Validation of Echocardiographic Assessment of Pulmonary Vascular Resistance in Children with Left to Right Shunt

Thesis

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ABSTRACT

Advanced pulmonary vascular disease secondary to congenital heart disease remains a major problem in the developing world. It is imperative to be certain of operability before referring such patients for surgery, therefore, cardiac catheterization must be performed in all borderline cases for decision-making.

This study aimed at echocardiographic versus catheterization assessment of pulmonary vascular resistance in patients with left to right shunt.

Key wods:

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Pulmonary hypertension is defined as a mean pulmonary artery pressure equal to or more than 25 mm Hg at rest or 30 mm Hg on exercise (1). Pulmonary hypertension can occur due to various cardiac, pulmonary, and other conditions.Pulmonary hypertension in association with congenital heart diseases is seen in large systemic-to-pulmonary communications such as ventricular septal defect, patent ductus arteriosus, etc. In addition, pulmonary hypertension is also present in several cyanotic congenital heart diseases with increased pulmonary blood flow. Examples include transposition of great arteries, truncus arteriosus, total anomalous pulmonary venous connection, single ventricle, etc. Advances in pediatric cardiology and cardiac surgery have made it possible to repair most congenital heart diseases associated with pulmonary hypertension, in infancy or early childhood. However, this standard of care is available to children in the developed world only. In most developing countries, only a small proportion of infants born with significant congenital heart disease receive timely intervention. Reasons for this state include delayed diagnosis, non-availability of well-equipped cardiac centers, inability to afford the high cost of treatment (2). Some children not operated upon, succumb to heart failure or one of the intercurrent illnesses. Those who survive may go on to develop irreversible changes in their pulmonary vasculature. Such children might in fact show symptomatic improvement for some time. Progressive pulmonary vascular disease leads to reversal of shunt and central cyanosis resulting in Eisenmenger syndrome that was first described by Dr. Paul Wood in 1958 (3). Advanced pulmonary vascular disease secondary to congenital heart disease remains a major problem in the

developing world. Echocardiography with color Doppler is the most important and most often performed investigation. It diagnoses the underlying congenital heart disease. The size, site, and numbers of systemic-to-pulmonary communications can be easily defined. The severity of pulmonary hypertension can be estimated by Doppler using jet of ventricular septal defect and/or velocity of tricuspid and pulmonary regurgitation (4). .

Outcome after repair of a large left-to-right shunt is determined primarily by age at the time of repair and preoperative pulmonary vascular disease. Clinical examination along with X-ray chest, ECG, and echocardiography is able to provide sufficient information required for repair of the defect in majority of cases. This is especially true for young children, below one to two years of age. However, in older children and adults where pulmonary vascular disease is likely, the decision to operate is more difficult. Closure of a large ventricular septal defect in a patient with advanced pulmonary vascular disease can be fatal either in the immediate postoperative period or on long-term follow up. Natural history of such patients is considerably worse than those with Eisenmenger syndrome. Therefore it is imperative to be certain of operability before referring such patients for surgery (4). Cardiac catheterization must be performed in all borderline cases for decision-making. It provides vital information in the form of pulmonary blood flow to systemic blood flow ratio, pulmonary vascular resistance, ratio of pulmonary vascular to systemic vascular resistances. Recommendations solely based on pulmonary vascular resistance values may not be correct as several other factors such as age, individual variability, location of defect, etc. may influence the operability status. Despite all this, an

indexed pulmonary vascular resistance of <6-8 Woods units may be considered in the operable range(5)

This study was aimed to compare echocardiograpghic versus invasive cardiac catheterization assessment of pulmonary vascular resistance in patients with left to right shunt lesions and pulmonary hypertension by echo.

ANATOMY AND PHYSIOLOGY OF THE PULMONARY CIRCULATION AND RIGHT HEART

The right ventricle is comprised of inflow (sinus) and outflow (conus) regions, separated by a muscular ridge, the crista supraventricularis. The inflow region includes the tricuspid valve (TV), the chordae/papillary muscles as well as the body of the RV. The boundaries of the body of the RV are formed by the RV free wall, extending with a radius of curvature approximating that of a large sphere, from the anterior and posterior aspects of the interventricular septum. The normal septal curvature is convexed toward the RV cavity, imparting a crescentic shape to the right ventricle in cross section. The interior surface of the RV is heavily trabeculated; this feature along with the moderator band and more apical insertion of the TV-annulus impart key morphologic differences that distinguish the RV from the LV by echocardiography. In contrast, the infundibulum is a smooth, funnel shaped outflow portion of the RV that ends at the pulmonic valve. Thus, the RV has a complex geometry which largely precludes calculation of RV volume (and thus RV ejection fraction) by 2D echo. However, this limitation does not preclude alternative, non-volumetric methods of RV function assessment (vide infra). [6]

Normal RV free wall thickness is 0.3-0.5 cm, imparting greater distensability and larger cavity volumes in the RV versus the LV, despite lower end-diastolic filling pressures. This translates to an RVEF that is typically 35% to 45% (versus 55-65% in the LV) yet generates the identical SV as the LV. Systolic function of the RV, like the LV, is influenced by changes in preload, afterload, and the intrinsic contractility of the ventricle. Differences in RV muscle fiber orientation dictate that the body of the RV shortens symmetrically in the longitudinal and radial planes; thus, longitudinal shortening accounts for a much larger proportion of RV ejection than in the LV. This relatively conspicuous RV shortening along the longitudinal axis can be exploited to measure RV systolic function using relatively simple techniques that do not require geometric assumptions or meticulous endocardial definition, both of which are known limitations to the noninvasive assessment of RV systolic function.[6,7]

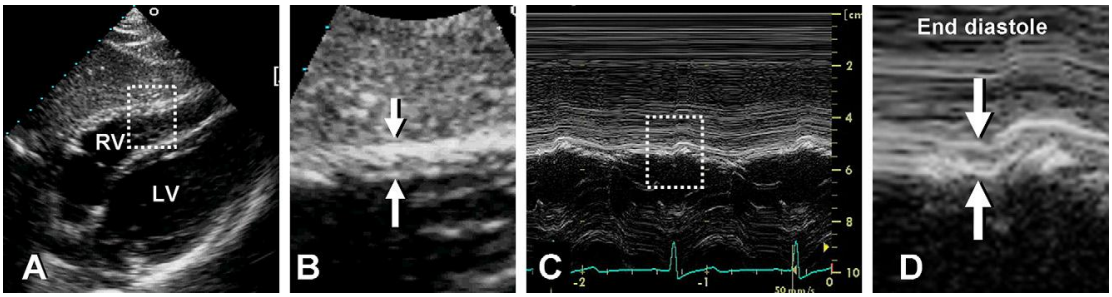

Figure 1: Measurement of end-diastolic right ventricular wall thickness. (A) Subcostal 2-dimensional image of right ventricular wall. (B) Zoom of region outlined in (A) with right ventricular wall thickness indicated by arrows. (C) M-mode image corresponding to arrows in (B). (D) Zoom of region outlined in (C) with arrows indicating wall thickness at end-diastole 90

The right ventricle and the pulmonary circulation function as a coupled unit. In health, a normal pulmonary vasculature couples to an appropriately thin-walled, distensible RV that is designed to generate large amounts of blood flow without a resulting high pressure ('flow generator'). As long as this normal interaction holds, so will this physiologic paradigm. As pulmonary vascular disease develops, the pulmonary vascular resistance increases and the large arteries stiffen. As a result, the (formerly appropriate) non-muscular RV is typically incapable of completely matching, or coupling its contractile performance to its new afterload. This relative RV-PA uncoupling leads to a stereotypical triad of changes that occur at the level of the RV, including RV systolic dysfunction, increased size and altered shape of the RV, as well as varying degrees of systolic and diastolic bowing of the interventricular septum. This triad of changes forms the basis of the echocardiographic diagnosis of PVD. The degree to which these changes occur is contingent upon the degree of RV-PA uncoupling. At a PVR of 5 WU, a patient with depressed RV contractility is far more uncoupled to their vascular load than a patient with an intrinsically normal RV coupled to the same afterload. The RV dysfunction triad helps to adjudicate and assess the physiologic and clinical significance of any given degree of PVD. The greater the RV impairment, the greater the overall significance of the PVD, no matter what the noninvasive pressure estimate is reported to be. [7]

Hypertrophy typically denotes chronicity, thus in more chronic forms of PH, RV hypertrophy predominates over RV dilatation. In contrast, in more acute forms such as pulmonary embolism, or even pulmonary arterial hypertension, dilatation of the RV occurs disproportionate to hypertrophy. It also seems that chronicity affects the degree of adaptation of the RV to a given afterload. The RV in Eisenmenger's

syndrome is often massively hypertrophied, not dilated, and maintains relatively normal function despite decades of systemic level afterload; this is the most likely explanation for the more favorable long term prognosis of these patients as compared to other forms of pulmonary arterial hypertension (PAH) fig. 1 [7].

Doppler data provides further physiologic and hemodynamic characterization of the varying etiologies of pulmonary hypertension. Importantly, varying degrees of pulmonary hypertension often result from an abnormal RV-PA interaction. However, the increased pulmonary artery pressure is the result, not the cause, of the RV-PA mismatch. Thus, a simple, but critically important distinction is that PA pressure is a poor measure of RV afterload, which is why pulmonary artery pressure is also a poor predictor of clinical RV failure and prognosis in PAH. Understanding this physiologic paradigm puts the clinician at a distinct advantage when assessing a patient with known or suspected PH. The presence or absence (whether a true negative or false negative) of elevated pulmonary artery pressure should not necessarily dissuade the clinician from suspecting PVD if there is evidence of RV dysfunction, especially when occurring in the form of the above noted triad(8).

CAUSES OF PULMONARY HYPERTENSION[103]

1. Large left-to-right shunt lesions (hyperkinetic pulmonary hypertension): ventricular septal defect, patent ductus arteriosus, endocardial cushion defect
2. Alveolar hypoxia
    a. Pulmonary parenchymal disease
        1). Extensive pneumonia
        2). Hypoplasia of lungs (primary or secondary, such as that seen in diaphragmatic hernia)
        3). Bronchopulmonary dysplasia
        4). Interstitial lung disease (Hamman-Rich syndrome)
        5). Wilson-Mikity syndrome
    b. Airway obstruction
        1). Upper airway obstruction (large tonsils, macroglossia, micrognathia, laryngotracheomalacia, sleep-disordered breathing)
        2). Lower airway obstruction (bronchial asthma, cystic fibrosis)
    c. Inadequate ventilatory drive (central nervous system diseases, obesity hypoventilation syndrome)
    d. Disorders of chest wall or respiratory muscles
        1). Kyphoscoliosis
        2). Weakening or paralysis of skeletal muscle
    e. High altitude (in certain hyperreactors)
3. Pulmonary venous hypertension: mitral stenosis, cor triatriatum, total anomalous pulmonary venous return with obstruction, chronic left heart failure, left-sided obstructive lesions (aortic stenosis, coarctation of the aorta). Rarely, congenital pulmonary vein stenosis causes incurable pulmonary hypertension.
4. Primary pulmonary vascular disease
    a. Persistent pulmonary hypertension of the newborn
    b. Primary pulmonary hypertension—rare, fatal form of pulmonary hypertension with obscure cause
5. Other diseases that involve pulmonary parenchyma or pulmonary vasculature
    a. Thromboembolism: ventriculoatrial shunt for hydrocephalus, sickle cell anemia, thrombophlebitis
    b. Connective tissue disease: scleroderma, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis, rheumatoid arthritis
    c. Disorders directly affecting the pulmonary vasculature: schistosomiasis, sarcoidosis, histiocytosis X
    d. Portal hypertension, human immunodeficiency virus infection

PRESSURE ASSESSMENT BY DOPPLER

Despite its shortcomings as a measure of RV afterload, the pulmonary artery pressure assessment is a central component of the evaluation of patients with known or suspected PVD. This relates to the fact that varying degrees of pulmonary hypertension are nearly always present in patients with PVD, and the workup of these patients typically emanates from the initial noninvasive pressure assessment. A PASP>40 mmHg is generally accepted as the upper limit of normal in most subjects, however the cutoff may be higher in elderly subjects.[9,10]

The most common method used in Doppler pressure assessment utilizes continuous wave Doppler to determine the peak tricuspid regurgitant jet velocity, which estimates the pressure difference between the right ventricle and right atrium using the modified Bernoulli equation (4v2; v equals the peak velocity of the TR jet), as shown in (fig. 1). The TV must be interrogated from multiple different views (i.e. RV inflow, short axis, apical four chamber, subcostal views) to ensure that the ultrasound beam is parallel to the regurgitant signal, thus allowing optimal Doppler envelope quality and an accurate peak transtricuspid flow velocity (TTFV). In general, the highest velocity obtained should be used to calculate the peak RV systolic pressure. One exception is the inclusion of a post-extrasystolic beat, which will often have a substantially higher peak velocity than steady state beats, relating to the larger stroke volume generated following the compensatory pause. If pulmonic stenosis is present, the gradient across the pulmonic valve must be subtracted from the peak RV systolic pressure to obtain the peak PA pressure, otherwise, a distinction between ‘RV hypertension’ and pulmonary hypertension can be missed and PH medical therapy may be misapplied over mechanical intervention on the stenotic valve. In a technically limited study, agitated saline can be injected intravenously (IV) to enhance the TR jet signal and improve the measurement of the maximum TR jet velocity. The absence of TR precludes pressure assessment via this method. An estimated right atrial pressure (RAP) is

then added to the RV-RA pressure gradient to approximate PA systolic pressure. Thus, PASP≈4v2+ estimated RA pressure. [11, 76, 77]

When all “conditions” required for this method are met-namely sufficient TR for interrogation, proper Doppler alignment, optimal visualization of the peak of the TR jet, and accurate RAP estimation–this method indeed correlates strongly with invasive PA systolic pressure assessment.[12, 13]. However, one or more of these limitations frequently occur in clinical practice leading to varying degrees of discrepancy between Doppler and invasive pressure. Clinicians experienced in assessing patients with PH will attest to the limitations of the Doppler pressure estimate, and recognize that the Doppler PA systolic pressure estimates should not be viewed as synonymous with invasive pressure recordings. Fisher et al. examined the correlation between Doppler estimated and invasively measured PA systolic pressure in a cohort of 65 patients with more severe pulmonary hypertension (62% with pulmonary arterial hypertension).[14] Although the correlation between Doppler and invasive PA systolic pressure measurements was reasonable ($r=0.66$; $P<0.001$), Bland-Altman analysis revealed that 48% of patients had a Doppler-estimated PA systolic pressure that was at least 10 mmHg different from the catheterization (16 underestimates, 15 overestimates). Pressure overestimations arose from either overestimation of the peak velocity signal or an overestimated RAP arising from IVC diameter and collapsibility assessment (vide infra). The magnitude of underestimation (–30 mmHg) was significantly greater than the degree of overestimation (+19 mmHg), with the underestimates leading to more frequent and marked misclassification of the degree of PH. Subjects with Doppler pressure underestimation had lower quality TR Doppler signals, leading to peak velocity (and thus pressure) underestimation . Of note, of the 6 subjects in the study with no TR, 4 of these patients had pulmonary hypertension by catheterization. Thus, the absence of TR is not sufficient to exclude significant PH, even though it typically denotes a more compensated right ventricle. Twelve of the 16 patients in whom PA pressure was

underestimated by doppler had evidence of RV enlargement and/or dysfunction on their DE exam. Multiple studies have now shown a

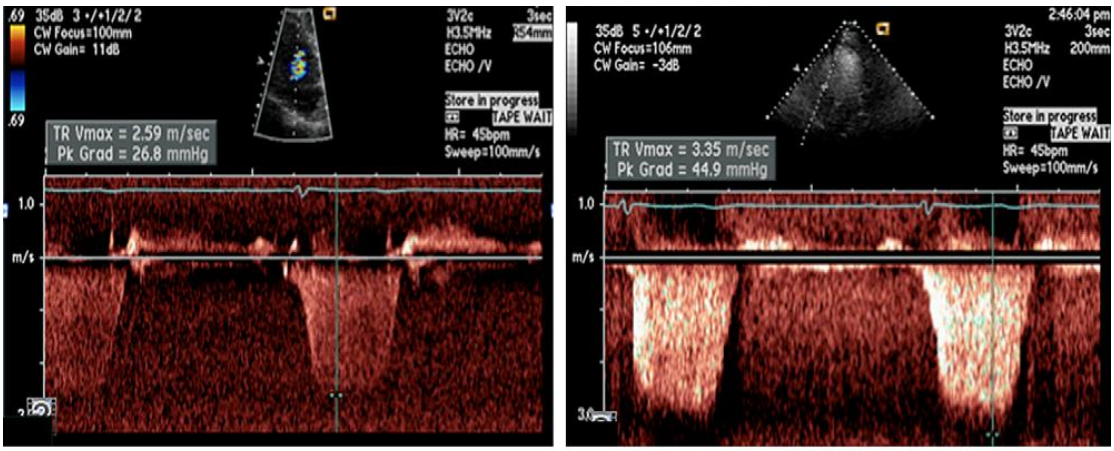

Figure 2 (A) Tricuspid regurgitation signal that is not contrast enhanced and correctly measured at the peak velocity. (B) After contrast enhancement, the clear envelope has been obscured by noise, and the reader erroneously estimated a gradient several points higher. As this example shows, it is critical that only well-defined borders be used for velocity measurement, as slight errors are magnified by the second-order relationship between velocity and derived pressure.91

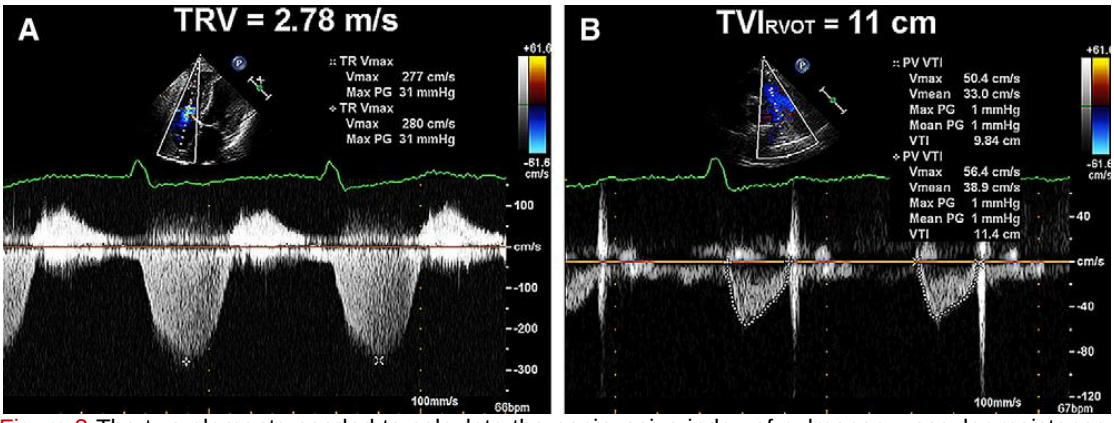

Figure 3 The two elements needed to calculate the noninvasive index of pulmonary vascular resistance (PVR) are found in this example. The ratio of peak tricuspid regurgitant velocity (TRV) (2.78 m/s) to the time-velocity integral (TVI) (11 cm) in the right ventricular outflow tract (RVOT) is abnormal at 0.25 (normal, #0.15). The estimated PVR is 2.68 using the formula (TRVmax/RVOT TVI) _ 10 +0.16.84 Adapted with permission from J Am Soc Echocardiogr.93

misclassification or improper estimation of PASP ranging from 48-54%.[15,16] (figure 2, 3).

A variety of techniques have been used to estimate RAP, most often using the inferior cava dimensions and/or the degree of IVC collapsibility with inspiration or “sniff.” None of these techniques have proved particularly accurate, with RAP overestimation being the more frequently observed limitation. In fact, an overestimated RAP was the primary source of error in nearly 50% of the subjects with an overestimated PASP.[14,17,18] The relative inaccuracy of the IVC-estimated RAP relates to a number of factors, including the fact that IVC dilatation and collapsibility are dictated not only by the intravascular distending pressure, but also by the relative compliance of the IVC, the degree of chronic remodeling of the IVC, and also the relative degree and transmission of the fall in pleural pressure to the vena cava. Recently, Utsunomiya et al. compared right atrial pressure estimates obtained via the ratio of tricuspid inflow E wave velocity to the tricuspid annular tissue Doppler E wave velocity (E/Ea) with near simultaneous invasive pressure values in 50 patients with chronic PAH. The echo measured E/Ea had a reasonable correlation to RHC measured mean RAP (r=0.80), with most error arising from echocardiogram overestimation. Given the significant variation in these methods, we prefer to add the clinically estimated right atrial pressure from the jugular venous pressure examination to the Doppler derived transtricuspid gradient in order to obtain the most accurate PA systolic pressure estimate. The Doppler pressure estimate should not be viewed as a “stand alone” test in the assessment of a patient with known or suspected pulmonary vascular disease. Rather, the Doppler pressure estimate should be integrated into the context of the remainder of the examination; if the Doppler examination estimates mild pulmonary hypertension in the context of moderate RV enlargement and systolic dysfunction, it is more likely that the pressure has been underestimated and a right heart catheterization should be performed. In contrast, borderline or mild pulmonary hypertension in the context of normal RV size, shape and systolic function often is associated with a false positive diagnosis of pulmonary hypertension. [17,18,19,]

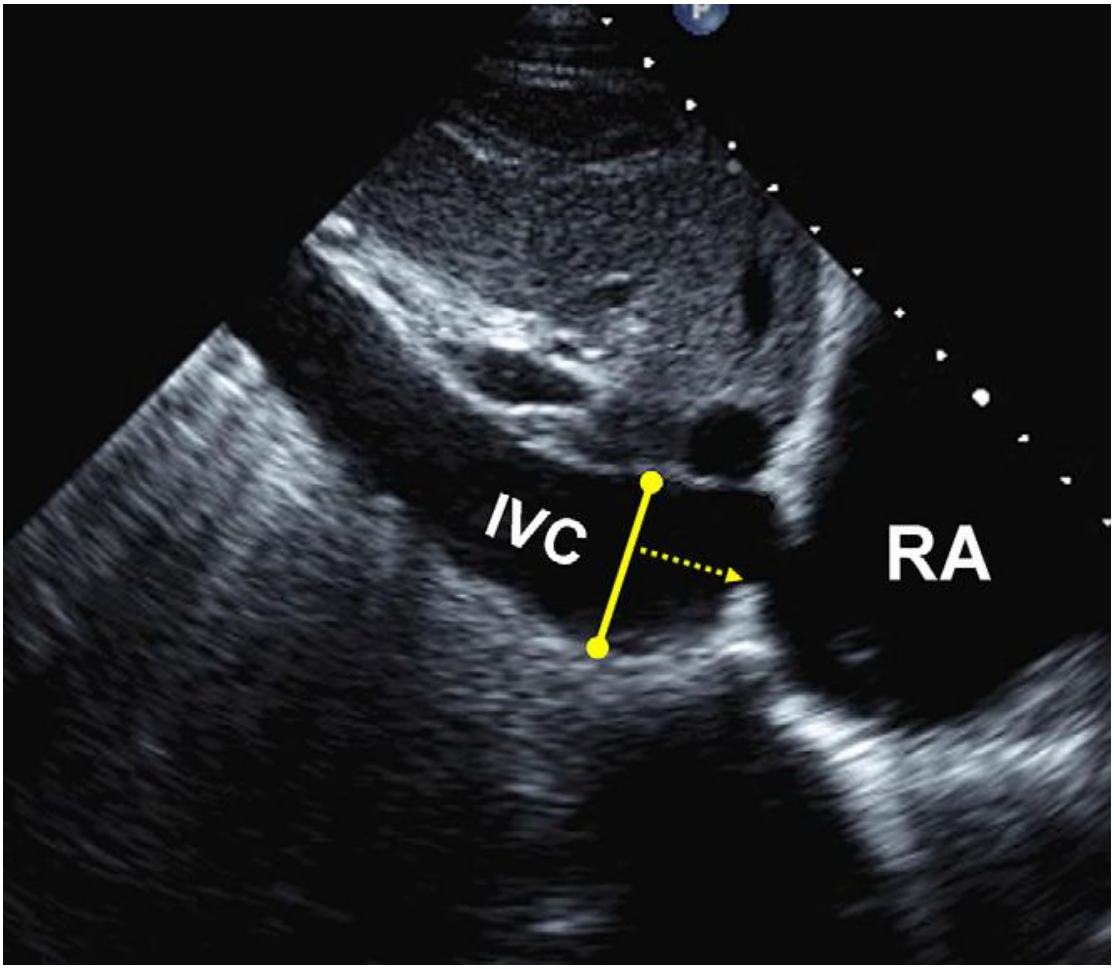

Figure 4 Inferior vena cava (IVC) view. Measurement of the IVC. The diameter (solid line) is measured perpendicular to the long axis of the IVC at end-expiration, just proximal to the junction of the hepatic veins that lie approximately 0.5 to 3.0 cm proximal to the ostium of the right atrium (RA). 92