliac axis or SMA • Retrograde flow in MCA	Retrograde blood flow in descending aorta or SMA or MCA

hsPDA: hemodynamically significant patent ductus arteriosus (when there are clinical signs of significant ductal shunt supported by the echocardiographic parameters); LA: left atrium; Ao: aorta; SMA: superior mesenteric artery; MCA: middle cerebral artery.

neonates needing intensive care management. Approximately one-third of preterm neonates have systemic hypotension and up to 40% require vasopressor therapy [23]. Unfortunately, unlike adults or older children, neonates have limited cardiovascular reserves, and a meticulous assessment of neonatal hemodynamics is of paramount importance in managing sick infants with hemodynamic instability. The traditional clinical parameters to evaluate neonatal hemodynamics include clinical examination, heart rate, capillary refill time (CRT), oxygen saturation, urine output and serum lactate level. All of these parameters are proxy-indicators of cardiovascular well-being and they lack sensitivity and specificity for accurate assessment of hemodynamics in neonates [3,24].

Blood pressure is often used as a marker of adequacy of systemic perfusion, which when used in isolation is problematic. End-organ perfusion is dependent on systemic blood flow and vascular resistance. Hence, reliance on blood pressure measurements alone provides limited information regarding the adequacy of organ blood flow [25]. There is poor correlation between blood pressure and cardiac output [26]. The traditionally used method to estimate the mean blood pressure equating to the gestational age lacks scientific evidence. Recently, blood pressure normograms for different gestational ages after 2 weeks of age have been published [27], but there is lack of consensus and robust scientific evidence for accepting these norms in this age group.

Unlike traditionally used indirect parameters of cardiovascular wellbeing, bedside functional echocardio-graphy can provide direct assessment of hemodynamics in real time. It can be used to assess cardiac filling (preload), afterload (systemic or pulmonary vascular resistance), cardiac function and cardiac output. Cardiac filling can be assessed on visual inspection (qualitative assessment) or by measuring inferior vena cava collapsibility and distensibility index [3,6,28]. Cardiac output can be easily assessed on echocardiography by measuring the cross-sectional area and velocity time integral using Doppler. Estimation of left output (LVO) and right output (RVO) provides additional hemodynamic information regarding the adequacy of blood flow. In the neonatal period, presence of shunts may contaminate these cardiac outputs – LVO represents left cardiac output and transductal shunt when ductus arteriosus is patent, while RVO represents systemic venous return (flow) and atrial shunt [3,29].

Superior vena cava (SVC) flow measurement has been proposed as a better marker of systemic blood flow from upper body and brain as it is not contaminated in presence of shunts [30]. Low SVC flow has been reported to be associated with an increased incidence of intraventricular hemorrhage and impaired neurodevelop-mental outcome [31,32]. SVC flow can be assessed using echocardio-graphy [30]. However, SVC diameter varies widely within the cardiac cycle which potentially predisposes to wide margin of error in estimating SVC flow. Researchers have questioned the validity of SVC flow due to high intra- and inter-observer variability [33,34]. Serial assessment studying the trend may be more useful than a single absolute value, and we do not consider this parameter a useful tool in our clinical practice.

Functional echocardiography may allow adopting a physiology-based targeted intervention in sick infants with hemodynamic instability – treating low preload states with volume resuscitation, use of vasodilator in presence of increased vascular resistance and treating reduced LV or RV contractility with appropriate inotropes.

ASSESSMENT OF CARDIAC FUNCTION

Bedside echocardiography can be used to assess cardiac function. The systolic function of left ventricle can be quickly assessed on visual inspection by 'eye-balling' the contractility, or quantitatively by measuring the shortening fraction on M-mode. Ejection fraction by planimetry using modified Simpson's method may give more accurate assessment but can be time consuming and getting good quality images for precise measurement may be challenging in mechanically ventilated infants. Quantitative assessment of RV function is even more difficult – the anatomy and geometrical shape of RV does not permit using similar parameters for assessing RV systolic function as used for LV [28]. Hence, RV systolic function is often assessed on visual inspection in emergency setting. Tricuspid Annular Plane Systolic Excursion (TAPSE) or S' wave on tissue Doppler imaging are good reflectors of RV systolic function, and can be reliably performed on bedside functional echocardiography [11,28,34-36]. The assessment of diastolic function relies essentially on mitral and tricuspid valve Doppler tracings (E/A wave ratio) or using Tissue Doppler Imaging (TDI) evaluation [11,28].

The myocardial performance index (Tei index) is calculated by dividing the sum of isovolumetric contraction and relaxation times by the ejection time. This requires measuring the time interval between the end and onset of mitral or tricuspid inflow and the ejection time of the LV or RV outflow, respectively. This may be more accurately calculated on TDI [3,5,15]. It is a valuable quantitative echocardiography index of ventricular function by incorporating both systolic and diastolic performance of the RV and LV and normal values in healthy neonates range from 0.25 to 0.38 [37,38].

Several other parameters are proposed for quantitative assessment of cardiac function such as TDI, speckle tracking and strain rate, and fractional area change [28,35,36]. However, there are limitations for their use in emergency situations and a detailed description of these echocardiographic parameters is out of the scope of this article.

DIAGNOSIS OF PERICARDIAL EFFUSION/TAMPONADE

Without cardiac surgery, cardiac tamponade and pericardial effusion are uncommon in neonates. However, when present they can have significant impact on the outcomes. Case reports of significant cardiac tamponade/ pericardial effusion secondary to parenteral nutrition *via* central line leading to sudden collapse or unfavourable outcomes have been reported [39,40]. Pericardial effusion can be easily recognized on functional echocardiography, and a timely intervention in presence of cardiac tamponade may improve the outcome.

OTHER CLINICAL APPLICATIONS

Echocardiography can play an important role in managing infants with neonatal shock. American College of Critical Care Medicine (ACCM) clinical guidelines and practice parameters have suggested using bedside echocardio-graphy in hemodynamic evaluation and its management in patients with neonatal shock [41]. Functional echocardiography can be used to assess hemodynamic status and understand the underlying pathophysiology. In conjunction with other clinical parameters, it can guide clinicians in making a logical choice of intervention – fluid resuscitation therapy or appropriate inotropic or vasopressor therapy.

Infants with moderate to severe hypoxic-ischaemic encephalopathy (HIE) often have ventricular dysfunction, systemic hypotension and pulmonary hypertension. Functional echocardiography may be used to guide the appropriate intervention to normalize hemodynamics and optimize tissue perfusion. Infants with cardiac dysfunction may benefit from the use of dobutamine to reduce afterload and improve contractility, and cardiac output assessment may help in optimizing blood flow and tissue perfusion [5,42].

Ultrasound-guided central line placement is a standard practice in adults and children. Point-of-care echocardio-graphy is increasing being used for central line placement and checking the position of umbilical catheters in neonates [43]. Imaging inferior vena cava-right atrial junction and descending aorta in subcostal view can easily facilitate checking the position of umbilical venous and arterial catheters, respectively. Few studies have suggested echocardiography may be more reliable than *X*-rays to confirm umbilical catheters position [44-46]. While confirming the position on *X*-ray is considered as gold standard, role of echocardiography is evolving and may have an important role in future.

IMPACT ON IMPROVING PATIENT OUTCOMES

Despite the weak published evidence, anecdotal clinical experience and current literature support the use of functional echocardiography in the NICU to detect hemodynamic compromise and improve outcomes [5,47-49]. A retrospective review of echocardiography performed by the neonatologists under cardiologist

BOX 1 KEY MESSAGES ON THE ROLE OF FUNCTIONAL ECHOCARDIOGRAPHY IN THE NICU

1. First echocardiogram should include a detailed structural assessment to rule out significant congenital heart defects or define normality.
2. Functional echocardiography is the investigation of choice in diagnosing pulmonary hypertension and assessing its severity. When clinically suspected, treatment should not be delayed while waiting for the echocardiography.
3. While the treatment of PDA remains controversial, a detailed evaluation of hemodynamics may help in rationalising the treatment approach - selecting the right patients for the right intervention at right time.
4. Echocardiography is mandatory in infants with PDA before any medical or surgical intervention.
5. Functional echocardiography may give added physiological information in infants with neonatal shock which can help in identifying the underlying pathophysiology and providing condition specific treatment.
6. Functional echocardiography may help in adopting a physiology-based logical approach to treatment in infants with hypotension or shock – it may be used in choosing fluid resuscitation therapy or inotropic therapy, and further what type of inotrope or vasopressor therapy indicated based upon preload, afterload and cardiac function on echocardiographic assessment.
7. A structured training program specifically designed for the neonatologists to acquire echocardiography skills is urgently needed. Adherence to standardised protocols and robust clinical governance is the key to ensure that high standards of echocardiography skills are being delivered in the NICU.
8. A close collaboration with pediatric cardiologists and neonatologists performing functional echocardiography is recommended.

NICU: neonatal intensive care unit; PDA: patent ductus arteriosus.

supervision was reported to result in change of management in two-third of cases [49]. NPE screening programme has been reported to result in reduction of severe IVH and ventilation duration [48]. Similarly, serial echocardiographic assessment during PDA treatment resulted in reduction of exposure to indomethacin doses [50]. Functional echocardiography may help in identifying patients at risk of developing post PDA-ligation syndrome [51,52].

TRAINING AND ACCREDITATION FOR NEONATOLOGISTS

The recently published expert consensus statements have emphasized on developing a structured training program specifically designed for neonatologists. Minor variations in the recommendations may be due to the heterogenicity in clinical practice, geographical location and different needs across the countries. Published guidelines have emphasized on developing an accreditation process, establishing a robust clinical governance system to improve the patient safety and professional assurance. A close collaboration between pediatric cardiologists and neonatologists is pivotal in developing a successful training program and accreditation process.

Studies have reported that is a very low risk of missing underlying significant CHD on neonatologist performed echocardiography – significant CHDs were almost always detected, even if a full diagnosis may not be made [53]. Although it is reassuring, it is worth emphasizing that first echocardiogram should include a comprehensive structural assessment of the heart to rule out major congenital heart defects or at least establish the normality [5-7].

The key messages on clinical application of functional echocardiography in the NICU are summarized in ***Box* 1**.

CONCLUSIONS

Bedside functional echocardiography has the ability to provide physiological information in real time, and it is increasing being used in making clinical decisions in the NICU. The role of neonatologist-performed functional echocardiography is rapidly evolving, and it is now being considered as an extension of clinical examination while assessing hemodynamics in critically-ill infants. There is an urgent need of developing a structured training program and accreditation process for the neonatologists to develop echocardiography skills. Standardized training, robust clinical governance and a close collaboration with the pediatric cardiologists are the key elements to ensure patient safety and professional reassurance.

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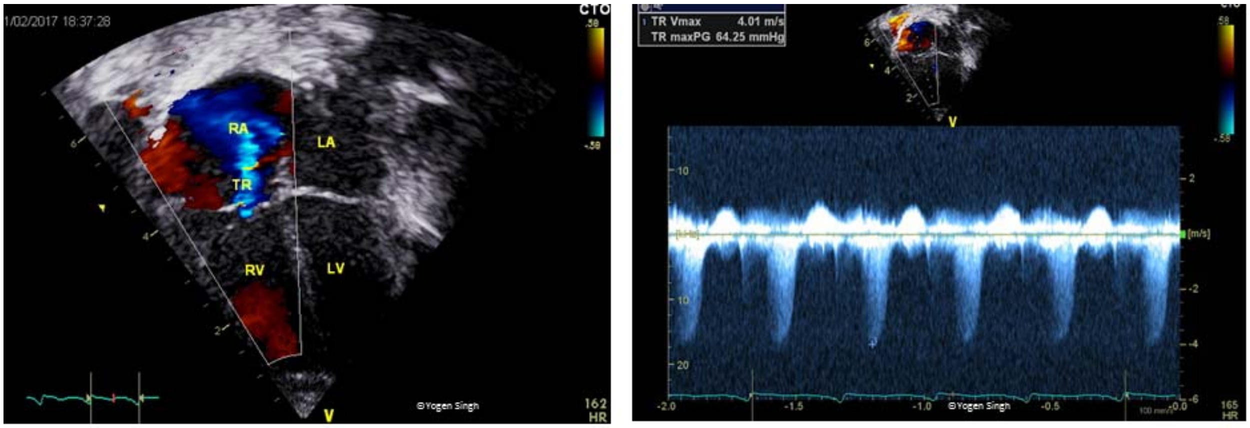
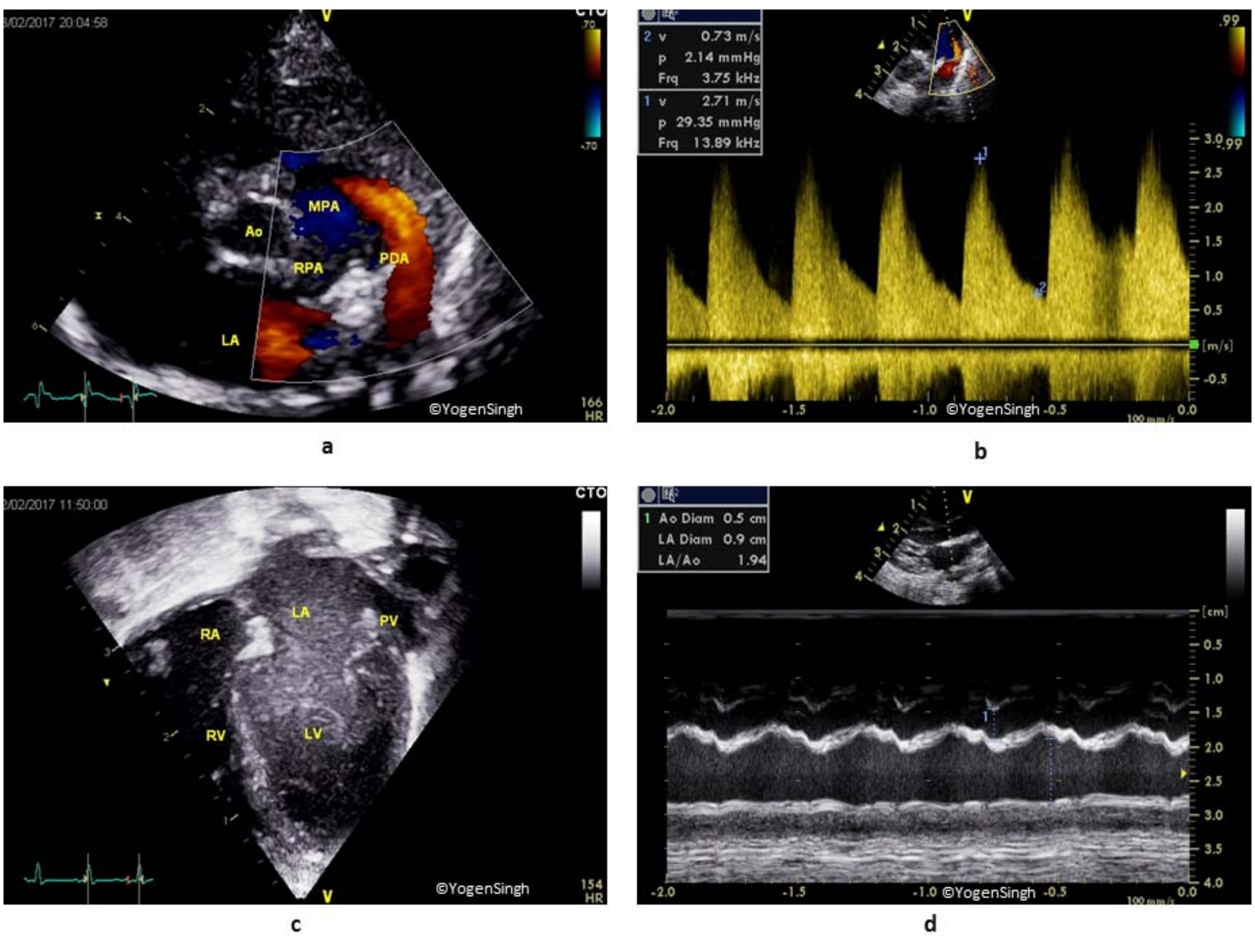


a: TR jet on A4C **b: TR Doppler**

WEB FIG. 1 *Quantitative assessment of pulmonary artery systolic pressure (PASP) by measuring tricuspid valve regurgitation velocity (TR jet): (a) TR jet on colour flow mapping (CFM in apical 4-chamber view (A4C); (b) TR Doppler reflecting gradient between right ventricle and right atrium.*



WEB FIG. 2 *Echocardiographic diagnosis of patent ductus arteriosus (PDA): (a) PDA on colour flow mapping (CFM); (b) with pulsatile Doppler in high left parasternal short axis view; (c) volume overloading of the left side of the heart in apical 4-chamber view; and (d) left atrium to aorta (LA/Ao ratio) in parasternal long axis view.*