Editorial Commentary on Right Ventricular Dysfunction

Peri-operative right ventricular dysfunction—the anesthesiologist's view

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Introduction

Recent years have seen an increasing number of adult and pediatric patients with right ventricular dysfunction (RVD) presenting for both cardiac and non-cardiac surgery.

Right ventricular dysfunction is broadly defined as abnormal RV structure or function (1,2). Inclusive in this definition is consideration of the coupling between the RV and the pulmonary vascular bed. The etiologies of RVD are diverse with acute, acute-on-chronic and chronic subsets and can be summarized as follows (2):

(I) RV pressure loading pathologies such as precapillary pulmonary hypertension (PH), moderate to severe RV outflow tract obstruction/pulmonary stenosis, acute lung injury/acute respiratory distress syndrome, massive pulmonary thromboembolism, postcapillary PH due to elevated left atrial pressure from left heart systolic or diastolic dysfunction, or valvular disease (mitral, aortic);

(II) RV volume loading caused by congenital heart disease lesions or valvular pathologies such as large left to right intracardiac shunts (usually pre-tricuspid shunts such as large atrial septal defect), Epstein's anomaly [tricuspid regurgitation (TR)], and repaired tetralogy of Fallot with free pulmonary regurgitation;

(III) Impaired RV contractility associated with cardiomyopathies, ischemia, single ventricle physiology, left ventricular assist devices (LVAD) and post-cardiotomy states.

Independent of the underlying pathophysiology, RVD is associated with poor clinical outcomes (2) and there is increasing recognition that peri-operative management of patients with RVD is challenging. With expanded therapies for PH and congenital heart disease and advanced technologies for mechanical support of the failing left ventricle (LV), anesthesiologists are likely to encounter more patients with RVD. This article highlights strategies to recognize, risk stratify, prevent and treat peri-operative RVD.

Pre-operative assessment

Successful pre-operative assessment of RV function requires a multi-modal approach with trending of clinical symptoms and signs, hematological, hemodynamic, and imaging parameters (2).

Clinical profile

Right heart failure (RHF) as strictly defined is "*a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to sub-optimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures at rest or with exercise*" (3). Consequently, while RV systolic dysfunction is an important cause of RHF, RHF can be present in the absence of RV systolic dysfunction due to volume or pressure overload lesions or RV diastolic dysfunction.

Assessment of recent clinical changes is important in assessing disease progression. Symptoms and signs of

Table 1 Pre-operative assessment of RV failure illustrating some "red-flag" indicators

Red flag indicators	Adult	Infant/child
Symptoms	Fatigue/exercise intolerance/dyspnea on exertion	Fatigue/inability to keep up with peers/long naps
	Pre-syncope or syncope	Syncope
	Feeding intolerance	Feeding intolerance/diaphoresis
	Cachexia	Poor growth curve
Signs	Tachycardia/S3 gallop/parasternal heave	Tachycardia/S3 gallop/parasternal heave
	Tachypnea	Tachypnea
	Elevated JVP	Peri-orbital/ankle/presacral edema
	Ankle/presacral edema	Abdominal distension/ascites
	Abdominal distension/ascites	Hepatomegaly
	Hepatomegaly	
Serum markers	Elevated plasma Cr, Bilirubin/BNP/NT-proBNP	Elevated plasma Cr, Bilirubin/BNP/NT-proBNP
ECG	Sinus tachycardia	Sinus tachycardia
	Atrial arrythmias	Atrial arrythmias
Echocardiography parameters	IVS bowing (end-systole or end-diastole) into LV	IVS bowing (end-systole or end-diastole) into LV
	RVFAC <25%	RVFAC <25%
	TAPSE <1.4 cm	TAPSE <2SD of age-related values
	RV longitudinal strain ≤–15%	RV longitudinal strain

RV, right ventricular; JVP, jugular venous pressure; Cr, creatinine; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECG, electrocardiogram; IVS, interventricular septum; LV, left ventricle; RVFAC, right ventricle fractional area change; TAPSE, tricuspid annular plane systolic excursion.

early RHF such as fatigue and exercise intolerance may be non-specific and difficult to identify, especially in the pediatric population who may be unable to verbalize abnormal sensations or in the older adult with associated co-morbidities. Clinical manifestations of more advanced RHF (*Table 1*) include peripheral edema, elevated jugular venous pressure (JVP), RV parasternal heave, hepatomegaly, right sided S3 gallop, holosystolic murmur at the left lower sternal border, abdominal discomfort and bloating, ascites, pleural effusions, right under quadrant pain from liver capsule stretch and poor growth curves in children. Patients with severe RHF may appear malnourished, tachypneic and cyanotic and are frequently in a state of vasodilation, interstitial fluid leakage, systemic inflammation and fever in the absence of infection (2). Systemic venous congestion may be harder to recognize in children than adults because extracellular fluid may not accumulate in obvious places like ankles, JVP can be difficult to interpret and sudden weight gains from fluid overload may be attributed to normal somatic growth (4). End organ effects of chronic right heart dysfunction are related to elevated central venous pressures with or without reduced cardiac output and include cardiorenal syndrome and cardio-hepatic syndrome. Splanchnic venous congestion and abnormal lymph flow can cause interstitial edema, reduced gastro-intestinal absorption and malnutrition. Increased intra-abdominal pressure may also contribute to renal failure (2). Hemodynamic studies have shown that venous congestion is more common than reduced cardiac output in children and adults with end-stage heart failure listed for heart transplant, with a consistent relationship between elevated right atrial pressure (RAP) and renal failure (4). Pre-operative laboratory studies may show elevated blood urea or creatinine (Cr) or altered hepatic synthetic function such as elevated prothrombin time. In chronic RHF, transaminases may be normal or minimally elevated whereas in acute RHF they are commonly high. Markers of cholestasis such as elevated bilirubin, gamma-glutamyl

transpeptidase and alkaline phosphatase are independently associated with mortality in patients with heart failure and hyperbilirubinemia is a risk factor for poor outcomes in patients with PH (2). Protein losing enteropathy (PLE) may be seen with decreased serum albumin and increased stool alpha 1 antitrypsin (2).

Biomarkers

Risk stratification may be enhanced by inclusion of plasma biomarkers as part of the pre-operative assessment. The biomarkers currently receiving attention are those associated with myocardial stretch (brain type natriuretic peptide), myocardial fibrosis (galectin-3), and myocardial injury (high sensitivity troponin T) (5). Expert consensus guidelines recommend measuring brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) for diagnosis and prognosis in left heart failure and galectin-3 for added risk stratification (6). Elevated pre-operative BNP has been shown to be a strong predictor of major adverse cardiac events after non-cardiac surgery (7,8). Glomerular filtration rate (GFR) must be considered in the interpretation of BNP and NT-proBNP since reduced GFR levels results in elevation of NT-proBNP out of proportion to elevation of BNP (9). Despite this, when appropriate cut-off points are utilized, baseline elevation of BNP in renal dysfunction still have high prognostic value for detection of LV failure. High sensitivity troponin T is minimally affected by a patient's renal function and is thought to reflect the pathophysiology of heart failure on a longer timescale (5,9). Although the role for biomarkers has not yet been established in RHF, studies have shown that NT-proBNP may have prognostic value for RHF accompanying PH (10) and acute pulmonary embolism (11).

Non-invasive imaging

Transthoracic echocardiography (TTE) remains the first line non-invasive imaging tool for pre-operative assessment. Some useful parameters include (12):

(I) RV afterload such as pulmonary artery systolic pressure (PASP) using peak velocity of TR jet and simplified Bernoulli equation;
(II) RV systolic functional indices such as tricuspid annular plane systolic excursion (TAPSE), right ventricle fractional area change (RVFAC) and tricuspid annular systolic velocity by tissue doppler;
(III) Variables of ventricular interdependency such as analysis of septal curvature. LV eccentricity index is the ratio of LV vertical to horizontal diameter measured from a short axis view of the LV at the mid-papillary level (e.g., parasternal short axis). D shape LV and eccentricity index >1 at end diastole reflects RV volume overload whereas at end systole it reflects RV pressure overload;
(IV) Deformation indices such as RV longitudinal strain and strain rate by speckle tracking technology.

Reference values for echo parameters exist for both adults and children (13). Limitations of TTE include suboptimal image acquisition due to the complex RV geometry and its retrosternal position. Functional parameters measured are dependent on preload and angle of insonation and significant intra-observer variability exists in their acquisition. That said, deformation indices are less load dependent and RV longitudinal strain is emerging in the adult population as an independent prognostic marker in PH (14), an independent predictor of RV failure for LVAD implants (15,16) and a predictor of the need for high post-operative vasoactive support (17).

Due to the limitations associated with TTE, multiparametric echocardiographic approaches to RV assessment are proving to be more useful than over-reliance on any single index (18). An example is TAPSE which reflects systolic RV longitudinal function but does not take into account radial systolic function of the RV or segmental RV contraction (12). Radial systolic function is believed to play an important part in RV contractility in PH and can be severely impaired in severe PH patients despite a normal measured TAPSE. Combining TAPSE with afterload parameters in children to obtain a TAPSE/PASP ratio has recently been shown to be superior to TAPSE alone in differentiating patients with different NYHA functional class (FC)/modified Ross scores (18).

Despite advances with echocardiography, including an increased use of 3D echocardiography for volumetric parameters, cardiovascular magnetic resonance imaging (cMRI) remains the gold standard for quantitative non-invasive measurement of RV volume, function, mass, blood flow and tissue characterization including children with congenital heart disease (2). In contrast to most adults, young children and those with psychomotor delay may be unable to tolerate a cMRI without sedation or general anesthesia which can limit the feasibility of this investigation in hemodynamically marginal children. A more in-depth review of non-invasive imaging is discussed elsewhere in this journal (19).

Clinical prediction scores for RVD

Right ventricular dysfunction negatively impacts post-operative outcomes after cardiac surgery both in adults (20,21) and congenital heart disease patients (22-24). Recent studies have also shown that RVD is independently associated with major adverse cardiac events and a longer hospital stay in patients undergoing non-cardiac surgery (25). However, current pre-operative risk assessment for non-cardiac surgery in adults still focus on left heart dysfunction and do not incorporate markers of RV function. Contemporary publications addressing risk assessment scores for the pediatric population undergoing non cardiac surgery (26-28) as yet have not incorporated indices of RV function. One of the obstacles to incorporating RV function into risk stratification scores is the complexity, heterogeneity and lack of a universal definition for RVD which makes it difficult to compare or validate risk scores.

The majority of data on clinical prediction scores for RVD in both adults and children comes from two patient cohorts: (I) RVD associated with PH and (II) RVD in LVAD supported patients.

RVD associated with PH

Risk stratification scores from global adult PH registries have identified six consistent high yield variables indicative of deteriorating RV function (29): WHO FC, 6-minute walk distance (6MWD), NT-proBNP/BNP plasma levels, cardiac index, RAP and mixed venous oxygen saturation (SvO_2). However, the majority of adult scoring systems do not incorporate age, underlying cause of PAH, co-morbidities, echocardiography or cMRI.

Variables which identify high risk pediatric PH patients include, WHO FC III/IV, clinical evidence of RV failure, syncope, mean pulmonary arterial pressure (mPAP)/mean systemic arterial pressure (mSAP) >0.75, RV systolic dysfunction, RAP >15 mmHg, elevated NT-proBNP, TAPSE, age <2 years and complexity/increased duration of procedure/anesthesia (30-32). Although these variables may serve as a guide for the risk of adverse peri-operative events and RV failure none have been formally validated in the peri-operative arena (28). Additionally, the impact of congenital syndromes such as Alagille's or Williams syndrome have yet to be accounted for.

The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) has developed a novel pediatric PH risk score based on variables defining a low- and high-risk group (30). Prospective validation of this novel risk score has commenced in children treated with "off-label" PH-targeted medication already approved for use in adults with PH (33,34).

Experts have suggested that the degree of RV adaptation in PH may be a more accurate predictor of outcomes rather than isolated measurements of PA pressure in both the adult and pediatric PH population (23). RV adaptation in PH initially involves coupling of the RV to the high arterial load (*Figure 1*) and is maintained by increasing contractility and wall thickness followed by RV dilation and finally RV uncoupling (35). In PH when RV-PA coupling is still present, volumetric data such as right ventricular end diastolic volume (RVEDV), right ventricular end systolic volume (RVESV) and stroke volume (SV) may provide important prognostic information but needs further validation from large scale studies (35). Emerging studies have also recommended the ratio of TAPSE/PASP as a reflection of the extent of ventriculo-arterial uncoupling since TAPSE indicates RV contractile function and PASP a marker of RV afterload (2,18,36).

RVD in LVAD supported patients

Approximately 20–30% of patients (37,38) develop RVD after LVAD implantation. Currently no consistent identifiers can predict which patients will develop RVD.

Published literature addressing clinical prediction scores of RHF after LVAD implant includes parameters such as pre-implant age, vital signs, invasive hemodynamic metrics, echo parameters (e.g., TAPSE and TAPSE/RVEDV) mechanical ventilation, Cr and total bilirubin (16,37,38). RV longitudinal strain has been reported by several independent groups as a strong independent predictor of RV failure (15,16). However these scores only have modest performance in validation cohorts (16) and currently do not account for the heterogeneity of populations studied and dynamic intra-operative factors that increase pulmonary vascular resistance (PVR) and precipitate acute right heart dysfunction such as blood product transfusions, hypoxemia, acidosis, positive pressure ventilation, RV-LVAD interactions and change in RV volume loading and geometry with LVAD implantation (2,38). Recently, there has been interest in the use of the pulmonary artery pulsatility index (PAPi) as a predictor of RVD following LVAD placement. Pulmonary artery pulsatility index is

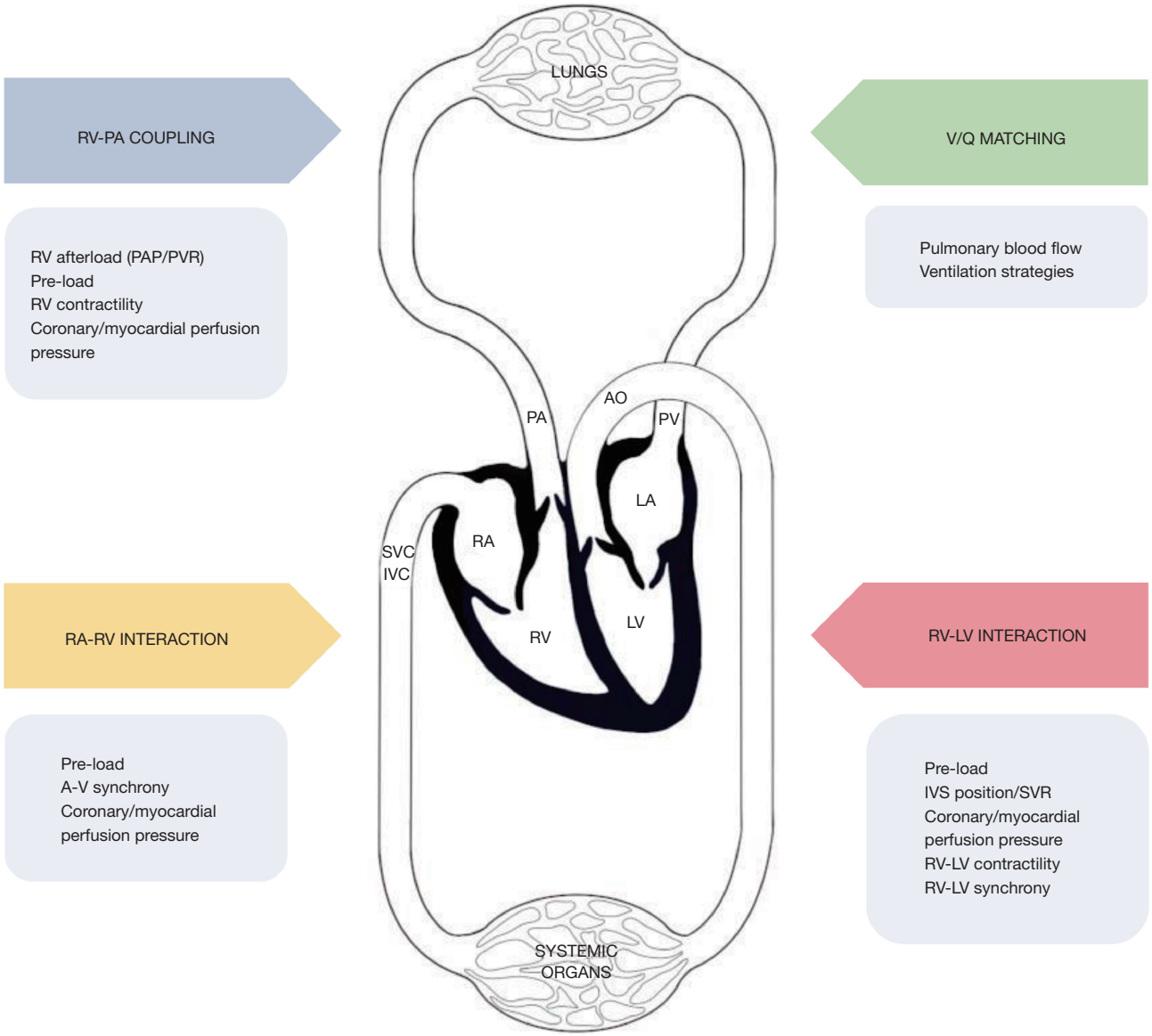

Figure 1 Targets for peri-operative management of RVD. The figure illustrates a simplified diagram of the right heart as an integral part of the cardiopulmonary unit and depicts factors which should be optimized as part of targeted strategies for peri-operative management of RVD. RVD, right ventricular dysfunction; RV, right ventricle; PA, pulmonary artery; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; A-V, atrio-ventricular; V/Q, ventilation/perfusion; IVS, interventricular septum; SVR, systemic vascular resistance; LV, left ventricle.

defined as [(PA systolic pressure – PA diastolic pressure)/ mean RAP]. A PAPi <1.85 has 94% sensitivity and 81% specificity for identifying RVD post-LVAD placement in adults (39,40). A cut-off point for this parameter in children has not been established, and PAPi may be "artificially high" when severe pulmonary regurgitation is present.

RV diastolic dysfunction

Only a few studies have assessed the importance of RV diastolic filling profiles in cardiac surgery (20). Although abnormal pre-operative RV diastolic profiles were associated with difficult separation from CPB (41), the independent

value of RV diastolic function in cardiac surgery has not been clearly defined and may change depending on the underlying pathophysiology. In Tetralogy of Fallot, a restrictive RV filling profile is associated with low cardiac output state and longer ICU stay immediately post repair. However, in the long-term, restrictive RV diastolic function counteracts the effects of chronic pulmonary regurgitation and is associated with smaller RV, shorter QRS and increased exercise tolerance (20). Patients with single ventricle palliation are predisposed to diastolic ventricular dysfunction although the pathophysiology remains poorly understood and early detection is difficult (42). Diastolic and systolic dysfunction in the single ventricle physiology are thought to be closely intertwined (42). Clinical signs and symptoms of heart failure may manifest in a single ventricle palliation with progressive diastolic dysfunction even if contractility remains unchanged due to decreased stroke volume and a lower tolerance to increased end-diastolic pressures (42). A more in-depth review of RVD in congenital heart disease is found elsewhere in this journal (24).

Peri-operative management

The goals of successful peri-operative management include identifying patients at risk for RVD and employing risk mitigating strategies. Multidisciplinary discussions are vital in determining the risks and benefits of the procedure specific to the individual patient, determining optimal timing for non-urgent surgery, ensuring adequate pre-operative optimization, planning post-operative care and discussing feasible exit strategies should complications occur. Rescue strategies for decompensation include extra-corporeal membrane support, percutaneous RV assist devices and paracorporeal RV assist devices such Levitronix CentriMag (Abbott, Chicago, IL, USA).

Patients may be on a variety of medications depending on their underlying pathology, age and associated co-morbidities. Consideration should be given as to whether to continue these medications through the peri-operative period. Angiotensin-converting enzyme (ACE) inhibitors may cause profound vasodilatory hypotension in conjunction with anesthesia medications and it is advisable to withhold them 12–24 hours prior to surgery whereas chronic pulmonary vasodilator therapy such as sildenafil, endothelin receptor antagonists (ERA), and prostacyclin analogs should be maintained throughout the peri-operative period. Consideration should be given as to whether the patient's clinical condition can be pre-optimized in the days or weeks prior to non-urgent procedures. Examples include pre-operative initiation of pulmonary vasodilators in untreated patients with PH, optimizing diuretic therapy or commencing inodilators such as milrinone or levosimendan in patients with significant venous congestion.

A pre-operative reduction in PVR or mPAP with inhaled pulmonary vasodilators indicates a reversible element to RV afterload and is a predictor for improved post-operative performance (43). Vasoreactivity testing for patients with isolated post-capillary PH may provoke pulmonary edema from increased LAP. However as post-capillary PH progresses, some patients develop small vessel disease and have mixed pre- and post-capillary PH and may also benefit from a pulmonary vasodilator (44).

There is no ideal anesthesia agent or technique and a variety of balanced multimodal regimes have been described in the literature (23). The physiologic goals, regardless of technique, are as follows:

(I) Decreasing RV afterload while maintaining RV preload, RV contractility and RV perfusion;
(II) Maintaining sinus rhythm, atrial contraction and atrio-ventricular (A-V) node synchrony;
(III) Maintaining LV output, interventricular septum (IVS) position and avoiding RV dilation;
(IV) Avoiding the vicious cycle of systemic hypotension and RV ischemia.

Management of positive pressure ventilation in a patient with RVD is challenging and in some instances spontaneous ventilation can be maintained with the caveat that factors that may increase PVR such as hypoventilation, hypoxia, hypercarbia, atelectasis, airway obstruction and respiratory acidosis must be avoided. When positive pressure ventilation is initiated the goal is to prevent mechanical obstruction to pulmonary blood flow and a precipitous increase in RV afterload and reduction in preload during the inspiratory phase (45,46). Ventilatory parameters such as inspiratory: expiratory ratios (I:E time), tidal volume (PVR increases at high and low lung volumes), respiratory rate, and positive end-expiratory pressure (PEEP) should be optimized to generate the lowest possible mean airway pressure compatible with the desired lung recruitment, minute ventilation and gas exchange. The change from spontaneous ventilation to positive pressure ventilation is a critical time that requires vigilance and attention to detail. In patients previously known to be responsive to inhaled pulmonary vasodilators such as inhaled iloprost or nitric oxide, peri-intubation administration of these agents should be considered.

Adequate peri-operative monitoring is essential for early detection and treatment of RHF. Consideration should be given to placing a pre-induction arterial line for high risk patients and TTE during anesthesia induction can be useful to monitor RV dilation, IVS position and LV function especially during the transition from spontaneous to positive pressure ventilation. Since increases in central venous pressures may indicate RV failure, there should be a low threshold for placement of central venous catheters especially for longer or more complex procedures with anticipated fluid shifts and in selected cases pulmonary artery pressure catheters (PAC) can be useful.

Near infrared spectroscopy (NIRS) offers a non-invasive measurement of regional mixed arterio-venous oxygen saturation and is used for cerebral and somatic oximetry during the perioperative period. NIRS trends can be used as a surrogate marker of adequacy of blood flow to the brain and has been used to assess somatic tissue oxygen delivery when placed over the kidneys.

Focused transthoracic or transesophageal echocardiography is an important intra-operative diagnostic tool for any hemodynamically unstable patient (47). Echocardiographic indicators for peri-operative RV failure include signs of RV dilation (e.g., systolic or diastolic D shaping, moderate-severe TR), signs of impaired RV systolic function (e.g., TAPSE, RVFAC), and signs of elevated RV preload (e.g., plethoric IVC) (47). Acquisition of quantitative parameters can be time consuming and technically challenging in the operating room. Some experts have suggested that physicians should also be familiar with qualitative echocardiography assessment of RV dilation and function acknowledging that there may be a steep learning curve associated with acquiring this skill set (47).

Any systemic hypotension should be aggressively treated with judicious use of fluids and vasoactive medications to avoid the downward spiral of hypotension and RV ischemia. There is currently insufficient evidence to show superiority of one inotrope over another but first line agents to rapidly stabilize hemodynamics include epinephrine, dopamine and dobutamine. Some patients may benefit from initiation of vasoactive infusions prior to anesthesia induction (e.g., epinephrine or vasopressin). Inotropes such as epinephrine or dobutamine will increase RV contractility but may induce tachycardia which may impair diastolic filling and coronary perfusion. Vasopressor therapy such as norepinephrine, vasopressin, or terlipressin may be indicated to increase SVR, reduce leftward septal shift and improve tissue perfusion, including coronary/myocardial blood supply. Vasopressin has a theoretical advantage of being a selective systemic vasopressor and is not believed to increase PVR (48) as opposed to norepinephrine and epinephrine which can increase PVR at high doses. Inodilators such as milrinone or the calcium sensitizer levosimendan may be useful once hemodynamics have stabilized or as part of pre-optimization but are not first line therapy in the setting of systemic hypotension.

Tachyarrhythmias seen in association with RVD include sinus tachycardias, atrial fibrillation and atrial flutter. Cautious rate or rhythm control should be attempted, in addition to treatment of RV failure and its underlying cause (47). Bradyarrhythmias associated with RVD usually signify a pre-terminal event or severe ischemia of conduction system and should be treated immediately.

Post-operative management

After patients leave the operating room they remain at risk for adverse events and require vigilant monitoring of their oxygenation, ventilation and perfusion pressure. Appropriate monitoring of RV function and early detection of RV failure (including decreased forward flow and venous congestion) in the ICU remains challenging. PAC remains a useful modality in the adult population. Optimizing post-operative RV function involves balancing fluid titration with fluid restriction, optimizing heart rate and rhythm, maintaining normal acid-base status, avoiding positive pressure ventilation and hypoxia, adequate analgesia, temperature management and early use of pulmonary vasodilators and inotropes.

Conclusions

Peri-operative management of patients with significant RVD can be very challenging. Thorough pre-operative assessment, risk stratification and multi-disciplinary planning is essential for successful outcomes. Understanding the right heart as an integral part of the cardiopulmonary unit (*Figure 1*) with assessment of factors affecting inter-ventricular interactions, ventricular-arterial coupling, ventilation-perfusion matching and atrio-ventricular interactions should help the anesthesiologist formulate targeted peri-operative strategies.

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Footnote

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