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Right ventricular performance in the cardiac surgical patient

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Right Ventricular Performance in the Cardiac Surgical Patient

Inge Tjitske Bootsma

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Right ventricular performance in the cardiac surgical patient

PhD thesis

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“Being intelligent—being good with numbers, or being well educated, or even winning a Nobel Prize—is not a shortcut to global factual knowledge. Experts are experts only within their field.”

– Hans Rosling

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Chapter 1

Introduction

INTRODUCTION

THE RIGHT VENTRICLE IN HISTORICAL PERSPECTIVE

Historically, the right ventricle (RV) had been considered a non-essential part of the cardiovascular system. In the 1940s, severe damage to the RV or even surgical removal of the RV free wall did not result in consequences on the performance of animals in daily life.^{1,2} In the clinical setting, patients with a Fontan circulation have a completely bypassed RV but often manage to lead a nearly normal life.³ Both these experimental and clinical settings gave the impression that the RV has only one function: to conduct the blood from the venous circulation to the lungs. The paradigm was that when the RV failed to conduct, the contractile action of the LV could continue to maintain RV output.

THE RIGHT VENTRICLE AS A PART OF THE CARDIOVASCULAR SYSTEM

Further research emphasized the true significance of the RV. These studies revealed that the RV does not only conduct blood, but plays an essential role in maintaining low pressure in the venous system.⁴ In addition, the importance of the interaction between the left and right ventricle gained more attention. The RV and left ventricle (LV) share muscle fibres, the intraventricular septum, and the pericardium. The pericardium is highly resistant to acute distension, which means the intrapericardial volume is more or less fixed. The size, shape, and performance of one ventricle are therefore influenced by those of the other ventricle.⁵ Negative consequences of this ventricular interaction manifest only in disease states. RV pressure or volume overload can result in dilation of the RV. A closed pericardium decreases

Figure 1: Vicious circle of RV dysfunction and failure

the LV size due to the bulging of the intraventricular septum into the LV cavity, resulting in a diminished cardiac output and this may end up as a vicious circle.⁶ (Fig 1.) With a better understanding of the connections of the RV with the pulmonary circulation, venous return, atria, and left ventricle, the RV was more and more seen as a part of the whole cardiovascular system instead of a rudimentary conduit and the amount of research on the RV steadily increased over time.

ASSESSMENT OF RIGHT VENTRICULAR PERFORMANCE

One challenge in research on RV function is the accurate assessment of RV performance. This is due to the complex anatomy of the RV. In contrast to the more or less circular shape of the LV, the RV is triangular

in shape when observed from a lateral view, and has a crescent shape in its cross-sectional view. The RV can be divided into three functional components: the inlet, the trabeculated myocardium, and the outlet (infundibulum or conus). All of these three sections contract in their own way. This makes the RV technically difficult to image and analyse.⁷ Angiography, nuclear imaging, CT, MRI, echocardiography, and invasive haemodynamic measurement using pulmonary artery catheters (PAC) can all be used to obtain and quantify RV performance. Although cardiac MRI is the current gold standard for anatomical and functional assessment of the right ventricle,^{8,9} echocardiography and PACs are better tools for monitoring RV function at the bedside and during surgery. Transthoracic or transesophageal echocardiography allows visualization of structural components of the heart and great vessels, and might play an important role in the diagnosis of structural deviations. However, assessing RV function with echocardiography is difficult and might be unreliable due to higher interobserver agreement, limited image quality, and single spot measurements.^{10,11} The only tool that can continuously assess and monitor RV function at the bedside is the PAC. The contemporary PAC can measure multiple values: the pulmonary artery pressure, cardiac output, right atrial pressure, right ventricular pressure, right ventricular end-diastolic volume, right ventricular ejection fraction, mixed venous oxygen saturation, wedge pressure, stroke volume, and body core temperature. Despite its invasive character, monitoring with the PAC appears to be safe and has been a widespread monitoring device in the operation room and intensive care units.¹²⁻¹⁴

THE CLINICAL IMPORTANCE OF THE RIGHT VENTRICLE

Present-day research on RV assessment and monitoring remains a challenge. The studies that have been conducted on RV function in the past were very diverse in the ways in which the research was conducted, in the medical conditions of their subjects, and in the tools and methods they used to establish their data. This makes that the result of these studies incredibly difficult to compare to one another. Moreover, despite the amount of research on this subject, there is a lack of universal nomenclature and definitions describing the RV function. Despite these challenges, there is substantial agreement that RV dysfunction is associated with higher morbidity and mortality.¹⁵⁻²² Initially, research focused mainly on right ventricular impairment combined with impaired LV function, diseases influencing RV afterload (i.e. pulmonary embolism, chronic pulmonary disease and pulmonary arterial hypertension)²³, and diseases of the RV chamber itself influencing the contractility (ischemic heart disease, congenital diseases).^{19,24} Although impaired LV function and pulmonary arterial hypertension are major risk factors for the development of RV failure, there is growing evidence that RV failure might be partially independent of pulmonary haemodynamics or left ventricular function.^{25,26} The number of disease states in which the RV appears to play

an important role is still expanding. These include sepsis, arrhythmogenic RV dysplasia, and certain heart valve diseases.²⁷

Nowadays, RV function appears to play an important role in the cardiac surgical setting as well. However, data on RV function in post cardiac surgical patients are limited to small sample sized studies, mainly performed in patient populations preselected for LV failure or pulmonary hypertension.^{18,28} Although these studies draw attention to the possible relevance of RV function in the perioperative cardiac surgical setting, the incidence, assessment, clinical consequences, aetiology, and adequate management strategies of RV dysfunction in the cardiac surgical population remain still unclear.

THESIS OUTLINE

Since the introduction of the PAC in 1971²⁹, the classical PAC evolved into a monitoring tool that provides continuous data on cardiac output, oxygen supply and-demand balance, as well as right ventricular (RV) performance. Successful application of the PAC in clinical practice requires a thorough understanding of measurements obtained from the PAC. In **chapter 2** a detailed review is provided on the placement, waveform analysis, measurements, limitations, and clinical application of the contemporary PAC.

Using the PAC as a monitoring device, we primarily aimed to establish the incidence of RV dysfunction and the possible association between RV function and mortality in a heterogeneous high-risk cardiac surgery population. The results of this study are described and discussed in **chapter 3**.

Since mortality only reflects the burden of cardiac surgery to a limited extent, the prognostic value of postoperative RV function in relation to markers of morbidity seems equally relevant. Data on this topic are provided in **chapter 4**.

As the aetiology of RV failure in the setting of cardiac surgery often remains unclear, a prospective observational trial was conducted in which ultrasound-derived RV parameters were assessed simultaneously with PAC-derived variables of RV function during several pivotal moments in cardiac surgery. This way, we aimed to identify whether a reduction in global RV performance accompanies the well-known decrease in echocardiographic variables that reflect the RV systolic function.^{30,31} In addition we aimed to unravel the critical influence of different surgical processes on RV performance. Results of this study are described in **chapter 5**.

Being aware of the clinical importance of the RV after cardiac surgery, an important issue that remains is the management of RV dysfunction. One of the cornerstones in the treatment of acute RV dysfunction or failure is

increasing systemic pressures and thereby increase coronary perfusion. Since this current practice is predominantly based on experimental studies, it is of interest if such an intervention is also effective in the clinical setting. **Chapter 6** describes the results of a randomized controlled trial of the norepinephrine-mediated effect of high versus normal blood pressure targets on right ventricular function in post-cardiac surgery patients with RV dysfunction.

Chapter 7 is a small step outside the world of RV dysfunction. Haemodynamic monitoring is the foundation of many studies described in this thesis. However, randomized controlled trials fail to demonstrate an improvement in patient outcome as a result of monitoring. Whether or not haemodynamic monitoring improves clinical success depends on far more than mere accuracy and precision of the monitoring device. In order for it to be effectively implemented into therapeutic strategies, it is important to be aware of and understand the factors that might influence haemodynamic monitoring.

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Chapter 2

The Contemporary Pulmonary Artery Catheter

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INTRODUCTION

In 1970 the floating pulmonary artery catheter (PAC) was introduced by Swan and Ganz.¹ The underlying objective of the two physicians was to apply physiologic principles to the understanding of the circulatory abnormalities characterizing an illness in an individual patient, and to provide a rational basis for selection of therapy with objective, quantitative assessment of patient response.¹ The principal stimulus for the development of the PAC was the aim to improve the care and study of acutely ill patients in whom fluoroscopy was not readily available or who were not in a condition to be readily moved to a diagnostic facility.¹ Despite these noble intentions, over time the PAC has predominantly become a topic of debate concerning safety, indication and clinical utility, with the main focus on the potential of the PAC to improve clinical outcome.²⁻⁴ Fuelled by large randomized controlled trials (RCT) that failed to demonstrate any outcome benefit in relation to PAC-use in a large variety of disease states, the verdict on general application in the clinical setting has become predominantly negative.⁵⁻⁸ In spite of this the use of PAC's is still widespread, especially in the fields of cardiology and cardiac surgery.^{9,10} This seeming controversy may be due to the understanding of clinicians on the potential limitations of PAC oriented RCT's, including patient selection, timing and the general absence of a protocolized strategy based on PAC-derived variables.^{5,11-14} However, the most probable explanation might be that clinicians from all over the world value the fundamental understanding of physiological principles in the management of complex disease states.^{15,16} In this respect it remains key to acknowledge that adequate interpretation of PAC-derived data requires both skills and knowledge about the correct use of the device, as well of its pitfalls. The classical PAC evolved from a device that enabled intermittent cardiac output measurements in combination with static pressures to a contemporary PAC, which in turn provided continuous data on cardiac output (CCO-PAC), oxygen supply and demand balance, as well as right ventricular (RV) performance. This CCO-PAC, further mentioned as PAC, is a 7.5 F continuous cardiac output/mixed venous oxygen saturation [SvO₂]/continuous end diastolic volume [CEDV]-pulmonary artery catheter (model 774F75; Edwards Lifesciences, Irvine, CA, USA).

The additional information that comes from these technological innovations is specifically included in this review. First we discuss adequate placement, interpretation of waveforms, as well as pitfalls. Secondly, we highlight measurements of the contemporary PAC including continuous cardiac output measurement, RV ejection fraction, end-diastolic volume index, and mixed venous oxygen saturation. Limitations of all of these measurements are addressed in detail. At last, we aim to provide a concise overview of the characteristics of the currently available PAC-derived measurements and the subsequent integration of these data into clinically relevant scenarios.

PLACEMENT OF THE PULMONARY ARTERY CATHETER

The PAC is introduced via a dedicated sheath during a sterile procedure using the Seldinger technique. Ultrasound guidance during catheter placement is highly recommended.^{17,18} Placement of the sheath can be into either one of the internal jugular veins (IJV), the subclavian veins, or the femoral veins. The right IJV is the favoured site for sheath placement since it provides the most direct route towards the right ventricle. Although subclavian access is associated with fewer infectious complications compared to femoral or jugular access, bleeding complications may have more serious consequences and anatomical location and vessel size vary considerably.¹⁹⁻²¹ Furthermore, ultrasound visualization of the subclavian vein is technically demanding, due to interference by the collarbone.²² After successful placement of the introducer, the PAC can be inserted through the sheath. The PAC is 110 cm in length, marked at 10 cm intervals, and has at least 2 channels. The distal channel at the tip of the catheter allows for transducing pulmonary artery pressure (PAP) and SvO₂ sampling, while the proximal channel is used for measuring central venous pressure (CVP) and central venous saturation (ScvO₂) sampling. A balloon is located just above the tip of the catheter, in which 1.5 ml of air can be inflated once the PAC is inserted beyond the sheath (at least 20 cm). Before placement, in vitro calibration of the SvO₂ should be performed using a photodetector before removal of the catheter from the package. After calibration, the catheter can be connected to the monitor and transducer. Subsequently, both the proximal and distal channel should be flushed and filled with fluid. In case in vitro calibration is not performed, in vivo calibration may be performed after correct placement of the catheter by drawing a blood sample from the distal channel and analysing this sample for SvO₂. It is of note that this calibration process is only applicable for the contemporary PAC and not for the older PAC, which obtains cardiac output from intermittent thermodilution.

Placement of the PAC is guided by the characteristics of vascular pressures and waveforms (Fig. 1). In order to facilitate this, the distal lumen of the catheter should be attached to a pressure transducer. Despite individual variety, specific landmarks are well-related to insertion length, depending on the puncture site. After introduction via the right IJV or the right/left subclavian vein, the right atrium should be reached at approximately 20 cm insertion depth; the right ventricle at 30-35 cm, the pulmonary artery at 40-45 cm, and the wedge position at 50 cm (Fig. 1).²³ For the left IJV one should add 5 cm to each of the previously mentioned landmarks. However, in populations with shorter statures, the insertion length is usually less deep.²⁴ In case of heart failure with dilatation of the RV, or in tall patients, an insertion length of greater than 50 cm might be necessary. When removing the PAC from its packaging, it has a natural curvature which should be pointed towards the heart. Counter clockwise rotation during insertion with an inflated balloon increases the odds of entering the right

atrium and passing the tricuspid valve.²⁵ When the RV waveform does not appear after 40–45 cm of insertion, or if the PAP waveform does not appear after 50–55 cm, the balloon should be deflated and the catheter should be withdrawn until 20 cm with subsequent repetition of the procedure. To facilitate successful placement of the PAC, positioning the patient head-down will aid flotation past the tricuspid valve. In order to facilitate the passage through the pulmonary valve, positioning the operation table or ICU bed with head up (15–20°) and rotated to the right may be helpful.^{23,26} Most catheters float toward the right pulmonary artery catheter. In order to selectively catheterize the left pulmonary artery, the patient should be positioned with the right side down. In the setting of low cardiac output, deep inspiration in non-intubated, spontaneously breathing patients will increase right ventricular output transiently and therefore may facilitate catheter flotation.²³ After correct placement, in vivo calibration should be performed.

Fig. 1 Placement of the PAC guided by the characteristics of normal vascular pressures and waveforms.

* For placement in the left internal jugular vein or left subclavian vein one should add 5 cm to each of the landmarks. CVP central venous pressure. PAC pulmonary artery catheter. PAP pulmonary artery pressure. RVP right ventricular pressure.

ZEROING

Zeroing and leveling of the catheter are a prerequisites to obtaining accurate measurements and both have revealed to be susceptible to error.²⁷ Opening the stopcock to ambient air, the hemodynamic monitoring system will be exposed to atmospheric pressure. After pressing 'zeroing' on the monitor and confirming the calibration, the transducer stopcock can be turned back into its original position. The atmospheric pressure is now the zero-reference point. From there on, only variations in pressures which exist inside the heart chamber or blood vessel will be measured, as long as the position of the pressure transducer remains the same.²⁸

LEVELING

The main goal of leveling the external transducer is to eliminate additional hydrostatic pressure from the fluid column. This hydrostatic pressure is proportional to the height of the fluid column. The level of the transducer should be even with the top of the fluid column in the chamber or vessel in which the pressure is measured.²⁹ The correct position in supine patients is the phlebostatic axis, which is about 5 cm below the sternal angle.³⁰ When patients are in prone or sitting position reference levels might be different.³¹ In case the transducer is placed above the phlebostatic axis, the pressure will be underestimated. Vice versa, the measured pressure will be erroneously high in case the transducer is placed below the phlebostatic axis.

WAVEFORMS OF THE PULMONARY ARTERY CATHETER

RIGHT ATRIAL WAVEFORM

Initially, the PAC is passed through the introducer sheath until it reaches the IJV, the superior vena cava, and the right atrium. Reaching this point, the monitor will depict either a CVP or right atrial pressure waveform, which are considered to be identical. A normal CVP waveform consists of 5 phases; three peaks (a-wave: atrial contraction; c-wave: isovolumic ventricular contraction, tricuspid motion toward right atrium; v-wave: systolic filling of the atrium), and two troughs (x: atrial relaxation; y: early ventricular filling). Identification of CVP waveform components is facilitated by aligning the pressure waveform with the ECG trace. The a-wave follows the ECG P-wave, the c-wave always follows the ECG R-wave and the v-wave follows the ECG T-wave.³² CVP should be measured at the base of the c-wave, just after the R-wave of the ECG, because this represents the final pressure in the ventricle before onset of the systole. If the c-wave is not identified and the patient has sinus rhythm, the base of the a-wave can be used. A normal range in healthy, spontaneously breathing humans in the supine position is between 0 and 10 mmHg (Fig. 1).³³

RIGHT VENTRICULAR PRESSURE WAVEFORM

When advancing the PAC with an inflated balloon through the tricuspid valve, RV pressures will be recorded. The major difference with the CVP characteristics is a marked increase in systolic pressure. A normal RV-waveform is characterized by a steep, rapid systolic slope. Due to the substantial compliance of the normal RV, the diastolic slope is typically horizontal.^{34,35} Diastolic pressure in the RV of a healthy individual is almost equal to zero. End diastolic pressure is measured right before the R-wave on the ECG, before the beginning of the systolic upslope.³⁴ Normal systolic pressure of the RV ranges between 15 and 28 mmHg (Fig. 1).

PULMONARY ARTERY PRESSURE WAVEFORM

By advancing the catheter further with the use of an inflated balloon, the PAC will float across the pulmonary valve into the pulmonary artery, displaying a PAP waveform. The most distinctive feature in comparison to the RV pressure waveform is the increment in diastolic pressure in the pulmonary artery compared to the diastolic pressure in the normal RV (Fig. 2A). This is otherwise known as the diastolic pressure step up.²³ It is of note that this diastolic pressure step up can be minimal in the setting of right heart failure. The PAP waveform consists of 4 phases, the first being a steep, rapid systolic upstroke, which is followed by a systolic peak. In a normal PAP waveform, there should be no significant pressure difference between the peak systolic RV pressure and peak systolic PAP. The normal gradient between systolic RV and PAP is 0 to 3 mmHg.³⁶ The third phase is the dicrotic notch, which represents the closure of the pulmonary valve, and thus the beginning of the diastole. The dicrotic notch always follows the T-wave on the ECG. After the dicrotic notch comes the diastolic run-off, which marks the diastolic phase of the waveform. Normal systolic PAP ranges between 14-28 mmHg, normal diastolic PAP ranges between 5 and 16 mmHg, and normal mean PAP between 10 and 22 mmHg (Fig. 1).

WEDGE POSITION

After further insertion the PAC will finally reach its wedge position. Balloon occlusion stops all distal flow and creates a static fluid column between the tip of the catheter and the junction point of the pulmonary veins and left atrium. The pulmonary artery wedge pressure (PAWP) is believed to reflect both the pressure in the pulmonary veins as well as in the left atrial pressure.³⁷ In general, PAWP and pulmonary artery occlusion pressure (PAOP) can be used interchangeably and both refer to the same measurement. The PAWP waveform usually depicts two pressure peaks: the a-wave and the v-wave, as well as two descents called x and y. The v-wave is generally the most prominent peak. The c-wave is often difficult to discern in a normal wedge pressure trace due to the delayed representation of the left atrial pressure, the damped reflection, and a shorter time interval between atrial and ventricular contraction of the left atrium compared to that of the right atrium.³⁸ It is important to keep in

mind that the PAWP is a delayed representation of the left atrial pressure since the pulmonary vascular bed is positioned between the PAC and the left atrium. In addition, PAWP is also a damped reflection of phasic atrial pressure waves. The amount of damping is variable; however pressure peaks can potentially be significantly underestimated.³⁹ As a result of this time lag, the a-wave of the wedge pressure will be visualized shortly after the R-wave on the ECG, although the a-wave represents the end-diastolic phase.³⁸ Since the wedge position of the balloon does not stop flow in the antegrade direction completely, PAWP is always lower than the mean PAP. After reaching the wedge position the balloon should be deflated and not advanced any further. After deflating the balloon, the PAP waveform should re-appear. If not, the catheter should be retracted for about 2 cm. PAWP should be measured at the end of the a-wave or before the QRS complex, at the end of the expiration, when pleural pressures are minimal, and should ideally be recorded as the mean of three measurements. However, most devices provide digitized mean PAWP. A normal range is between 5 and 12 mmHg (Fig. 1).⁴⁰

INTERACTION WITH WAVEFORMS

CATHETER POSITION

In the human lung there are 3 zones, called the West zones, each with a different physiology. In West zone 1 (apex), alveolar pressure exceeds the pulmonary artery and pulmonary venous pressures. In West zone 2 (central), the alveolar pressure exceeds only the pulmonary venous pressure, and in West zone 3 (base) the alveolar pressure is lower than both the arterial and venous pulmonary pressures (Fig. 3).⁴¹ When the alveolar pressure exceeds the pulmonary vein pressure in West zone 1 or 2, the pressure derived at the tip of the PAC is the alveolar pressure instead of pulmonary venous pressure (or left atrial pressure; LAP or left ventricular end-diastolic pressure; LVEDP). Therefore, positioning the tip of the PAC and measurement in West zone 3 is a prerequisite for PAWP to accurately reflect LAP (Fig. 3). Absent a and v-waves, marked as PAWP variation during the respiration cycle, and pulmonary artery diastolic pressure exceeding wedge pressure (in the absence of tall a or v-waves) can indicate an incorrect wedge position in West zone 1 or 2.⁴²

RESPIRATORY CYCLE

CVP, PAP, and PAWP values should be measured at the end of expiration. At this point, the pleural pressure is closest to atmospheric pressure, and thus the influence of pleural pressures on measurements which are being compared to atmospheric pressure is minimal, both during spontaneous and positive pressure ventilation. Exceptions from this rule are spontaneously breathing COPD patients with forced expiration, where CVP should be measured early in expiration, before the patient begins to push. One should be aware of the fact that this may not necessarily be the highest or lowest pressure measured during the respiratory cycle.⁴³

Normal waveforms

A. Distinction between RV and PAP waveform

Characteristics:
Upslope of the diastolic portion of the waveform. The PAP has a downslope part of the curve.

B. Catheter motion artefacts

Characteristics:
Very sharp pressure wave at the beginning of systole.

C. Underdamping

Characteristics:
Overestimation of the systolic blood pressure, underestimation of diastolic blood pressure and amplification of waveform artifacts.

D. Overdamping

Characteristics:
Underestimation of systolic blood pressure, overestimation of diastolic blood pressure and attenuation of the waveform.

E. Overwedging

Characteristics:
Overwedging can be suspected if the pressure exceeds diastolic pulmonary pressure, continuous rising until the balloon is deflated, non-pulsatile pressure or wedge tracing recorded at a low balloon volume.

F. Right bundle branch block

Characteristics:
Arterial upstroke precedes the pulmonary artery upstroke.

G. Left bundle branch block

Characteristics:
Pulmonary upstroke precedes the arterial upstroke

H. Atrial fibrillation/flutter

Characteristics:
- Absence of A-wave;
- C and V-waves most prominent peaks;
- Beat to beat changing morphologies;
- Small amplitude pressure waves (fibrillation/flutter waves)

I. AV dissociation

Ventricular tachycardia, AVNRT, Complete heart block

Characteristics:
- Cannon A-wave during ventricular systole

J. Tricuspid insufficiency

Characteristics:
- Early holosystolic large V-wave;
- Merge with the C-wave;
- Disappearance of X-descent

K. Mitral valve insufficiency

Characteristics:
- Early holosystolic large V-wave;
- V-wave merge with the C-wave;
- Disappearance of X-descent

L. Tricuspid valve stenosis

Characteristics:
- Large A-wave;
- Slow Y-descent

M. Mitral valve stenosis

Characteristics:
- Large A-wave;
- Slow Y-descent

N. Pericardial constriction, RV infarction or restrictive cardiomyopathy

Characteristics:
- Tall A-wave
- Tall V-wave
- Steep X-descent
- Steep Y-descent

O. Tamponade

Characteristics:
- Tall A-wave
- Tall V-wave
- Absent or diminished Y-descent

Fig. 2 Pressure waveform pitfalls and abnormalities.

CA cannon a-wave. CVP central venous pressure. ECG electrocardiogram. RV right ventricle. RVP right ventricular pressure. PAP pulmonary artery pressure. ART arterial.

AIRWAY PRESSURE

Positive end-expiratory pressure (PEEP), either intrinsic or extrinsic, can influence measured pressures by its effect on pericardial pressure. During spontaneous breathing, and even during positive pressure ventilation with zero end-expiratory pressure, the pericardial pressure is minimal at the end of expiration. With PEEP applied, the pericardial pressure exceeds zero and can lead to overestimation of LVEDP and CVP.^{33,37} Therefore, CVP and PAWP might not be true indications of LAP when a patient is receiving a PEEP of 10 cmH₂O or more.⁴⁴ Different methods to correct for applied PEEP are suggested, including various formulas or abrupt airway disconnection.⁴⁴⁻⁴⁷ An often used formula is: corrected pressure (mmHg) = measured pressure (mmHg) - [0.5x (PEEP/1.36)].⁴⁸ Awareness of possible overestimation of PAWP due to PEEP from various lung compliance during mechanical ventilation is critical in the correct interpretation of the data.

Fig. 3 Pulmonary artery catheter location in relationship to West's zones of the lung.

Pap = pulmonary arterial pressure. Pa = pressure in the alveoli. Ppv = pulmonary venous pressure

WAVEFORM PITFALLS

The most common artefact is the catheter whip.⁴⁹ At the onset of systole, the catheter may be set into motion by closure of the tricuspid valve and by RV contraction. Fluid within the catheter might accelerate due to the movement of the catheter, or the catheter might strike either the walls of the heart or pulmonary artery. In the waveform, a very sharp pressure wave will appear at the beginning of systole (just after the R-wave of the ECG) and will only be visible in the RV and PAP tracing (Fig. 2B). This will not only result in a waveform artefact but also in artefactual pressure peaks.⁵⁰ Repositioning of the catheter with 1 or 2 centimetres may be helpful when trying to obtain more accurate pressures. It is of note that, although it might result in more accurate pressures, the artefact will probably still be visible.

DAMPING

Catheter-transducer monitoring systems have three characteristic physical properties: elasticity, mass, and friction. These properties determine the system's operating characteristics, referred to as the dynamic response. An optimal dynamic response is required to measure pressures accurately. The dynamic response is characterized by both the natural frequency and the damping coefficient. The natural frequency describes how rapidly the system oscillates and the damping coefficient describes how rapidly it comes to rest.⁵¹ The fast-flush test has been invented in order to evaluate the dynamic bedside response by briefly giving a fast flush several times, preferably during the diastolic run-off.⁵² The clinician should observe the natural frequency by counting the distance between oscillations, and the damping coefficient by counting how quickly the systems returns to baseline. In an optimally damped waveform, 1.5 to 2 oscillations are seen. When there are more oscillations, the system is underdamped; when there are less, the system is overdamped. An underdamped system will overestimate the systolic blood pressure and/or underestimate diastolic blood pressure, which will result in amplification of waveform artifacts (Fig. 2C). Overdamped systems will underestimate systolic blood pressure and/or overestimate diastolic blood pressure (Fig. 2D).⁵² Due to the intrinsic properties of the monitoring set-up, waveform analysis at high heart rates might be unreliable and difficult to execute.

Failure to remove all air from the catheter or tubing, or obstruction of the pressure channel of the catheter by blood clots, might result in overdamping of the waveform, which would lead to falsely low systolic pressure measurements. In case of an underdamped system, it is not advised to introduce a small air bubble into the tubing. By adding an air bubble the natural frequency of the system will be lower, resulting in further amplifying systolic pressure overshoot.⁵² A clinician should be aware of artefacts producing erroneous values on the monitor. This can be the result of artefactual pressure troughs, resulting in nadir pressures that

are recorded as diastolic pressures but which are not the factual diastolic pressure. Advancing or withdrawing the catheter might be helpful when removing the artefact and replace the pressure with a more accurate measurement of the diastolic pulmonary artery pressure.⁵¹ In the event that overdamping or underdamping cannot be corrected, the clinician may consider replacing the catheter. If this is impossible or undesirable, the clinician should not use the absolute values of systolic and/or diastolic PAP for the correct interpretation of the clinical situation. However, the trend of these variables over time may still reflect actual hemodynamic changes.

ELEVATED RIGHT VENTRICULAR PRESSURES

In case end-diastolic pressure of the RV is elevated, as in RV failure, it might be difficult to distinguish RV pressure from PAP. Close examination of the diastolic component of the waveform is likely to reveal the answer, since a diastolic step up is limited in the setting of right heart failure. The PAP is always going to decrease during the diastolic phase (after the dicrotic notch), as blood flows toward the left atrium, whereas the pressure in the RV steadily increases during diastole due to filling of the RV. In addition, the RV waveform can also depict a notch, called the incisura, caused by closure of the pulmonic valve. However, this notch will originate simultaneously with the T-wave instead of after the T-wave, as is the case with the dicrotic notch of the PAP waveform (Fig. 2A).²³ Analysis of the RV waveform can be useful in early detection and subsequent management of RV dysfunction, especially during cardiac surgery.^{35,53} Under conditions of impaired RV function, the diastolic slope may change. In the early stage of RV failure, the diastolic phase is characterized by a progressively oblique upslope. During severe impaired RV function the diastolic RV waveform will become square-root shaped. In addition, elevated systolic pressures have been described in the setting of RV outflow tract obstruction. This condition, defined as a pressure gradient between RV and PAP of at least 25 mmHg, can happen in up to 4% of cardiac surgery patients and is associated with hemodynamic instability.⁵⁴ Since RV pressure monitoring requires a different PAC with a dedicated RV pace-port, further details are beyond the scope of this review. An excellent review of this topic is provided by Raymond and colleagues.³⁵ It is of note that the PAC used for RV pressure monitoring does not enable continuous cardiac output and RV ejection fraction measurements.

OVERWEDGING AND UNDERWEDGING

Overwedging occurs when eccentric balloon inflation causes the catheter tip to occlude against the pulmonary artery wall, after which it thus no longer measures intravascular pressure. Pressure is now produced by a pressurized continuous flush system as it builds up against obstructed distal opening. Overwedging can be suspected under any of the following

circumstances: if the pressure exceeds diastolic pulmonary pressure, if the waveform continuously rises until the balloon is deflated, if the pressure is non-pulsatile, and/or if wedge tracing is recorded at a low balloon volume (<1.5 cc) (Fig. 2E). Since overwedging is mostly caused by distal migration of the catheter, the solution is usually to withdraw the PAC to a more proximal position.⁵⁰ It is of note that inflation of the balloon, while the catheter is migrated to a distal position, should be avoided because it may cause rupture of a small pulmonary vessel, which can lead to serious lung hemorrhage. In patients with high PAP, underwedging can occur from incomplete occlusion of the pulmonary artery branch, which is related to poor compliance of the pulmonary arteries and will lead to an overestimation of the PAWP.⁵⁵

WAVEFORM ABNORMALITIES

Several clinical pathologies can have impact on PA waveform appearances. All described clinical conditions and their corresponding waveforms can be found in figure 2.

HEART RHYTHMS AND BUNDLE BRANCH BLOCKS

When interpreting waveforms, simultaneous observation of pulmonary artery waveforms with the ECG registration and with arterial waveform monitoring could be useful. Under normal conditions, the PAP upstroke precedes the arterial upstroke due to the longer duration of left ventricular isovolumetric contraction.⁵⁶ Since this lag time is small under normal conditions, the waveforms may seem to overlap. However, the presence of a bundle branch block may alter this relation between PAP and systemic arterial pressure. A left bundle branch block delays left ventricular contraction, increasing the lag time between the PAP upstroke and arterial upstroke even more (Fig. 2G). A right bundle branch block has the opposite effect; arterial upstroke now precedes PAP upstroke (Fig. 2F).²³ Tachycardia might produce fusion of waveform components, particularly the a and c-waves, whereas bradycardia can reveal a mid-diastolic plateau pressure wave (h) between the x-descent and v-peak.⁵⁷

In case of atrial fibrillation, the a-wave will disappear from the CVP waveform due to the loss of atrial contraction. The c-wave is more prominent compared to normal sinus rhythm due to high end-diastolic atrial volume and subsequent isovolumetric ventricular contraction, displacing the tricuspid valve toward the right atrium. Atrial fibrillation leads to variability in chamber filling, and thereby to the contractile state with concurrent changes in waveform morphologies. In addition to the c- and v-waves, small amplitude pressure waves may be superimposed to the waveform, reflecting atrial activity (Fig. 2H).^{57,58}

In case of atrioventricular dissociation (ventricular tachycardia, complete heart block, re-entry tachycardia), cannon a-waves are inscribed in the CVP because of atrial contraction against a closed tricuspid valve during systole. Cannon a-waves may occur before, during, or after the c-wave. Cannon a-waves can also be noted in the wedge waveform (Fig. 2I).⁵⁹

TRICUSPID VALVE DISEASE

In case of severe tricuspid regurgitation, blood leaks back towards the right atrium across the incompetent valve. This will result in an early systolic large v-wave on the CVP waveform. Since this v-wave is holosystolic, it will merge with the c-wave and make the x-descent disappear (Fig. 2J).⁶⁰ Tricuspid stenosis causes an obstruction between the right atrium and the RV, resulting in diminished right atrial emptying, impaired RV filling, and elevation of mean CVP. Tricuspid stenosis affects the diastolic portion of the CVP; the waveform will depict a prominent a-wave and a slow y-descent (Fig. 2L). Other diseases which impair RV filling by increasing RV stiffness (RV infarction, pericardial constriction, pulmonic stenosis, pulmonary hypertension) may produce a prominent end-diastolic a-wave and a taller v-wave, but the y-descent should be preserved.^{57,58}

MITRAL VALVE DISEASE

Mitral valve regurgitation has similar implications for the PAP/PAWP waveform as the previously described tricuspid regurgitation has for the CVP waveform. The holosystolic prominent v-wave with fusion of the c-wave and obliteration of the x-descent will define the PAP and PAWP waveform in the presence of mitral valve regurgitation (Fig. 2K). However, due to the delayed, damped reflection of the left atrial pressure, c-wave merging can be less evident.⁶⁰ It is of note that the height of the v-waves does not predict the intensity of the mitral valve regurgitation.⁶¹ The presence of a large v-wave in PAWP waveforms may complicate a true distinction between PAWP and PAP waveform. In case this happens, drawing a comparison with the ECG and arterial waveform may be helpful. The PAWP will start after both the arterial upstroke and the T-wave on the ECG, while the PAP will slightly precede both systemic arterial pressure upstroke and the T-wave.⁶² Like tricuspid stenosis in the CVP waveform, the PAWP waveform will depict a prominent end-diastolic a-wave, and a slow y-descent in case of mitral valve stenosis (Fig. 2M). Increased left ventricular (LV) stiffness (left ventricular infarction and hypertrophy, pericardial constriction, aortic stenosis, and systemic hypertension) will produce a prominent a-wave, but the y-descent should be preserved.⁶⁰

RESTRICTIVE PHYSIOLOGY

In pericardial constriction, the pulmonary artery pressure waveform is markedly different. All of the waveform components are amplified; tall a and v-waves with steep x and y-descents are visible, creating a sawtooth M (in

case of a fast heart rate) or W configuration (in case of a slow heart rate).⁵⁸ These morphologic features may also be seen in the waveform of patients with RV infarction or restrictive cardiomyopathy, since both pathologic conditions share the same underlying pathophysiologic mechanisms (Fig. 2N).^{63,64}

CARDIAC TAMPONADE

Compression of the heart due to pericardial fluid results in an increased CVP, as well as in a reduced cardiac diastolic volume, stroke volume, and cardiac output. Despite the hemodynamic similarities between pericardial constriction and tamponade, the pulmonary artery waveform is slightly different.⁶⁵ The characteristic of the CVP waveform in cardiac tamponade is monophasic and dominated by a systolic x-descent. The y-descent is diminished, or altogether absent, due to impaired RV filling (Fig. 2O).⁵⁸ This is caused by the difference in blood flow from the vena cava to the right atrium between pericardial constriction and tamponade. In cardiac tamponade, venous return to the right atrium is limited to the period of atrial relaxation (x-descent), whereas in restrictive pathophysiology, it is biphasic with a peak during atrial relaxation and early ventricular filling (x- and y-descent).⁶⁵

LEFT VENTRICULAR END DIASTOLIC PRESSURE

According to the principle of communicating tubes, the PAWP may be used as an indicator of LV filling pressure (LVEDP). The mitral valve is open at the end of diastole and thus, to some extent, PAWP represents to some extent the pressure in the left atrium and LV as well. However, these pressures are not necessarily the same. The left ventricular end diastolic pressure determines the force of ventricular contraction, whereas the mean left atrial pressure is the pressure level which, on average, must be exceeded if blood is to return to the heart.⁶⁶ The true filling pressure is the net result of the intracavitary LVEDP and the transmural pressure. Therefore, pericardial pressures (or juxtacardiac pressures) and mediastinal pressures should be taken into account. Under normal conditions, these pressures are respectively zero and between -1 and -3 mmHg, and thus PAWP is assumed to accurately reflect LVEDP.⁶⁷ However, in certain specific pathophysiological situations, measurements of PAWP do not accurately reflect LVEDP due to changes in pericardial or mediastinal pressures. Underestimation can occur during diminished LV compliance, in case of obstruction of pulmonary blood flow, during aortic or pulmonic valve regurgitation, or during right bundle branch block. Overestimation can be caused by positive end-expiratory pressure, pulmonary veno-occlusive disease, pulmonary arterial hypertension, mitral valve stenosis or regurgitation, tachycardia, or ventricular septal defect.⁴²

Table 1: Hemodynamic variables obtained from the pulmonary artery catheter

Variable	Abbreviation	Equation	Normal range
Mixed venous oxygen saturation	SvO ₂	n.a.	60-80%
Cardiac output	CO	HRxSV/1000	4.0-8.0 L min ⁻¹
Cardiac index	CI	CO/BSA	2.5-4.0 L min ⁻¹ m ⁻²
Cardiac power index	CPI	(MAP-CVP) x CI/451	0.5-0.7 W m ⁻² , population specific
Central venous Pressure	CVP	n.a.	2-6 mmHg
Stroke volume	SV	CO/HR x 1000	60-100 mL
Stroke volume Index	SVi	CI/HR x1000	33-47 mL m ⁻²
Stroke volume variation	SVV	(SVmax-SVmin)/SVmean x100	10-15%
Systemic vascular resistance	SVR	80 x (MAP - CVP)/CO	800-1200 dynes sec cm ⁻⁵
Systemic to pulmonary pressure ratio	MAP/MPAP	MAP / MPAP	4.0 ± 1.4 in uncomplicated cardiac surgery
Pulmonary artery systolic pressure	PASP	n.a.	15-30 mmHg
Pulmonary artery diastolic pressure	PADP	n.a.	8-15 mmHg
Pulmonary artery wedge pressure	PAWP	n.a.	6-12 mmHg
Pulmonary vascular resistance	PVR	80 x (MPAP-PAWP)/CO	<250 dynes sec cm ⁻⁵
Pulmonary artery pulsatility index	PAPI	(PASP - PADP)/CVP	population specific
LV stroke work index	LVSWi	SVi x (MAP - PAWP) x 0.0136	50-62 mmHg ml m ⁻²
RV stroke work index	RVSWi	SVi x (MPAP - CVP) x 0.0136	5-10 mmHg ml m ⁻²
RV function index	RFI	PASP / CI	31.7 ± 16.7 in ICU survivors with PH
RV end-diastolic volume	RVEDV	SV/EF	100-160 mL
RV end-diastolic volume index	RVEDVi	RVEDV/BSA	60-100 mL m ⁻²
RV end-systolic volume	RVESV	EDV-SV	50-100 mL
RV ejection fraction	RVEF	(SV/EDV) x 100	40-60%
RV systolic pressure	RVSP	n.a.	15-30 mmHg
RV diastolic pressure	RVDP	n.a.	2-8 mmHg

BSA body surface area; CI cardiac index; EDV end diastolic volume; EF ejection fraction; HR heart rate; LV left ventricle; MAP mean arterial pressure; MPAP mean pulmonary arterial pressure; n.a. not applicable; PAWP pulmonary artery wedge pressure; PH pulmonary hypertension; RV right ventricle. Adapted from: Edwards Clinical Education Quick Guid to Cardiopulmonary Care.¹²⁷

MEASUREMENTS

Measurements obtained from the PAC can be found in table 1. It is of note that for accurate measurements the PAC should be placed in the correct position within the pulmonary artery.

CARDIAC OUTPUT

INTERMITTENT CARDIAC OUTPUT MEASUREMENTS

The Fick method is the gold standard for indirect cardiac output (CO) determinations. This method determines the cardiac output as the quotient of systemic oxygen consumption ($\dot{V}O_2$) and the difference between arterial and mixed venous oxygen content.

The oxygen concentration in arterial blood is a function of the haemoglobin concentration (Hb) and the percent saturation of haemoglobin with oxygen (SaO_2). The cardiac output can then be calculated using the following formula:

$$CO \text{ (ml min}^{-1}\text{)} = \frac{\dot{V}O_2}{1.34 \times Hb \times (SaO_2 - SvO_2)}$$

In this formula, $\dot{V}O_2$ (in mL min⁻¹) = oxygen consumption as directly measured by respirometry⁶⁸, SvO_2 (in %) is the mixed venous oxygen saturation.

Since this direct Fick technique is technically demanding at the bedside, it is rarely used in clinical practice. Intermittent pulmonary artery thermodilution is the clinical reference method for CO measurement.¹⁰ To measure CO using pulmonary thermodilution, a bolus of cold crystalloid solution is injected in the central venous circulation. The cold indicator bolus injection causes a decrease in blood temperature that is detected downstream using a thermistor near the catheter tip. From the thermodilution curve, which represents the changes in blood temperature over time, CO can be calculated using a modified Stewart-Hamilton formula:

$$CO = \frac{V \times (Tb - Ti)}{A} \times \frac{SI \times CI}{(SB \times CB)} \times \frac{60 \times CT \times K}{1}$$

In this formula, CO = cardiac output, V = volume of injectate, A = area of thermodilution curve in square mm divided by paper speed (mm/sec), K = calibration constant in mm/°C, Tb = temperature of blood, Ti = temperature of injectate, SB = specific gravity of blood, SI = specific gravity of injectate, CB = specific heat of blood, CI specific heat of injectate, $SI \times CI / (SB \times CB)$ = 1.08 when 5% dextrose is used, CT is correction factor for injectate warming.

Intermittent pulmonary artery thermodilution with cold-saline bolus injections has multiple limitations. The modified Stewart-Hamilton

equation shows that the bolus-derived information depends on injected volume, rate, and temperature. Overestimation of CO can occur in the presence of left-to-right or right-to-left intracardiac shunts, the use of a small injection volume, or a higher injectate temperature as compared to the reference temperature. All of these causes result in a smaller area under the thermodilution curve, resulting in an overestimated CO. Tricuspid regurgitation (TR) might both under- and overestimate CO due to increased transit time and modified blood temperature in the right atrium. Pulmonary valve insufficiency changes the appearance of the thermodilution curve, but CO measurement generally remains accurate since the area under the thermodilution curve is not affected, unless the CO is very low.⁶⁹ Underestimation of CO is mainly seen in high-flow states due to rapid temperature changes in the pulmonary artery.⁷⁰⁻⁷³ In addition, inadequate timing during the respiratory cycle and variability in injection technique may further influence the accuracy of bolus thermodilution measurements.⁷⁴ Bolus CO measurements are therefore highly user-dependent.⁷⁵

Over the years a continuous measurement system has been developed in order to overcome these disadvantages. In the early days, placement of a heating filament was severely compromised due to background thermal noise in the pulmonary artery or because of limitations either in maximum peak heat flux or in temperatures.^{76,77} To overcome these limitations, a combination of thermal indicator dilution and a stochastic system is now used in the modern PAC. To this end, the contemporary PAC is equipped with a 10 cm long thermal filament, positioned 4 cm from the tip of the catheter. This filament heats up the blood in a random on-off pattern. The change in blood temperature is measured downstream by the thermistor throughout the entire respiratory cycle. Based on a repeating on-off signal, a relaxation waveform can be generated. This technique enables measurement of true volumetric flow and is independent of the physical geometry of the system. Detailed information about the used algorithm and the stochastic system has been described previously.⁷⁸

CONTINUOUS CARDIAC OUTPUT MEASUREMENT

Using the area under the relaxation thermodilution waveform, near-continuous and almost real-time measurement of continuous cardiac output measurements (CCO) can be obtained. CCO measurement with PAC is well-validated in experimental settings nowadays, as well as in different patient categories.⁷⁹⁻⁸² CCO was shown to be more accurate when compared to various other measurement methods for CO, including electromagnetic measurement of aortic blood flow, bolus thermodilution, the Fick method, and aortic transit-time ultrasound.^{80,83-87} In addition, CCO showed to be more accurate and less variable when compared to the intermittent bolus thermodilution technique. The CCO method is independent of the clinician, injection technique, and injection volume.

Furthermore, the CCO method is not influenced by ventilator settings due to a high sampling rate at random time points in the ventilatory cycle (Fig. 4). This allows for detection of smaller variations in CO, as well as good performance over a wide range of CO and blood temperatures.^{86,88}

Fig. 4 Relaxation waveform for continuous cardiac output and concomitant calculations of right ventricular ejection fraction and right ventricular end-diastolic volume calculations.

Shown are the thermal signal sent out by the proximal part of the PAC, how this is received in the more distal part of the PAC, and how this is transformed to derive the specific variables.

PRBS Pseudo-Random Binary Sequence; RVEF right ventricular ejection fraction. CEDV continuous right ventricular end-diastolic volume. CCO continuous cardiac output. τ = exponential decay time constant.

* This step is skipped when using STAT-CCO over trend CCO monitoring.

Adapted from: Wiesenack C et al.⁴⁴

LIMITATIONS OF CARDIAC OUTPUT MEASUREMENTS

DELAYED RESPONSE IN CCO MEASUREMENT RESULTS

It is important to distinguish two different ways of depicting CCO measurement results: trend CCO and STAT CCO. The trend CCO reflects the average CCO over the previous 4 to 12 minutes (depending on the monitor setting).^{89,90} During rapid alterations of hemodynamic state there is a clinically important time lag in the response of the trend CCO.⁹⁰ The STAT CCO was designed to improve the response time. Using a faster algorithm, STAT CCO is updated every 30 to 60 seconds and has shown good accuracy and precision compared to Intermittent pulmonary artery thermodilution.⁹⁰ Pacing-induced hemodynamic changes, for instance, were detected in mean arterial pressure (MAP) recordings after 30 seconds, and an increase in SvO₂ reached significance after 90 seconds. A significant increase in CCO using the STAT algorithm was reached after a minimum of 270 seconds.⁹⁰ Physicians should be aware of a delayed response, even when using the STAT mode (Fig. 4).^{91,92}

INTRACARDIAC SHUNTS

In vitro experiments have shown that shunting 50% of total blood flow results in mean systematic errors of -26.8 ($\pm$ 8.2%) for CCO measurements during an intracardiac left-to-right shunt, overestimating true values as a result of altered waveform configuration.⁸⁶ Although the CO is falsely high in the setting of intracardiac shunts, the PAC may be useful in both detecting the presence and assessing the magnitude of the intracardiac left-to-right shunt.

TRICUSPID REGURGITATION AND TACHYCARDIA

TR has been associated with an underestimation or overestimation of CO, and even with no influence on CO measurements.^{93,94} In general, a high degree of TR is associated with an underestimation of true CO.⁹⁵ In patients with pulmonary hypertension, the agreement between the Fick method and thermodilution CO was not affected by the severity of tricuspid regurgitation.⁹⁶ However, despite possible under- or overestimation of CCO in the presence of TR, CCO measurements remain clinically relevant when using this method for trend monitoring, as well as to assess the response to hemodynamic interventions.⁹⁷ Furthermore, when using the CCO method, it might be expected that the influence of tricuspid regurgitation is less pronounced when compared with the intermittent bolus technique, because CCO represents an average value over time and is less dependent on interindividual variations in infusion. However, firm data on this remain scarce.⁸⁸

FLUID ADMINISTRATION

The infusion of fluid through the side-ports of the sheath, or through the venous port of the PAC, influences the thermodilution washout curve.

During bolus thermodilution this leads to an artefactual increase in the area under the curve, and thus to an underestimation of CO.^{98,99} Although it is suggested that the continuous measurement system is less accurate during fluid infusion¹⁰⁰, various infusion rates of lactated Ringer's solution (100, 200, 500, 1000 ml hr⁻¹) only influenced the CCO values at a low-flow rate equal to or below 2 L min⁻¹. In contrast, intermittent bolus CO measurements were affected at all flow rates. Thus, CCO measurements seem to have a better resistance to the thermal noise produced by high rates of infusions as compared to the bolus method.⁸⁶

EXTREME TEMPERATURE VARIATIONS

Extreme temperature variations can cause a poor correlation between intermittent bolus CO measurements and CCO measurements. In patients treated with therapeutic hypothermia, for instance, the correlation coefficient was observed to be low with broad limits of agreement when compared with indirect Fick CO measurements.¹⁰¹ Conflicting results were found in small, non-randomized trials in the setting of post cardiopulmonary bypass.^{102,103} In patients undergoing orthotopic liver transplantation, both CCO and bolus CO methods showed decreased accuracy and precision after caval clamping and reperfusion.⁸² However, since the accuracy of bolus CO among hypothermic patients is a topic of debate, this method may not necessarily be considered the standard for comparison in this specific setting. It is of note that in vitro measurements indicate that the CCO technique has a greater resistance to thermal noise compared to bolus measurements providing a higher accuracy.⁸⁶

RIGHT VENTRICULAR EJECTION FRACTION AND END-DIASTOLIC VOLUME

At the end of the 1980's, a PAC enabling measurement of both right ventricular ejection fraction (RVEF) and right ventricular end-diastolic volume (RVEDV) was introduced. This PAC was validated against various other RVEF measurements methods, including angiography, contrast ventriculography, and echocardiography¹⁰⁴⁻¹⁰⁶. Nowadays, the PAC enables continuous measurement of the RVEF and RVEDV by using the exponential decay time constant (τ) of the thermodilution relaxation waveform, combined with the heart rate (HR). RVEF is calculated as follows:

$$RVEF = 1 - \exp \frac{-60}{\tau \times HR} \quad \text{or} \quad RVEF = 1 - \frac{Tb2 - Tb0}{Tb1 - Tb0}$$

Where Tb0 = blood temperature before heat application, Tb1 = blood temperature during systole, and Tb2 = blood temperature during systole¹⁰⁷. Once RVEF is obtained, calculations of RVEDV are based on CCO, HR, and RVEF using the following calculation:

$$RVEDV = \frac{(CCO/HR)}{RVEF} \quad 44$$

Because RVEDV is derived from RVEF and CO, errors in RVEDV are a combination of errors in both CO and RVEF measurements. Nevertheless, RVEDV is proven to be highly predictive for volumes in a pulsatile flow model.¹⁰⁸ Measurements of RVEF and RVEDV are neither dependent on bolus volume nor on the temperature of the injected saline. Moreover, in CCO, the PAC filaments heat up the blood directly in the right ventricle (RV), bypassing the influential effects of the right atrium, leaving the conservation of energy and RV dynamics and RV afterload as the primary determinants of the thermal washout curve.¹⁰⁹ As a result, previous studies using the bolus thermodilution technique may not directly be comparable with the CCO approach using the heating filament. Although the continuous thermodilution technique is currently validated for CO measurements, there is lack of data concerning validation of RVEF and RVEDV. Overall, both reproducibility and accuracy of the continuous method are superior compared to the intermittent bolus technique.^{86,88} Since the RVEF uses the washout thermodilution curve, all factors that confound CO measurements will also interfere with an accurate determination of RVEF.

LIMITATIONS OF THE CONTINUOUS RVEF MEASUREMENTS

UNDERESTIMATION

In general, every measurement method has its own unique reference values. Thermodilution-derived RVEF seems to underestimate RVEF when compared to other measurement methods such as ultrasound, magnetic resonance imaging (MRI), and radionuclide angiography.^{104,105,107,110-112} Animal research revealed that this underestimation was most likely explained by the fact that the blood in the right atrium did not return to baseline temperature in a single heartbeat after the cold saline injection.¹⁰⁹ Although thermodilution with the continuous measurement technique takes place in the RV instead of the right atrium, the continuous RVEF still seems to be underestimated by the PAC.¹⁰⁷ New 4D MRI technology has revealed that the blood temperature did not return to baseline in a single heartbeat as a result of the phasic contraction pattern of the RV. For every systolic beat, only 44% of the end-diastolic volume contributed directly to the pulmonary artery flow.¹¹³ Recirculation of blood in the ventricle might result in it taking more time for the heat mass to reach the thermistor. As a consequence of the prolonged relaxation, waveform RVEF will be underestimated and RVEDV will be overestimated. Whether or not the absolute volume data is completely correct does not influence whether these measurements are precise, and the fact remains that they can be of great value for trend monitoring. In general, an absolute correction factor of +11% will result in a more realistic absolute RVEF.¹⁰⁹

MATHEMATICAL COUPLING

Since the formula of RVEDV contains the CO by dividing stroke volume (SV) by RVEF, the correlation between those two variables may be explained by mathematical coupling. However, various studies examined the relationship between RVEDV and CCO, and this relationship remained significant even after statistical correction for potential mathematical coupling or by including an independent technique for CO measurements. Therefore, mathematical coupling alone does not explain the correlation between RVEDV and CO.¹¹⁴⁻¹¹⁶

MIXED VENOUS OXYGEN SATURATION

SvO₂ can be measured periodically in blood samples drawn from the distal lumen of the PAC in order to stave the measured values. Adding reflective fibreoptic oximetry at the distal end of the PAC enabled the clinician to accurately measure the SvO₂ on a continuous base.¹¹⁷ Oximetry is based on the technique known as spectrophotometry. The absorption of specific wavelengths of light, as it passes through a medium, is proportional to the concentration of the substance that absorbs both the light waves and the travel length. Oxygenated Hb does not absorb red light waves (wavelength 660 nm) as well as deoxygenated Hb does. On the contrary, infrared light waves (wavelength 940 nm) are better absorbed by oxygenated Hb. The determinants of SvO₂ are identified in the following equation: $SvO_2 = SaO_2 - (VO_2/CO \times 1.34 \times [Hb])$, where SaO₂ is arterial oxygen saturation and VO₂ is systemic oxygen consumption. As such, SvO₂ reflects the balance between oxygen delivery (DO₂) and consumption (VO₂). A change in SvO₂ indicates an imbalance between oxygen delivery and consumption. However, further information is needed to assess the cause of this change. Therefore, SvO₂ is not a simplified index of inadequate CO, since there are more determinants in the formula. Alterations in SvO₂ might be due to changes in oxygen transport (arterial SaO₂, Hb, CO) or a change in body oxygen consumption.⁶⁸

CLINICAL APPLICATION OF PAC-DERIVED DATA

ASSESSING FLUID RESPONSIVENESS

Over the years it has become clear that static filling pressures (CVP and PAWP) and cardiac preload should not be used interchangeably.¹¹⁸⁻¹²⁰ The pressure-volume relationship of the RV has a triangular shape, due to the low pressure and high capacitance characteristics of the pulmonary vascular bed. The pressure-volume relationship changes with different loading conditions, which can result in an increased filling pressure associated with a decreased filling volume.^{121,122} A change in preload does not result in a proportional change in filling pressures.¹²³ Although CVP and PAWP are not suitable for preload assessment, this does not mean that they should not be measured at all. An important determinant of organ perfusion pressure is the difference between the inflow pressure (MAP)

and the outflow pressure (CVP). Both lower MAP and elevated CVP can result in diminished organ perfusion. Among different patient categories, an association between elevated CVP and impaired microcirculatory blood flow or increased risk of acute kidney and liver injury has been demonstrated.¹²⁴⁻¹²⁶ Elevated or rapidly rising values of CVP and PAWP may serve as a stop rule for fluid resuscitation.¹²⁷ An increase in CVP in response to a fluid challenge without a change in CO is an indicator for poor fluid responsiveness.¹²⁸ The work of Guyton showed how venous return curves interact with cardiac function curves, i.e. right atrial pressure not being the primary determinant of CO rather than itself being determined by CO.^{129,130} When combining this knowledge with blood pressure difference (MAP-CVP) and CO, clinicians are offered a potential approach regarding the application of CVP in the clinical setting (Table 2).¹³¹ Although it has been shown that many intensive care physicians do not measure CO, it is highly recommended when trying to obtain a better understanding of both the haemodynamic situation and the effects of goal-directed management.¹³²

Today, static filling pressures are replaced by the concept of fluid responsiveness. The Starling curve depicts SV on the vertical axis and cardiac preload on the horizontal axis. On the steep part of the curve, an increase in preload will result in a significant increase in SV. At higher values of cardiac filling pressures, the curve flattens and an increase in preload will not result in an increase in SV.¹³³ In this respect there are three relevant questions in the clinical setting: 1) At which part of the Frank-Starling curve does the heart of the patient operate? 2) Is the patient fluid responsive? 3) Are fluids beneficial? Irrespective of the answers to question 1 and 2, the clinician does need to determine whether fluids are beneficial to the patient, or whether another therapeutic approach is needed or better suited to the situation, since being fluid responsive is not equivalent to being in need for fluids. Fluid challenges should be performed with 250 ml or 3 ml kg⁻¹ crystalloid, which is infused over a short period of time (5-10 min). Fluid responsiveness is most often defined as an increase $\geq 15\%$ in stroke volume index (SVi) or cardiac index (CI) after a fluid challenge (Table 2).¹³⁴ SVi or CI should be the primary target, and neither arterial blood pressure nor ventricular filling pressures or volumes should not be used as a surrogate for fluid responsiveness.¹³⁵ CI and SVi measured with the PAC are highly predictive of actual pulsatile flow.¹⁰⁸ Since the PAC is able to measure both fluid responsiveness variables (SVi and CI) and target/safety thresholds (CVP and PAWP) in a continuous manner, it can be used to manage fluid therapy adequately.^{91,92} In addition, a rise in RVEDP during fluid administration, in the absence of a change in CO, is indicative for RV volume overloading and a reason for the clinician to stop the intervention.

Table 2: PAC-derived variables in the clinical setting

Clinical situation	PAC derived variables	Clinical interpretation
Low arterial blood pressure	↓ CCI + ↑ CVP	Decrease in venous return, e.g. reduced cardiac function or hypovolemia
	↑ CCI + ↓ CVP	Increase in venous return, e.g. distributive shock
Fluid responsiveness	↑ SV or CCI ≥15% after 250 ml or 3 ml kg ⁻¹ of crystalloid	Patient will probably benefit from fluid administration
RV dysfunction and failure	Early stage (moderate RV dysfunction = RVEF 20-30%): ↓ RVEF, ↑ EDVi, CCI =N, SvO ₂ =N, CVP N or ↑	
	Advanced stage (severe RV dysfunction = RVEF <20%): ↓↓ RVEF, ↑ EDVi, ↓ CCI, ↓ SvO ₂ , ↑ CVP	
LV failure	↑ PAP, ↑ PAWP, ↓ CCI	
Intracardiac shunt	↑↑ SvO ₂	≥ 6% step up ScvO ₂ to SvO ₂ indicates a L-R shunt
Weaning- from-ventilator	↑ PAWP, ↓ SvO ₂ during weaning trial	Weaning-induced cardiac failure
Pulmonary hypertension	Pre-capillary: ↑ PAWP (>15 mmHg) Post-capillary: PAWP = N	Echocardiographic assesment should rule out HFpEF
Tamponade post cardiac surgery*	↓ CCI, ↑/= CVP, ↓ SvO ₂ , ↓ EDVi, ↓ RVEF, ↑ PAWP	Compression of the RV free wall causes low RVEDV despite substantial fluid administration
Distributive shock	↑ CCI, ↑ SvO ₂ , ↓/= CVP, ↓/= PAWP	Septic, neurogenic, anaphylactic, toxin-induced, or endocrine shock
Hypovolemic shock	↓ CCI, ↓ SvO ₂ , ↓CVP, ↓ PAWP	Hemorrhagic, gastrointestinal, skin, renal, or third space fluid losses
Cardiogenic shock	↓ CCI, ↓ SvO ₂ , ↑/=CVP, ↑ PAWP	Cardiomyopathic, arrhythmic, or mechanical causes
Obstructive shock	↓ CCI, ↓ SvO ₂ , ↑ CVP, ↑ PAWP	PH, pulmonary embolism, tension pneumothorax, tamponade, pericarditis, restrictive cardiomyopathy

* The location of the bleeding/hematoma determines the hemodynamic profile of the patient.

N normal; CCI continuous cardiac index; CVP central venous pressure; SV stroke volume; RV right ventricle; RVEF right ventricular ejection fraction; EDVi end-diastolic volume index; SvO₂ mixed venous oxygen saturation; ScvO₂ central venous oxygen saturation; PAP pulmonary artery pressure; PAWP pulmonary artery wedge pressure; LV left ventricle; HFpEF heart failure with preserved ejection fraction; PH pulmonary hypertension; HFpEF heart failure with preserved ejection fraction

RIGHT VENTRICULAR DYSFUNCTION AND FAILURE

Acute RV dysfunction can occur due to a variety of diseases, resulting in an increase in RV afterload, decreased contractility, or an increase/decrease in RV preload. A decreased RV function can induce a vicious circle of RV failure. When having a closer look at haemodynamics during RV failure, ventricular interdependence is an important concept to keep in mind. Due to shared muscle fibers, septal wall, and pericardium, forces can be transmitted from one ventricle to the other, both in systole and diastole.¹³⁶ Right ventricular volume/pressure overload or diminished contractility will result in RV dilatation. The intraventricular septum will flatten during diastole in case of volume overload and mainly during systole in case of pressure overload, creating a D-shaped LV.^{136,137} RV diastolic dysfunction and RV dilatation will shift the pressure-volume curve of the LV towards higher pressures, due to decreased LV diastolic compliance.¹³⁶ Furthermore, increased LV end-diastolic pressure (LVEDP), reduced LV transmural filling pressure, and impaired LV diastolic filling as a result of the septal shift will contribute to low CO and ultimately to low blood pressure.¹³⁸ In severe RV failure, low blood pressure in combination with high RV filling pressures result in severely reduced organ perfusion, due to a reduced difference between MAP and central venous pressure, being an important determinant of the driving force for venous return.¹³⁹ It is of note that a normal CO, or normal pulmonary artery pressure (PAP), does not exclude RV dysfunction.^{140,141}

Classically, the diagnosis of RV failure is made by combination of clinical assessment (i.e. signs of impaired organ perfusion in combination with venous congestion) and echocardiographic evaluation. To classify RV failure, a number of reference values for a variety of echocardiographic parameters have been suggested.¹⁴² Providing RV volume and pressures with the PAC, as well as contractility measurements, can be helpful in diagnosing and managing RV failure. In table 1 reference values for RVEF and RVEDV have been provided, as stated by the manufacturer. However, it is pivotal to understand that reference values for PAC-derived RVEF in the clinical setting are considerably lower, also in comparison to 2D or 3D echocardiography. Based on datasets, combining RVEF with long-term outcome in cardiac surgery and sepsis, we suggest the following classification: RVEF < 20%: severe RV failure; RVEF 20-30%: moderate RV failure; RVEF > 30%: no RV failure.^{143,144} Under physiological conditions, an increase in RVEDV is compensated by an (immediate) increase in SV, referred to as heterometric autoregulation.¹⁴⁵ However, in the early stage of RV dysfunction, RV dilatation becomes an adaptive mechanism for the preservation of adequate preload, reflected by a higher end-diastolic volume and lower RVEF. When RV failure is combined with, or secondary to, LV failure, PAWP can be elevated (Table 2). In a more progressive disease state, CO will be diminished as well. The CVP waveform can reveal a prominent v-wave due to TR in response to RV dilatation.¹⁴⁶

Nowadays, new hemodynamic indices, derived from PAC measurements, might be helpful in early identification of right ventricular dysfunction. The pulmonary artery pulsatility index (PAPi) is defined as: $\text{systolic PAP} - \text{diastolic PAP} / \text{CVP}$. This index predicts severe RV failure and has additive value in the setting of advanced heart failure, cardiogenic shock, and left ventricular assist device therapy. However, PAPi measurements and thresholds vary significantly between studies of different patient populations and thresholds from one patient population should not be extrapolated to another patient group.¹⁴⁷

Another index is the ratio of pulmonary artery effective elastance (E_a) to RV maximal end-systolic elastance ($E_{\max}$). This right ventriculo-arterial coupling parameter relates to the mechanical efficiency of the RV, and is ideally derived from RV pressure-volume loops. Nowadays, bedside estimation can be obtained by this ratio, using the contemporary PAC. E_a and $E_{\max}$ can be defined as $E_a = \text{meanPAP} - \text{PAWP} / \text{SV}$, and $E_{\max} = \text{meanPAP} / \text{RVEDV} - \text{SV}$. The ratio $E_a / E_{\max}$ equals 1 in case of optimal ventricular-vascular coupling. Hence, $E_a / E_{\max}$ may help in early identification of RV dysfunction in critically ill patients.¹⁴⁸

Under conditions of impaired RV function, analysis of the RV waveform can be useful in early detection and subsequent management of RV dysfunction, especially during cardiac surgery.¹⁴⁹⁻¹⁵¹ Since RV pressure monitoring requires a different PAC with a dedicated RV pace-port, further details are beyond the scope of this review.

LEFT HEART FAILURE

To distinguish isolated RV failure from a combination of RV and LV failure, the use of PAC may be helpful. Of note, LV filling pressures cannot be reliably estimated by means of clinical examination.¹⁵² Classically, in case of combined LV and RV failure, CI and SvO_2 are low, and PAWP is elevated.¹⁵³ In patients with a PAWP ≥ 15 mmHg, LV failure is likely, since high wedge pressures are associated with left heart disease.¹⁵⁴ In case of a low or normal PAWP, isolated RV failure is more likely. However, a PAWP ≤ 15 mmHg does not rule out the presence of LV failure, in particular in patients with LV heart failure and preserved ejection fraction (HFpEF).¹⁵⁵ In this case, further echocardiographic evaluation of diastolic LV function is recommended (Table 2).

THE DETECTION OF LEFT-TO-RIGHT SHUNTS

A high $\text{SvO}_2 > 75\%$ may indicate a cardiac left-to-right shunt. For oximetric shunt detection, blood sampling from the distal channel in the PAC and the proximal channel in the vena cava superior or right atrium is needed. Under physiological conditions, oxygen saturation in the pulmonary artery is lower than that in a central vein, due to the contribution of desaturated

blood flow from the coronary sinus. However, when a left-to-right shunt is present, oxygenated blood can cause an increase in oxygen saturation at the tip of the PAC. A step up of >6% in oxygen saturation from the vena cava superior to the pulmonary artery is suggestive of the presence of a left-to-right shunt (Table 2).¹⁵⁶ Using the SvO₂ and the central venous saturation (ScvO₂) in combination with the arterial oxygen saturation (SaO₂), a shunt fraction can be calculated according to the following equation: $Q_p/Q_s = (SaO_2 - SvO_2) / (SpvO_2 - SpaO_2)$, where Qp = pulmonary blood flow, Qs = systemic blood flow, SaO₂ = arterial oxygen saturation, SvO₂ = central venous oxygen saturation, SpvO₂ = pulmonary vein oxygen saturation (in the absence of a right to left shunt, this is identical to SaO₂), and SpaO₂ = pulmonary artery oxygen saturation.¹⁵⁶

WEANING-INDUCED CARDIAC FAILURE

When switching from positive pressure ventilation (with and without positive end-expiratory pressure; PEEP) to spontaneous breathing, intrathoracic pressure falls during both inspiration and expiration compared to assisted ventilation. In response, right atrial pressure falls and venous return increases, resulting in an increase in RV preload, an increase in CO (in the fluid responsive patient), and in LV preload. In addition, the negative intrathoracic pressure results in an increase in LV afterload.¹⁵⁷ Besides these pressure changes, hypoxemia, hypercapnia, and an increased sympathetic tone can result in an increase of RV or LV afterload. However, in a specific subgroup of patients, right atrial pressure may rise during a spontaneous breathing trial.¹⁵⁸ This might be explained by an increase in intrinsic PEEP due to expiratory muscle activity or dynamic hyperinflation.^{159,160} When following this line of thought regarding physiology, one can see that an elevated PAWP can be the result of an increase in LV preload in patients with an already elevated LV end diastolic volume (LVEDV), an increase in afterload, for example due to a subsequent increase in mitral insufficiency, or a decrease in LV compliance (or a combination of these). In a landmark paper,¹⁶¹ elevated PAWP (>18 mmHg) during a spontaneous breathing trial was shown to be associated with subsequent weaning failure in patients diagnosed with severe chronic obstructive pulmonary disease. After restarting mechanical ventilation, all patients received diuretics, and the PAWP decreased markedly as compared to before treatment (9 vs. 25 mmHg). In addition, failure to wean was also accompanied by a decrease in PAC-derived SvO₂ measurements, whereas SvO₂ remained unchanged in the successfully weaned patients. The same study revealed no change in CI combined with an elevation of PAP and PAWP, indicating an increase in both LV and RV afterload.¹⁶² PAC measurements can reveal weaning-induced cardiac failure, showing the response of the RV and LV during spontaneous breathing, as well as providing information about the change in the oxygen consumption/delivery balance during this critical period. In daily practice, PAWP should be measured before and after a 30 minutes spontaneous breathing trial.¹⁶³ A T-piece weaning trial challenges patients'

efforts and the LV performance the most. Other ways of conducting weaning trials, such as applying low levels of pressure support ventilation, might not reveal an elevation in PAWP (Table 2).¹⁶⁴

PULMONARY HYPERTENSION

Right heart catheterization is the diagnostic gold standard for assessing pulmonary hypertension (PH), which was classically defined as a mean PAP ≥ 25 mmHg at rest, and recently updated to > 20 mmHg at rest.¹⁶⁵⁻¹⁶⁷ In patients with high mean PAP, PAWP ≤ 15 mmHg is used to distinguish precapillary PH from high PAP pressures due to LV failure, since higher wedge pressures are related to left heart disease (Table 2).¹⁵⁴ However, PAWP ≤ 15 mmHg does not rule out the presence of left heart failure, in particular in patients with HFpEF.¹⁵⁵ Relying on a single measurement can falsely label patients with an inaccurate diagnosis. In order to distinguish precapillary PH from HFpEF, additional echocardiographic assessment in combination with the assessment of risk factors associated with HFpEF may avoid misclassification.¹⁶⁵ Once the suspicion of PH has risen because of high PAP measurements, it is recommended to refer patients to an expert PH centre for further diagnosis and treatment early in the diagnostic process.¹⁶⁸ In the ICU, PH is rarely the primary cause of admission; however, exact data remain scarce.¹⁶⁹ Upon hospital admission, high PAP values are mostly seen as secondary to acute conditions, such as pulmonary embolism, acute respiratory distress syndrome, LV failure, or mitral valve regurgitation.¹⁷⁰ The classification of chronic PH is not always applicable in critical care settings and a different classification, one according to the underlying cause, has been suggested.¹⁷¹ Since the RV is not resistant to acute increases in afterload, acute PH can result in RV failure.^{172,173}

RESTRICTIVE PATHOPHYSIOLOGY AND TAMPONADE

Pericardial constriction, restrictive cardiomyopathy, and RV infarction share the same underlying pathophysiologic feature; reduced RV diastolic compliance due to an increase in RV stiffness or impaired RV relaxation.¹⁷⁴ CVP waveform analysis can provide additional diagnostic clues for these conditions. Cardiac tamponade can be distinguished by the attenuation or disappearance of the y-descent in the CVP waveform. Obstructive shock due to tamponade results in a low CO, low SV, low MAP, and high CVP and RV filling pressures. Pulsus paradoxus can be present. In the final stage, there will be an equilibration of all cardiac and pulmonary artery diastolic pressures, which will result in an absence of coronary flow. This will finally lead to a circulatory arrest (Table 2).¹⁷⁵

However, in the setting of postoperative cardiac surgery, the above described classical forms of waveforms and haemodynamic patterns may not be present during tamponade. The specific location of well-defined hematomas, rather than free mobile accumulation of fluid, determines the specific combination of alterations in waveforms, pressures, and volumes.

For example, compression of the RV free wall by a localized hematoma may cause low RVEDV and low continuous cardiac index (CCI), despite substantial fluid administration, in combination with elevated or normal CVP (Table 2).

DETERMINATION OF SHOCK TYPE

In shock, there is a mismatch between systemic oxygen delivery and oxygen demand. There are four types of shock; hypovolemic, cardiogenic, obstructive, or distributive. The PAC can be useful in identifying the type of shock, and it can be beneficial during the assessment of the haemodynamic status, as a prerequisite to select the adequate therapeutic intervention, and to evaluate the response to therapy. In current guidelines, if clinical examination alone does not lead to a diagnosis, the PAC is recommended in complex patients for the determination of the type of shock, in patients with refractory shock, and for shock in combination with RV dysfunction or acute respiratory distress syndrome.^{135,176}

AN INTEGRATIVE APPROACH

Combining various parameters may help to further elucidate the underlying mechanisms of RV failure, and strives beyond the strict interpretation of reference values. For example, at first glance PAP values may not seem too far above the threshold for PH. But in case systemic blood pressure is below normal at the same time, such value may gain additional importance. The systemic to pulmonary pressure ratio (MAP/meanPAP) is a tool to quantify such 'relative' PH and appeared useful in the prediction of hemodynamic complications during and after cardiac surgery.¹⁷⁷ Adjusting the PAP for a specific CI, helps to quantify the RV workload, needed to maintain its performance in the presence of a given afterload. The RV function index (RFI), defined as the systolic PAP(SPAP)/CI, may be helpful to assess the additional amount of effort for the RV in case the flow or the afterload increases, and has predictive value as an independent risk factor for mortality in ICU patients with PH.¹⁷⁸ Finally, integrating the driving pressure (MAP-CVP) with the flow (CI), by means of a cardiac power output (CPO), elegantly acknowledges the fact that maintenance of the CI with the normal range, at the expense of an elevated CVP is less energy effective than when an equal CI is maintained during normal CVP.¹⁷⁹ As such, the CPO may be helpful to guide therapy into an acceptable range of MAP and CI, at the lowest possible level of oxygen consumption.

COMPLICATIONS OF THE PAC

The invasive nature of the PAC can result in complications. First of all, central venous access can result in accidental arterial puncture, air embolism, and pneumothorax. However, using ultrasound guidance during placement has been demonstrated to reduce the risk of catheter misplacement.¹⁸⁰⁻¹⁸² Secondly, several complications can arise due to the catheterization itself,

such as severe dysrhythmias, right bundle branch block, or complete heart block. Minor dysrhythmias occur often during catheter insertion or withdrawal but resolve spontaneously after advancing the catheter through the RV.¹⁸¹ Lastly, prolonged catheter residence can result in pulmonary artery rupture, pulmonary infarction, or venous thrombosis.¹⁰ Catheter-related infections with the PAC are uncommon and involve the introducer sheath rather than the PAC itself.¹⁸³ Increased infection risks are associated with prolonged PAC use, insertion via the internal jugular vein rather than the subclavian vein, and unsterile procedures.^{183,184} Right heart catheterizations performed in experienced centres are associated with low risk of serious complications, and there is high quality evidence that PAC use does not alter mortality.^{10,185} Absolute contraindications of PAC placement are right-heart-sided endocarditis, tumours, or masses. Relative contraindications for PAC placement include severe coagulopathy including severe thrombocytopenia, and presence of a tricuspid & pulmonary valve prosthesis, new pacing lead and large atrial septal defect. PAC insertion in patients with a left bundle branch block may induce complete heart block. In patients with tricuspid regurgitation catheter passage might be more difficult.¹⁸⁶ Clearly, contraindications related to central venous cannulation, including skin infections and thrombosis of the selected vein, apply to PAC insertion also.

CONCLUSION

The contemporary PAC provides accurate measurements of cardiac output, volume status, fluid responsiveness, left and right ventricular performance, and of the balance between oxygen supply and consumption. It provides a multi-variable integration of haemodynamic data which can be useful in diagnosing RV failure, LV failure, in determining the type of shock, in order to distinguish cardiogenic from noncardiogenic pulmonary edema, and to predict weaning failure. In addition, clinical application of PAC may be valuable in the setting of pulmonary hypertension, cardiac valve abnormalities, intracardial shunt, and restrictive cardiac diseases. However, like every tool in daily medical practice, the user of the tool should be trained in the accurate measurement, interpretation, and application of its data, as misjudgement bears with it the potential of deciding on inadequate therapies. Thorough understanding of PAC-derived measurements and its limitations are the first step towards successful application of the PAC in daily clinical practice.

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Chapter 3

Right Ventricular Function after Cardiac Surgery is a Strong Independent Predictor for Long Term Mortality

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ABSTRACT

OBJECTIVE: To establish the all-cause mortality of right ventricular dysfunction after cardiac surgery in a heterogeneous group of cardiac surgery patients

DESIGN: Retrospective analysis of a heterogeneous group of 1109 cardiac surgery patients in a four year period.

SETTING: Single-centre study in a tertiary teaching hospital.

PARTICIPANTS: 1109 cardiac surgery patients. By protocol patients were equipped with a pulmonary artery catheter, enabling continuous right ventricular ejection fraction (RVEF) measurements.

INTERVENTIONS: none

MEASUREMENTS AND MAIN RESULTS: Measurements were performed once per minute for the first 24 postoperative hours and expressed as average over the complete period. Primary outcome was two year all-cause mortality. RVEF was categorized into three subgroups: <20%, 20-30% and >30%. Median follow-up time was 739 days. Two year mortality was significantly different across groups: 4.1% for patients with RVEF >30%, 8.2% in the group with RVEF 20-30%, and 16.7% for patients with RVEF <20%, $p<0.001$. Additional risk factors for a poor RVEF were age, bodyweight, New York Heart Association class, chronic obstructive pulmonary disease, poor left ventricular function and higher risk scores (APACHE IV and euroSCORE). In a multivariate analysis, RVEF as a continuous variable was independently associated with the primary outcome (odds ratio 0.95 confidence interval 0.91-0.99, $P=0.011$.) Odds ratios for RVEF<20% were 1.88 (confidence interval 1.18-3.00, $p=0.008$).

CONCLUSION: Right ventricular function is independently associated with two year all-cause mortality in a heterogenic cardiac surgery population.

INTRODUCTION

In cardiac surgery, impaired left ventricular (LV) function has been recognised as an independent risk factor for morbidity and mortality.¹ However, data on impact of right ventricular (RV) function on mortality in cardiac surgery are scarce. Most data on RV function in cardiac surgery are limited to small sample sized studies, performed in patient populations selected for well-known hemodynamic features already associated with RV failure.²⁻⁴ Pulmonary hypertension has been recognized as a risk factor for RV dysfunction with subsequent prognostic value.⁵ Others observed a significant correlation between pre-coronary artery bypass grafting (CABG) RV dysfunction and outcome among patients with pre-existent poor LV function.³ Furthermore, RV function was found to be a strong predictor of long-term postoperative survival in a small, preselected population undergoing mitral valve repair.⁴ As of now, the overall prognostic impact of RV dysfunction on mortality in a large cardiac surgery population, not selected for RV-related risk factors, remains unclear. Therefore, we performed a large sample size observational study on long term mortality in a cohort of heterogeneous cardiac surgery patients.

METHODS

STUDY POPULATION

This study is a single-centre retrospective observational study involving a heterogeneous group of cardiac surgery patients admitted to the intensive care unit (ICU) between January 2011 and January 2015. According to our institution protocol all cardiac surgery patients were admitted to the ICU in the direct postoperative phase. Patients who fulfilled predefined criteria (Table 1) (in short: valve surgery or poor LV) were by protocol equipped with a pulmonary artery catheter after induction of anaesthesia and included in the study. Exclusion criteria were an age <18 years and a non-functioning pulmonary artery catheter after ICU admission. The study was approved by the local ethical and scientific committee and the need for informed consent was waived in accordance with applicable laws.

Table 1. Inclusion criteria

Mitral valve repair/replacement including MitraClip
Aortic valve replacement, including TAVI
Aortic arch surgery, including Bentall procedure
Any combination of heart valve surgery
CABG + heart valve surgery
Isolated CABG procedure with poor LV function

TAVI Trans Aortic Valve Intervention. CABG Coronary Artery Bypass Grafting LV function. Left Ventricular function

DATA COLLECTION

Data were extracted from several hospital information systems. Immediately after induction, LV function was semi-quantitatively assessed as good, moderate or poor by board-certified echo cardiographers using the Philips IE33 trans-oesophageal echocardiography (TEE) system (Philips Medical Systems, Eindhoven, the Netherlands).

Hemodynamic parameters were derived from a pulmonary artery catheter (7.5F CEDV-Pulmonary Artery Catheter, model 744H, Baxter Healthcare Corporation, Irvine, CA, USA), which interfaced with a computerised monitoring system (Vigilance® CCO / SvO₂ / CEDV Monitor, Baxter Healthcare Corporation, Irvine, CA, USA). A thermal filament on the catheter, placed in the RV enables continuous measurement of the RVEF. During the postoperative ICU admission RVEF was continuously measured at a rate of one sample per minute from the start of ICU admission. Measurements were started at the start of the ICU admission and were averaged over the first 24 hours of ICU admission, or until ICU discharge in case patients were transferred from the ICU to the ward within 24 hours postoperatively. Data on long term outcome after hospital discharge were derived from a linkage between the social security number of the patient and a national registration of demographic characteristics of all Dutch individuals.

Normal values of RVEF in current literature gives a lower limit of 30% up to 45%.^{3,4,6} However, this limit is based on measurements with echocardiography (2D or 3D), angiocardiology or magnetic resonance imaging (MRI). Different studies in the past^{7,8} already established that the pulmonary artery catheter underestimates the RVEF in comparison with other measurement techniques. Since there are no international criteria for a cut off value of RVEF to define RV failure, we first composed a distribution curve of the RVEF. According to statistical law, patients were subsequently separated into three groups based upon the mean plus or minus one standard deviation. (Fig. 1) Furthermore, to corroborate this cut-off value, we also predefined RV failure as an RVEF below the 95% confidence interval of previous publications in cardio-surgical patients. Using this predefinition, we found a cut-off value for the RVEF measured with a pulmonary artery catheter < 20 %.⁸

SURGERY DETAILS

Patients were anesthetized according to local protocol based on a combination of sufentanil 3-7 µg/kg, rocuronium 0.6 mg/kg and midazolam 0.1 mg/kg for anesthesia induction and tracheal intubation, and sevoflurane for maintenance. All patients received tranexaminic acid and if below 75 years of age dexamethasone 1 mg kg⁻¹. Cardiopulmonary bypass was performed at a continuous blood flow (2.2-3.0 l/min/m²) during normo- or mild hypothermia (>34°C). The CPB hardware consisted

of a HL-30 heart-lung machine and HCU-30 heater-cooler and inline blood analysis monitor (CDI 500 Terumo Cardiovascular Systems Corporation, Ann Arbor, Michigan, USA). The CPB circuit consisted of a Rotaflow centrifugal pump, a Quadrox-D membrane oxygenator a Quart arterial filter, a JVR 1900 collapsible venous reservoir and a BCR 3500 cardiotomy-reservoir. The components are Bioline-coated, except for the venous reservoir which has a Safeline-coating (MAQUET Cardiopulmonary AG, Hirrlingen, Germany). Heparinisation started with an initial bolus of 300 IU/kg heparin (LEO Pharma BV, Amsterdam, the Netherlands), which was replenished until the Celite activated clotting time (ACT) test exceeded 480 seconds (Hemochron® Response, Edison, NJ, USA). The priming solution (1400 ml) contained 7500 IU heparin. After termination of the extracorporeal circulation heparin was reversed with protamine sulphate (Meda Pharma BV, Amstelveen, the Netherlands). The cell saver was used during full heparinisation of the patient. Surgical procedures were performed per local protocol. Cardioplegia was administered continuously (blood) or intermittently (St Thomas) every 45 min, by surgical preference.

STATISTICAL ANALYSIS

Statistical analyses were performed using the statistical package for social science (SPSS 22 for Windows; SPSS Inc., Chicago, IL, USA). Data are described as median [IQR] unless stated otherwise. Normal distribution was tested by a Kolmogorov-Smirnov test. Differences between groups were performed with applicable non-parametric tests for unpaired data. Patients contributed person-time in days from time of intervention and were censored at the time of death or at the end of the follow-up period. Multivariate modelling of the association between the RVEF and mortality was performed with the use of logistic regression using the backward likelihood ratio method. In our model, we included baseline characteristics with a p-value <0.25 in the univariate analysis. For multicategorical variables, the group with the highest number of patients served as reference category. All statistics were two-tailed and considered statistically significant if the p-value was <0.05.

OUTCOME

Primary endpoint of this study was two year all-cause mortality.

RESULTS

(Sub) group characteristics. Between January 2011 and January 2015, 3094 patients underwent cardiac surgery in our centre. 1109 patients matched our inclusion criteria and were included in the analysis. None of the patients were lost to follow-up. Median follow-up time was 739 days. We first composed a distribution curve of the RVEF (Fig. 1). In addition, patients were stratified into three groups based upon the mean $\pm$ one standard deviation: Group 1: RVEF <20%, group 2: RVEF 20–30%, group 3: RVEF >30%.

216 Patients were assigned to group 1 (median RVEF 18 [15–19]), 747 patients to group 2 (median RVEF 25 [23–27]), and 146 patients to group 3 (median RVEF 32 [31–34]). Baseline characteristics are listed in Table 2. We noted significant differences across groups in demographic features (age, bodyweight) and clinical characteristics. (Chronic Obstructive Pulmonary Disease (COPD); New York heart association score (NYHA); left ventricular function, and risk scores). Perioperative details are listed in Table 4. All-cause two year mortality was significantly different across groups: 4.1% for patients with RVEF >30%, 8.2% in the group with RVEF 20–30%, and 16.7% for patients with RVEF <20%, $p < 0.001$.

Figure 1: Gaussian curve of right ventricular ejection fraction in percentage and cut off values for groups.

PRIMARY OUTCOME

2-Year all-cause mortality was significantly different between groups (Fig. 2). In a multivariate logistic regression analysis both RVEF as a continuous variable or as group (RVEF <20%, Table 3) remained independently associated with the primary outcome. Thermodilution-derived RVEF was significantly different across groups of semi-quantitative assessment of postoperative TEE-derived RV function by eyeballing (poor-moderate-good); $p < 0.001$ (Fig 3.)

Figure 2: Kaplan-Meier curve for two year all-cause mortality. RVEF right ventricular ejection fraction

Table 2. Baseline characteristics

	RVEF < 20% (N=216)	RVEF 20-30% (N=747)	RVEF > 30% (N=146)	P-value
Demographics				
Age (years)	74 [67-79]	70 [63-77]	65 [58-73]	<0.001*
Male sex (%)	65	64	69	0.63
Bodyweight (kg)	76 [68-86]	80 [71-90]	83 [72-93]	0.02*
Comorbidities				
Diabetes mellitus (%)	18	21	16	0.37
Peripheral vessel disease (%)	15	15	17	0.79
TIA/CVA (%)	16	12	12	0.27
Neurological dysfunction (%) [†]	4	4	5	0.77
COPD (%) [‡]	22	17	12	0.04*
Preoperative serum creatinine	88 [76-107]	88 [75-102]	89 [77-100]	0.64
Cardiac status (%)				
NYHA class III or IV	50	36	35	0.01*
Recent myocardial infarction	12	12	9	0.60
Previous cardiac surgery	19	22	20	0.62
Preoperative LVEF (%)				
Good	41	58	64	<0.001*
Moderate	33	25	23	
Poor	21	12	7	
Risk scores				
Additive euroSCORE I	8 [6-10]	7 [5-9]	6 [4-8]	<0.001*
APACHE IV	52 [43-62]	48 [40-59]	45 [36-54]	<0.001*
Intra-operative characteristics				
Aortic cross-clamp (min)	98 [70-129]	97 [68-140]	93 [65-133]	0.58
ECC (min)	139 [96-187]	137 [99-190]	126 [89-182]	0.36
Procedure (%)				
CABG	13	12	11	0.45
Valve	49	45	54	
CABG + valve	28	32	23	
Other	10	10	12	

*Indicates a significant difference across groups. Data are presented as median [IQR] unless stated otherwise. [†] Long term use of bronchodilators or steroids for lung disease. [‡] Disease severely affecting ambulation or day-to-day functioning. RVEF right ventricular ejection fraction. TIA transient ischaemic attack. CVA cerebral vascular accident. COPD chronic obstructive pulmonary disease. NYHA New York heart association. LVEF left ventricular ejection fraction euroSCORE European system for cardiac operative risk evaluation APACHE acute physiology and chronic health evaluation. ECC extracorporeal circulation CABG coronary-artery bypass grafting.

Table 3. Univariate and multivariate analysis for 2-year mortality

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P Value	OR (95%CI)	P Value
Model 1 (RVEF as continuous variable (%))				
Age	1.07 (1.04-1.10)	<0.001	1.02 (0.99-1.05)	0.321
Bodyweight	0.99 (0.98-1.00)	0.192	1.00 (0.99-1.02)	0.889
COPD	1.97 (1.24-3.15)	0.004	1.32 (0.80-2.19)	0.280
NYHA class	1.38 (0.81-2.35)	0.188	1.17 (0.89-1.54)	0.267
Preoperative LVF	1.52 (1.14-2.02)	0.005	1.00 (0.74-1.36)	0.980
euroSCORE	1.41 (1.31-1.52)	<0.001	1.33 (1.23-1.45)	<0.001*
APACHE IV	1.04 (1.03-1.05)	<0.001	1.03 (1.01-1.04)	<0.001*
RVEF (%)	0.91 (0.88-0.95)	<0.001	0.95 (0.91-0.99)	0.011*
Model 2 (RVEF as categorical variable)				
RVEF <20%	2.25 (1.44-3.50)	<0.001	1.88 (1.18-3.00)	0.008*

*Indicates a significant difference across groups. Odds ratios (OR) and 95% confidence intervals (CI) comparing patients 2-year survivors versus non-survivors. Right ventricular ejection fraction (RVEF) is represented both as continuous variable (model 1) and as categorical variable (model 2). COPD chronic obstructive pulmonary disease. NYHA New York heart association class. LVF left ventricular function. euroSCORE European system for cardiac operative risk evaluation, APACHE IV acute physiology and chronic health evaluation

Table 4. Perioperative details

	RVEF < 20% (N=216)	RVEF 20-30% (N=747)	RVEF > 30% (N=146)	P-value
RVEF(%)	18 [15-19]	25 [23-27]	32 [31-34]	<0.001*
Mean postoperative PAP (mmHg)	21 [17-25]	19 [15-22]	18 [16-21]	<0.001*
PEEP level (mmHg)	10 [9.6-10.4]	10.1 [9.8-10.4]	10.1 [9.9-10.5]	0.04*
Use of inotropic drugs (%)	76	61	48	<0.001*
Length of hospital stay (days)	7 [4-9]	6 [5-9]	6[4-8]	0.62
Laboratory measurements				
Peak serum creatinine (umol/L)	101 [83-134]	92 [76-119]	90 [75-109]	0.276
Peak CK-MB (ukat/L)	0.39[0.24-0.72]	0.44[0.28-0.76]	0.40[0.27-0.66]	0,095
Complications				
Re-sternotomy (%)	7.4	6.6	6.8	0.912
Tamponade (%)	4.6	3.6	4.8	0.686
Transoesophageal echocardiography				
Postoperative LVF by eyeballing TEE (%)				
Good	52	70	72	<0.001*
Moderate	31	23	21	
Poor	17	7	6	

*Indicates a significant difference across groups. Data are presented as median [IQR] unless stated otherwise. RVEF right ventricular ejection fraction. PAP pulmonary artery pressure. PEEP positive end-expiratory pressure. CK-MB creatine kinase-MB. LVF left ventricular function. TEE transoesophageal echocardiography.

Figure 3: Comparison between right ventricular ejection fraction (RVEF) in percentage, determined with a pulmonary artery catheter and the postoperative right ventricular (RV) function assessed with eyeballing trans esophageal echocardiography (TEE)

DISCUSSION

In our study we observed a significant association between the postoperative RVEF and long-term mortality in a large cohort of heterogeneous post-cardiac surgery patients. 2-Year mortality in the RVEF <20% group was 16.7%, whereas mortality was 4.1% in the RVEF >30% group. Although RV dysfunction may in part be accompanied by other well-known risk factors, such as LV dysfunction, (poor) RVEF per se remained a risk factor after correction for potential confounders. The dispersive shape of the Kaplan- Meier curve indicates that the observed effect on mortality is not restricted to a single 'hit' in the period around the surgical procedure, but that its effects continues to aggravate outcome in the years after the intervention.

Nowadays, there is an increasing amount of literature that recognises the importance of RV failure in a large variety of other cardiac disease states. In a landmark paper by Zehender et al. the presence of RV infarction was associated with a crude hospital mortality of 31%, in comparison to 5% in patients with an isolated inferior wall myocardial infarction.⁹ More recently, ultrasound assessed RV dysfunction appeared to be a strong independent risk factor for long term survival in patients with myocardial infarction and pulmonary hypertension.^{10,11} Furthermore, in patients with left ventricular heart failure and preserved ejection fraction, reduction in the fractional area change of the RV was associated with higher mortality rates.¹² However, prior information on mortality in relation to RV function in cardiac surgery patients in the literature is limited to a few studies, characterized by small sample sizes and a high mortality.¹⁻⁴ Maslow et al. identified pre-CABG RV dysfunction (defined by ultrasound derived RV fractional area change <35%) as an additional risk factor for morbidity and mortality in selected patients with severe systolic LV dysfunction.³ In patients with impaired LV function undergoing mitral valve repair a RVEF <30% was reported to be a strong predictor of long-term postoperative survival.⁴ In addition, similar observations have been performed in very specific cardiac surgery patient populations, such as congenital heart disease.¹³ The complicated interaction between RV and LV dysfunction in cardiac surgery was recently underlined by the observation that surgical ventricular reconstruction in addition to CABG was associated with worsening of long-term survival in patients with ischemic cardiomyopathy and moderate to severe RV dysfunction.¹⁴ To our knowledge, our study is the first large sample size study in heterogeneous cardiac surgery patients, not selected for well-known hemodynamic features already associated with RV dysfunction. It is of note that even in a population with an overall low mortality rate, we observed RVEF to be an independent risk factor for mortality. Lastly, we are not aware of any large sample size studies with thermodilution-derived RV measurements.

In order to understand the impact of our observation, several issues need to be addressed. First of all, there is an absence of consensus about the definition of RV failure. Although 2D and 3D echocardiography-derived RVEF correlated well with the thermodilution method, the absolute values were considerably different. Similarly, tricuspid annular plane systolic excursion (TAPSE) showed a close correlation with PAC derived RVEF.¹⁵ On the other hand, an observed significant incidence of RV dysfunction as assessed by 2D TAPSE, was virtually absent in the 3D ultrasound-derived RVEF, highlighting the peculiar 3D anatomy of the right ventricle.¹⁶ Comparison between (ultrasound-derived) RVEF and magnetic resonance imaging (MRI)-derived RVEF is even more cumbersome.¹⁷ Clearly, the thermodilution method has the disadvantage of its invasive characteristics. On the other hand, the thermodilution method is the only available tool to sample RVEF continuously, adding to the robustness of the data. The data in this study are restricted to the postoperative assessment of the RV function.

Therefore it remains to be elucidated to what extent the surgical procedure and concomitant interventions, such as mechanical ventilation, contributed to RV dysfunction. In low risk CABG surgery, RVEF did not differ considerably before and after an uncomplicated surgical procedure.^{3,7,8} A significant increase in RVEF after revascularisation of the right coronary artery was reported, suggesting a relation between ischemia and RV dysfunction.¹⁸ However, others observed a significant reduction three months after CABG in RV function.¹⁹

Our study has several limitations. Due to the retrospective design of the study, the groups were not matched for baseline characteristics. Secondly, the use of a pulmonary artery catheter is still subject to discussion. In a Cochrane database review of all randomized controlled trials over the past years, Rajaram et al.¹⁹ could not demonstrate any beneficial or harmful effects of pulmonary artery catheters. However, the pulmonary artery catheter is the only bedside measurement device that allow for measurements of RV variables continuously and reliably measurements of haemodynamic variables and recent literature shows that pulmonary artery catheter use remains a mainstay of cardiac anaesthesia practise.^{8,20} Lastly, the observed association between RV dysfunction and long term mortality does not allow to conclude a cause-effect relationship.

FUTURE DIRECTIONS

Understanding the true cause-effect relationship between RV function and cardiac surgery is key to establish the consequences of our observations. In case RV dysfunction was present prior to the surgical procedure, it seems imminent to include RV function assessment in the pre-operative workup of high risk cardiac surgery patients. However, if RV dysfunction is a result of the set of perioperative procedures, further unravelling of the aetiology is warranted.

CONCLUSION

RV dysfunction is independently associated with two year all-cause mortality in a heterogeneous high-risk cardiac surgery population. The strong association between RV function and outcome warrants further studies to elucidate the aetiology of RV dysfunction in cardiac surgery.

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Chapter 4

Impaired Right Ventricular Ejection Fraction after Cardiac Surgery is Associated with a Complicated ICU Stay

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ABSTRACT

BACKGROUND

Right ventricular (RV) dysfunction is a known risk factor for increased mortality in cardiac surgery. However, the association between RV performance and ICU morbidity is largely unknown.

METHODS

We performed a single centre, retrospective study including cardiac surgery patients equipped with a pulmonary artery catheter, enabling continuous right ventricular ejection fraction (RVEF) measurements. Primary endpoint of our study was ICU morbidity (as determined by ICU length of stay, duration of mechanical ventilation, usage of inotropic drugs and fluids, and kidney dysfunction) in relation to RVEF. Patients were divided into three groups according to their RVEF; <20%, 20-30%, and > 30%.

RESULTS

We included 1109 patients. Patients with a RVEF <20% had a significantly longer stay in ICU, a longer duration of mechanical ventilation, higher fluid balance, a higher incidence of inotropic drug usage, and more increase in postoperative creatinine levels in comparison to the other subgroups. In a multivariate analysis, RVEF was independently associated with increased ICU length of stay (OR 0.934 CI 0.908-0.961, $p < 0.001$), prolonged duration of mechanical ventilation (OR 0.969, CI 0.942-0.998, $p = 0.033$), usage of inotropic drugs (OR 0.944, CI 0.917-0.971, $p < 0.001$), and increase in creatinine (OR 0.962, CI 0.934-0.991, $p = 0.011$).

CONCLUSIONS

A decreased RVEF is independently associated with a complicated ICU stay.

BACKGROUND

Nowadays, a set of robust models for the prediction of perioperative mortality in cardiac surgery has been validated.¹⁻³ However, mortality only reflects the burden of cardiac surgery to a limited extent. Over the years, mortality has decreased despite rising age and complexity.⁴⁻⁶ A subset of patients successfully survive the perioperative period at the expense of substantial ICU (intensive care unit)-related interventions, length-of-stay (LOS) and morbidity. Both for individual patients and healthcare administrators it seems relevant to determine the potential risk factors for a complicated post-cardiac surgery course. As of now, it is unclear whether the individual components of established prediction models for perioperative mortality are also relevant for the prediction of ICU morbidity, such as duration of mechanical ventilation and ICU LOS. In addition, the prediction models at hand do not incorporate right ventricular (RV) performance.⁷⁻¹⁰ Nowadays, RV dysfunction has been recognized as an independent risk factor for mortality in coronary artery bypass surgery (CABG) in combination with a poor left ventricular (LV) function¹¹, in valve surgery¹², congenital heart disease¹³, and recently in a heterogeneous group of cardiac surgery patients not selected for well-known risk factors for RV performance.¹⁴

To this end, we aimed to determine the prognostic value of postoperative RV function in relation to ICU morbidity. Subsequently we investigated the additional value of individual components of the euroSCORE in a multivariate model.

METHODS

STUDY POPULATION

We performed a single-centre retrospective study in a tertiary teaching hospital with a closed-format ICU. We included all cardiac surgery patients equipped with a pulmonary artery catheter (PAC) and admitted to the intensive care unit in the postoperative phase between January 2011 and January 2015. Exclusion criteria for this retrospective analysis include isolated coronary artery bypass grafting (CABG) with a good LV function. According to our institutional protocol, a large proportion of patients are equipped with a PAC after induction of anaesthesia. The decision to insert a pulmonary artery catheter was protocol driven and was taken at the start of the surgical procedure by the attending cardio-anaesthesiologist. His/her decision is based upon predefined criteria, entirely restricted to the type of surgery. In practice, only patients with an anticipated uncomplicated CABG procedure were not included.

The same cohort of patients has been used in a previous publication to clarify the association between RV performance post cardiac surgery and all-cause long term mortality.¹⁴ The study was approved by the local ethical and scientific committee and the need for informed consent was waived in accordance with applicable laws.

DATA COLLECTION

In case of postoperative PAC monitoring, patients were equipped with a 7.5F CEDV-Pulmonary Artery Catheter (model 744H, Baxter Healthcare Corporation, Irvine, CA, USA), directly after induction of anaesthesia. During surgery, additional haemodynamic monitoring was performed by transesophageal echocardiography (TEE). Prior to transfer to the ICU the PAC was interfaced with a computerised monitoring system (Vigilance II® CCO / SvO₂ / CEDV Monitor, Edwards Lifesciences Corporation, Irvine, CA, USA). The catheter is equipped with a thermal filament positioned 4 cm from the tip of the catheter. This thermal filament generates heat pulses in a random on-off pattern. The change in blood temperature is measured downstream throughout the entire respiratory cycle. Based on a repeating on-off signal, a relaxation waveform can be generated. The right ventricular ejection fraction can be computed by the exponential slope of this waveform curve and the continuous averaged heart rate. The longer it takes for the curve to reach baseline, the lower the ejection fraction. The random on-off pattern is repeated every 60 seconds and reflecting an average of the measurements taken over the last 5 to 10 minutes (time averaging).¹⁵ This catheter enables continuous measurement of the right ventricular ejection fraction (RVEF), cardiac output, and end-diastolic volume index (EDVi) at a sample rate of one per minute. For each patient, all PAC-derived measurements (cardiac index, pulmonary artery pressure (PAP), central venous pressure (CVP), EDVi, Mixed Venous Oxygen Saturation (SvO₂), and RVEF) started directly after ICU admission and were averaged over the first 24 hours of ICU admission. Based upon the Gaussian distribution curve of the postoperative RVEF, patients were stratified into three predefined groups: Group 1: RVEF <20%, group 2: RVEF 20-30%, group 3: RVEF >30%.

POSTOPERATIVE DETAILS

All patients were admitted to the ICU direct postoperatively. In our institution, by protocol, all postoperative cardiac surgery patients are admitted to the ICU on mechanical ventilation. No cases were extubated in the operating room.

Settings of mechanical ventilation were standardized according to local protocol, with a respiratory frequency of 20-30 times per minute, tidal volumes limited up to 6ml/kg ideal bodyweight, and a postoperative end-expiratory pressure (PEEP) of 10 cm H₂O. Extubation was performed within two hours of ICU-admission in case the patient was haemodynamically stable and in absence of signs of (surgical) complications (bleeding, infarction). All patients were discharged from the ICU on the first postoperative day, unless they had unstable and/or insufficient haemodynamic parameters, need for inotropes or vasopressor, signs of surgical complications (bleeding, infarction), and/or signs of organ failure.

STATISTICAL ANALYSES

Statistical analysis was performed using the statistical package for social science (SPSS 21 for Windows; SPSS Inc., Chicago, IL, USA). Data are described as median with interquartile range (IQR) unless stated otherwise. Kolmogorov-Smirnov test was used to test normal distribution. Differences between groups were performed with applicable non-parametric tests for unpaired data. Correlations were tested with the Spearman Rho (R_s) test. Bivariate logistic regression of the association between the RVEF and morbidity was performed using the backward likelihood ratio method. Markers of morbidity were transformed into dichotomous variables by using the 75th percentile as a cut off value.

Baseline characteristics with a p-value <0.25 in the univariate analysis were included. For multi-categorical variables, the group with the highest number of patients served as reference category. All statistics were two-tailed and considered statistically significant if the p-value was <0.05 . All euroSCORE variables with a p-value <0.25 in the univariate analysis were incorporated in the multivariate model as separate components.

ENDPOINTS

The primary endpoint of our study was ICU morbidity (as determined by ICU LOS, duration of mechanical ventilation, usage of inotropic drugs and fluids, and kidney dysfunction) in relation to right ventricular ejection fraction.

Secondary endpoints included the correlation between RVEF and different haemodynamic variables (PAP, cardiac index, EDVi, CVP, and SvO_2).

RESULTS

BASELINE CHARACTERISTICS

In the 4-year study period cardiac surgery was performed in 3094 patients. A total of 1109 patients matched the inclusion criteria. 216 patients were assigned to group 1 (RVEF 18 [15-19]%), 747 patients to group 2 (RVEF 25 [23-27]%), and 146 into group 3 (RVEF 32 [30-34]%). Baseline characteristics are listed in Table 1. Differences between groups were observed in demographic parameters (age, bodyweight), cardiac status (unstable angina, pre-operative LV performance) and other clinical parameters (APACHE IV and preoperative pulmonary hypertension). In detail, patients with a low RVEF were older, had more often COPD, pulmonary hypertension or unstable angina pectoris, and had a reduced preoperative left ventricular function and a higher APACHE IV and EuroSCORE. No differences were found between intraoperative characteristics and type of procedure.

Table 1: Baseline characteristics

	RVEF <20% N=216	RVEF 20-30% N=747	RVEF >30% N=146	p-value
Demographics				
Age (years)	74 [67-79]	70 [63-77]	66 [58-73]	<0.001*
Male sex (%)	65	64	69	0.635
Body weight (kg)	76 [68-86]	80 [71-90]	83 [72-93]	0.002*
Comorbidities (%)				
Diabetes mellitus	18	21	16	0.367
Peripheral vessel disease	15	15	17	0.565
TIA/CVA	16	121	12	0.269
Neurological dysfunction	4	4	5	0.772
COPD	22	17	12	0.038*
Cardiac status (%)				
Recent myocardial infarction	12	12	9	0.602
Previous cardiac surgery	19	22	20	0.618
Unstable Angina	4	5	1	0.036*
Preoperative LVEF (%) (TTE)				
Good (>55%)	40	59	66	<0.001*
Moderate (30-49%)	33	26	24	
Poor (<30%)	27	15	10	
Preoperative status				
serum creatinine (umol/L)	88 [76-107]	88 [75-102]	89 [77-100]	0.638
pulmonary hypertension (%)	7	3	1	0.013*
Intraoperative characteristics				
Aortic cross-clamp (min)	98 [71-129]	97 [68-140]	93 [64-133]	0.578
ECC (min)	139 [96-187]	137 [99-190]	126 [89-182]	0.363
Procedure (%)				
CABG	13	12	11	0.285
Valve	49	45	54	
CABG + valve	28	32	23	
Other	10	10	12	
Risk scores				
Apache IV	52 [43-62]	50 [40-59]	46 [36-54]	<0.001*
EuroSCORE I	8 [6-10]	7 [5-9]	6 [4-8]	<0.001*

* Indicates a significant difference across groups

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; ECC, extracorporeal circulation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; TIA, transient ischemic attack. TTE, transthoracic echocardiography.

PRIMARY ENDPOINT

In a univariate analysis, patients with the lowest RVEF (<20%, group 1) had a significantly longer stay in ICU ($p < 0.001$, Figure 1A) and a longer duration of mechanical ventilation ($p < 0.001$, Figure 1B) compared to patients with RVEF >20%. Furthermore, there was a significant more positive fluid balance ($p < 0.001$), a higher incidence of inotropic drug usage ($p < 0.001$), and a larger increase in postoperative creatinine ($p = 0.004$) (Table 2). There were no differences in postoperative complications between groups.

Figure 1A: median and 10-90th percentile and length of stay ICU.

Figure 1B: median and 10-90th percentile of duration of mechanical ventilation

After multivariate analysis, RVEF as a continuous variable was independently associated with ICU LOS (OR 0.934 CI 0.908-0.961, $p < 0.001$), duration of mechanical ventilation (OR 0.969, CI 0.942-0.998, $p = 0.033$), the use of inotropic drugs (OR 0.944, CI 0.917-0.971, $p < 0.001$), and increase in creatinine (OR 0.962, CI 0.934-0.991, $p = 0.011$) (Table 3). In addition, we also observed a significant correlation coefficient between CVP and rise in serum creatinine ($rs = 0.21$, $p < 0.001$). The odds ratios are a decreased risk for every increase in RVEF per percentage in model 1, and in model 2 the odds ratios are an increased risk compared to the group with the best RVEF. (>30%, group 3).

SECONDARY ENDPOINTS

In a univariate analysis, patients with the lowest RVEF (<20%) had a significant higher PAP and EDVi. Furthermore, they had a significant lower cardiac index and SvO₂ (Table 2).

We observed a significant, but weak correlation between the PAP and RVEF ($R_s = -0.187$, $p < 0.001$), CVP and EDVi ($R_s = -0.135$, $p < 0.001$), and PAP and EDVi ($R_s = 0.062$, $p = 0.039$). In addition, there was no significant correlation between the CVP and RVEF ($R_s = -0.052$, $p = 0.084$). (Figure 2)

Figure 2: Relation between pressure (CVP or PAP) and volume (EDVi or RVEF) derived variables. N=1109. Mean values measured with a pulmonary artery catheter over the first 24 hours of ICU admission. *Indicates a significant correlation between variables. Abbreviations: CVP central venous pressure; PAP pulmonary artery pressure; EDVi end-diastolic volume index; RVEF right ventricular ejection fraction

To further elaborate potential confounding factors in the relationship to RVEF (predominantly, LV performance and pulmonary hypertension), we separated LV and RV performance in 4 groups: Group 1: normal LV and normal RV performance. Group 2: poor LV and normal RV performance. Group 3: Normal LV and poor RV performance and group 4: poor LV and poor RV performance. (Poor LV function defined as an EF < 30%, and poor RV function as an EF < 20%). Isolated poor LV performance is statistically associated with the presence of prolonged ICU stay. ($p \leq 0.001$, fig 3)) In addition, this is also true for those patients with a good LV function and an isolated poor RV performance ($p < 0.001$). Furthermore, both isolated poor LV and RV performance are also statistically associated with prolonged mechanical ventilation. (poor LV: $p < 0.010$, poor RV $p < 0.001$, figure 3)

The second main confounder is most likely pulmonary artery pressure (which relates to COPD as well). In addition to the correlation coefficient (figure 3), we separated the group according to the international definition of pulmonary hypertension (mean PAP ≥ 25 mmHg)¹⁶ in the first 24 hours

postoperatively). The percentage of patients with postoperative pulmonary hypertension was significantly different across groups: 7% in patients with RVEF >30%, 9% in patients with a RVEF between 20 and 30% and 24% in patients with a RVEF <20% (p<0.001).

In addition, 121/216 patient (56%) had a RVEF <20% in the absence of a poor LV performance or pulmonary hypertension. Interestingly, the percentage of patients with a prolonged length of stay ICU and prolonged mechanical ventilation was not significantly different between those two subgroups.

Figure 3: Percentage of patients with a prolonged ICU stay (above) and prolonged mechanical ventilation (below) when separated in 4 different groups according to their LV, measured with transthoracic echocardiography preoperatively, and RV performance measured with pulmonary artery catheter postoperatively.

*Means a statistical difference among groups. Abbreviations: LVEF: left ventricular ejection fraction. RV: right ventricular ejection fraction. ICU: Intensive Care Unit

Table 2: Postoperative details

	RVEF <20%	RVEF 20-30%	RVEF >30%	P-value
Mortality ICU (%)	4.2%	1.2%	0.7%	0.008*
LVEF (%) (TEE)				
Good (>55%)	52	69	72	<0.001*
Moderate (30-49%)	31	24	21	
Poor (<30%)	17	8	9	
Markers of morbidity				
Length of stay ICU (days)	2 [2-5]	2 [2-3]	2 [2-2]	<0.001*
Mechanical ventilation (h)	5.5 [3.5-17.8]	4.5 [3-8]	3.8 [2.5-5.6]	<0.001*
Fluid balance (L)	1.9 [1.2-3.2]	1.6 [0.8-2.8]	1.1 [0.3-2.0]	<0.001*
Use of inotropic drugs (%)	76	61	48	<0.001*
Postoperative laboratory details				
Delta creatinine (umol/L)‡	12 [-13 - 41]	5 [-9 -28]	0 [-10 - 19]	0.004*
Peak lactate (mmol/L)	2.6 [1.9-3.4]	2.7 [2.0-3.5]	2.7 [2.0-3.5]	0.431
Peak CK-MB (U/L)	39 [24-72]	44 [28-76]	40 [27-66]	0.095
Postoperative complications (%)				
Re-sternotomy	7.4	6.6	6.8	0.910
Tamponade	4.6	3.6	4.8	0.686
CVVHD	4.2	1.9	1.4	0.101
Haemodynamic variables†				
RVEF (%)	18 [15-19]	25 [23-27]	32 [31-34]	<0.001*
Mean PAP (mmHg)	20 [17-25]	19 [15-22]	18 [16-21]	<0.001*
Cardiac index (L/min/m ²)	2.2 [2.0-2.5]	2.4 [2.2-2.7]	2.7 [2.4-3.0]	<0.001*
EDVi (ml/m ²)	143 [124-167]	113 [100-128]	101 [85 - 115]	<0.001*
CVP (mmHg)	8 [5-10]	7 [5-9]	7 [5-9]	0.081
SvO ₂ (%)	64 [59-68]	65 [60-69]	68 [63-71]	<0.001*
PHT (%)	24	9	7	<0.001*

‡Postoperative delta creatinine is the difference between preoperative creatinine and postoperative peak value creatinine. †Mean values measured with a pulmonary artery catheter over the first 24 hours of ICU admission. Abbreviations: ICU, intensive care unit; CK-MB, creatine kinase-myoglobin binding; CVVHD, continuous veno-venous haemodialysis; LV, left ventricular; RVEF, right ventricular ejection fraction; PAP, pulmonary artery pressure; EDVi, end-diastolic volume index; CVP, central venous pressure; SvO₂, Mixed Venous Oxygen Saturation; PHT, pulmonary hypertension. TEE, transoesophageal echocardiography.

Table 3: Binary logistic regression analysis with odds ratios for markers of morbidity

Model 1: RVEF as a continuous variable					
	Lengths of stay ICU ≥ 3 days	Mechanical ventilation ≥8.5h	Fluid balance ≥ 2.8L	Use of inotropic drugs (Y/N)	Increase in creatinine ≥ 30 umol/l
	0.934	0.969	0.974	0.944	0.962
RVEF (%)	[0.908-0.961] p<0.001*	[0.942-0.998] p=0.033*	[0.947-1.002] p= 0.065	[0.917-0.971] p<0.001*	[0.934-0.991] p= 0.011*
	0.984	0.988	0.995	0.982	1.000
Age (years)	[0.969-0.999] p=0.038*	[0.972-1.004] p=0.143	[0.979-1.011] p=0.538	[0.968-0.997] p= 0.018*	[0.982-1.016] p=0.907
	1.001	1.000	0.998	0.996	1.019
Bodyweight (kg)	[0.991-1.010] p=0.914	[0.989-1.010] P=0.942	[0.988-1.009] p=0.760	[0.986-1.005] p=0.393	[1.009-1.029] p=<0.001*
	1.192	1.136	1.120	1.110	0.824
COPD	[0.833-1.706] p=0.336	[0.777-1.661] p=0.510	[0.774-1.620] p=0.548	[0.764-1.613] p=0.584	[0.557-1.219] P=0.332
	4.599	4.671	2.302	1.538	1.203
Unstable angina	[2.309-9.163] p<0.001*	[2.433- 8.969] p<0.001*	[1.237-4.284] p=0.008*	[0.665-3.552] p=0.314	[0.615-2,355] p=0.589
	1.385	1.044	0.806	11.579	1.453
Poor LVEF†	[0.950-2.020] p=0.091	[0.737-1.479] p=0.807	[0.536-1.212] p=0.300	[6.393-20.973] p<0.001*	[0.986-2.139] p=0.059
	1.321	1.187	1.067	2.284	2.179
Pulmonary hypertension	[0.662-2.635] p=0.430	[0.574-2.453] p=0.644	[0.516-2.206] p=0.861	[0.931-5.601] p=0.071	[1.113-4.268] p=0.023*
	1.061	1.057	1.044	1.038	1.050
Apache IV score	[1.049 - 1.073] p<0.001*	[1.045-1.068] p<0.001*	[1.034-1.055] p<0.001*	[1.027-1.050] p<0.001*	[1.039-1.061] p=<0.001*
Model 2: RVEF as a categorical variable with RVEF>30% as reference group					
	2,050	1.301	1.422	1.559	1.190
RVEF 20-30%	[1.258-3.340] p=0.004*	[0.794-2.131] p=0.297	[0.878-2.302] p=0.152	[1.050-2.316] p=0.028*	[0.741-1.910] p=0.472
	3,250	1.896	1.732	2.259	1.633
RVEF <20%	[1,879-5.621] p<0.001*	[1.093-3.288] p=0.023*	[1.007-2.977] p=0,047*	[1.359-3.754] p=0.002*	[0.949-2.812] p=0.077

*Indicates a significant difference across groups. †Left ventricular ejection fraction <30%. Abbreviations: CI confidence interval; RVEF right ventricular ejection fraction; ICU intensive care unit; COPD chronic obstructive pulmonary disease; LVEF left ventricular ejection fraction; APACHE Acute Physiology and Chronic Health Evaluation.

DISCUSSION

In this study, we aimed to evaluate the prognostic value of RV performance and to identify risk factors for ICU morbidity. There was a striking absence of association between well-known risk factors for mortality, such as left ventricular function and pulmonary artery pressure, and markers of ICU morbidity. With the exception of unstable angina, all variables of the euroSCORE model did not independently predict ICU LOS or duration of mechanical ventilation in our population. On the other hand, the performance of the RV (which is not included in the euroSCORE or APACHE IV) was independently associated with markers of ICU morbidity. However, it must be stressed that the total package of easily obtainable variables in the euroSCORE and APACHE IV score is a robust and well-validated method to predict outcome.

Over the last decades, mortality in cardiac surgery has decreased despite of an increase in age and complexity of surgery.^{6,17} At the same time, there has been an increase in postoperative morbidity, resulting in prolonged ICU stay and an increased use of ICU resources.^{17,18} This increase in ICU morbidity has great impact on the availability of ICU beds, costs, and the burden of suffering for individual patients.¹⁹ Several studies focused on the prediction of the LOS ICU.^{17,20,21} In contrast to our findings, previous studies mainly identified age, female gender, poor left ventricular function, type of surgery and renal failure as risk factors for prolonged ICU stay.

In addition, the euroSCORE and Parsonnet score were reported to be suitable as risk scores for ICU morbidity.^{17,18,22} It is conceivable that we could not reproduce the impact of the individual components of the euroSCORE, due to the limited impact of the separate variables. Moreover, the original validation of the Parsonnet score was performed in a cardiac surgery population with a considerably higher mortality (up to 20%) in comparison to our study.² Alternatively, the unique addition of the postoperative RV performance to these otherwise preoperative risk factors may have influenced our predictive model considerably.

Several studies addressed the contribution of RV performance on ICU morbidity and mortality in cardiac surgery. Among patients with hypotension, the majority of the non-survivors appeared to classify as isolated RV failure or biventricular failure. In contradiction, isolated LV dysfunction was associated with a significant better prognosis as compared to RV dysfunction.^{23,24} In CABG patients with a poor LV function, a fractional area change of the RV (RVFAC) $\leq 35\%$ was associated with prolonged duration of mechanical ventilation, ICU and hospital LOS and increased use of inotropic drugs.¹¹ Furthermore, RV dysfunction was associated with a high mortality rate in myocardial infarction²⁵ and valve surgery.¹² Recently we identified a poor RV performance as a strong independent risk factor for long-term mortality in a large mixed cardiac

surgery population.¹⁴ Although the clinical impact of RV performance on mortality seems to be established, robust data on the influence of RV performance after cardiac surgery on ICU morbidity are still lacking.^{7,26} Our data indicate to incorporate RV function into future predictive models.

A possible explanation for the absence of postoperative RV performance in predictive models is the fact that RV dysfunction may well be under-diagnosed. The complex anatomy of the RV makes it challenging to assess its function.²⁷ Although there are several reliable and reproducible echocardiographic variables to assess RV function, image quality by transthoracic echocardiography (TTE) in the postoperative phase after cardiac surgery is often limited due to mediastinal air, drains, dressings, and the supine position.²⁸⁻³⁰ The lowest image quality with TTE has been found on the first postoperative day.³¹ Generally, for transesophageal echocardiography (TEE) sedation is required for tolerance, which does not make it a suitable investigation for the awake patient in the postoperative phase. Furthermore, a trained user for TEE/TTE will not be available for 24 hours a day and data are based upon single spot measurements. Despite the general debate about the use of PAC, its newest generation enables continuous measurement of the RVEF, EDVi, cardiac index and SvO₂ and will overcome the above limitations. Furthermore, our data showed a significant correlation between TEE findings and PAC-derived RVEF. Despite all odds, recent data indicate a benefit of the use of PAC in the setting of cardiac surgery.^{32,33}

The lack of clinically relevant correlations between volumetric variables (RVEF/EDVi) and classical pressure variables, such as CVP and PAP, is an important observation in our study. Although an inconvenient truth, such observations are supported by physiological theory. First of all pulmonary hypertension is a well-known risk factor for RV dysfunction, since it is the main determinant of RV afterload.³⁴ However, this does not imply that other factors may not contribute to impaired RV function. It is noteworthy that in our study-population median PAP was as low as 20 [17-25] mmHg in the first 24 hours postoperatively in patients with a RVEF <20%. Only 24% of the patients with a RVEF <20% meets the criteria of pulmonary hypertension. These data underline what is known from literature: pulmonary hypertension is a risk factor for RV failure. However, it also implies that a substantial percentage of patients with a low RVEF does not have pulmonary hypertension. And vice versa, pulmonary hypertension does not necessarily result in RV dysfunction.³⁵ Although sensitive to a sudden increase in afterload, a more gradual increase in pulmonary vascular resistance may result in adequate coping of the RV by increased contractility and remodelling.³⁶

Pulmonary hypertension may not be the only contributing factor to RV failure in the postoperative setting; LV dysfunction, ischemia and

positive-pressure ventilation have been associated with RV performance as well.^{25,37,38} We separated our data into 4 groups according to their left and right ventricular performance. These data underline the idea that there is a subcategory of patients with an isolated poor RV performance (in the absence of a poor LV performance) that has similar prognosis as patients with an isolated poor LV performance (in the absence of a poor RV performance). Although RV and LV performance are clearly related to one another, isolated forms of RV or LV dysfunction seem to exist and have similar prognostic value. The fact that a combined poor LV and RV function did not seem to contribute to impair outcome is at first glance a somewhat unexpected finding. The simple explanation could be that the sample size of the group is apparently too small to detect differences whatsoever. But it is also conceivable that this subgroup may represent a selection bias. Since a poor LV and RV function is likely to be acknowledge preoperatively, surgery may only be performed in the best subgroup of these patients. Alternatively the combination of a low LV and RV function is a marker of a slowly progressive form of heart failure which allows for adaptation, whereas isolated right heart failure may reflect a more acute form of unadapted heart failure. In a previous report, additional surgery in ischemic heart disease to redress the size of the left ventricle was associated with a reduction in right ventricular function and subsequent a decrease in survival. This data underlines the importance of right and left ventricular remodelling in the setting of heart failure.^{39,40}

In addition, CVP may not serve as a surrogate for RV performance either, reflecting the non-linear end-diastolic pressure-volume relation.⁴¹ At low end-diastolic volumes, RV pressure increases minimally for a given increase in volume. At high end-diastolic volumes, the pressure rises disproportionately for a similar increase in volume. This lack of association between CVP and RVEF was illustrated by a correlation coefficient of 0.052 ($p=0.084$).

Lastly, we observed an independent association between RVEF and a postoperative increase in creatinine. In addition, we also observed a significant correlation between rise in creatinine and CVP. This is in line with the current literature. Venous congestion has been reported to be the strongest haemodynamic determinant for worsening of renal function, independent of cardiac output.⁴² The current hypothesis to explain this phenomenon is that an increase in venous pressure serves as an outflow obstruction for organ perfusion.⁴³

Our study has several limitations. Although the PAC used in our study allows for continuous assessment of RV performance, its use for this purpose may be a topic of debate. Alternatively, RV function may be determined by TEE-derived variables such as Tricuspid Annular Plane Systolic Excursion (TAPSE) and S' .^{44,45} However, although robust in the prediction of cardiac

surgery related mortality, the prognostic value of these variables for ICU morbidity remains to be established. The retrospective design of our study does not allow for the elaboration of cause-effect relationships. Although we built a multivariate model with a large variety of well-known risk factors, it is conceivable that a yet unknown factor may have served as a potential bias. In order to establish the clinical relevance of the prognostic value of RV function in relation to ICU morbidity, new models that include RV function have to be tested prospectively. Lastly, due to lack of pre-operative values of RV function, this study does not allow to differentiate patients with pre-existing impairment of RV function and those who develop RV dysfunction during cardiac surgery. Future studies are needed to elaborate this important topic.

CONCLUSION

In our dataset RVEF and unstable angina appeared to be independent risk factors for markers of ICU morbidity, such as length of ICU stay, duration of mechanical ventilation and increased use of inotropic drugs. There was a striking absence of prognostic value for the individual components of the euroSCORE in relation to ICU morbidity. CVP and PAP cannot be used as surrogates for volumetric RV variables. Selection of high-risk cardiac surgery patients in terms of individual burden, costs, and use of ICU resources warrants further research in this field.

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- Impaired Right Ventricular Ejection Fraction after Cardiac Surgery is Associated with a Complicated ICU Stay -

Chapter 5

The Reduction in Right Ventricular longitudinal Contraction Parameters is not Accompanied by a Reduction in General Right Ventricular Performance During Aortic Valve Replacement: an Explorative Study

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ABSTRACT

OBJECTIVE: The aim of this study was to identify whether the decrease of longitudinal parameters after cardiothoracic surgery, i.e. tricuspid annular systolic plane excursion (TAPSE) and systolic excursion velocity (S'), is accompanied by a reduction in global RV performance.

DESIGN: prospective observational study.

SETTING: single-center explorative study in a tertiary teaching hospital.

PARTICIPANTS: 20 patients who underwent aortic valve replacement with or without coronary artery bypass grafting.

INTERVENTIONS: During cardiac surgery, simultaneous measurements of RV function were performed with pulmonary artery catheter (PAC) and transesophageal echocardiography (TEE).

MEASUREMENTS AND MAIN RESULTS: TAPSE and S' were significantly reduced directly after surgery as compared to the time prior to surgery. (TAPSE from 20.8[16.6-23.4] to 9.1[5.6-15.5] mm, $p<0.001$ and S' from 8.7[7.9-10.7], to 7.2 [5.7-8.6] cm/s, $p=0.041$). However, the reduction in TAPSE and S' was not accompanied by a reduction in RV performance, as assessed by TEE-derived myocardial performance index (MPI) and PAC-derived right ventricular ejection fraction (RVEF). Both remained statistically unaltered before and after the procedure (MPI from 0.52 [0.43-0.58] to 0.50 [0.42-0.88], $p=0.278$ and RVEF from 27 [22-32] to 26 [22-28]%, $p=0.294$).

CONCLUSIONS: In the direct postoperative phase, the reduction of echocardiographic parameters of longitudinal RV contractility (TAPSE and S') was not accompanied by a reduction in global RV performance, expressed as MPI and RVEF. Solely relying on a single RV parameter as a marker for global RV performance may not be adequate to assess the complex adaptation of the RV to aortic valve replacement.

INTRODUCTION

Over the years, the prognostic value of the right ventricular (RV) function in cardiac surgery has increasingly been recognized. RV dysfunction is associated with morbidity and mortality both in patient populations with well-known risk factors for RV dysfunction as well as in more general cardiac surgery populations.¹⁻⁵

Clinical assessment of RV dysfunction remains a topic of debate.^{6,7} With longitudinal shortening as the main contributor for RV contraction, longitudinal echocardiographic parameters, such as tricuspid annular systolic plane excursion (TAPSE) and systolic excursion velocity (S') are considered to represent the systolic function of the RV.^{8,9,10} In the non-cardiac surgery setting, TAPSE and S' were associated with reduced right ventricular ejection fraction (RVEF). In addition, TAPSE was most predictive for survival in a variety of patient groups.¹¹⁻¹³

However, in post-cardiac surgery patients, the relationship between the well-established decrease in these longitudinal echocardiographic parameters and actual RV performance is unknown. Moreover, the etiology of this decrease remains unclear.¹⁴⁻¹⁶ A variety of factors, including the opening of the pericardium, have been suggested as contributors to this phenomenon.¹⁷⁻²⁰ Another theory is that the longitudinal contraction is reduced while the transversal contraction is increased. This would result in a stable RV function with diminished longitudinal parameters.²¹

The aim of this study was to assess ultrasound-derived RV parameters simultaneously with pulmonary artery catheter (PAC) derived variables of RV function, to identify whether the decrease of longitudinal echocardiographic parameters is accompanied by a reduction in global RV performance.

METHODS

STUDY POPULATION

A single-center prospective observational explorative study in a tertiary teaching hospital was performed. 20 patients with significant aortic stenosis (aortic valve area $<1\text{cm}^2$ and/or a mean aortic valve pressure gradient $>40\text{mmHg}$) who were scheduled for aortic valve replacement (AVR) with or without coronary artery bypass grafting (CABG) were prospectively included.

Exclusion criteria were; age <18 years, pre-operative tricuspid valve regurgitation, atrial fibrillation, non-elective surgery, significant stenosis in the right coronary artery (RCA), a pre-operative left ventricular ejection fraction less than 55%, and a previous history of cardiac surgery. According to our institutional protocol, intra-operative monitoring for the abovementioned procedures consists of transesophageal

echocardiography (TEE) and a PAC, enabling continuous measurements of RV performance. The study was approved by the local ethical and scientific committee and the need for informed consent was waived in accordance with applicable laws (Regionale Toetsingscommissie Patiëntgebonden Onderzoek Leeuwarden, nWMO 220). The study was registered prior to patient enrolment at clinicaltrials.gov (registration number NCT03183414).

DATA COLLECTION

Simultaneous TEE and PAC measurements were performed during six separate time points: 1: After general anesthesia, before sternal opening. 2: After sternal opening. 3 After pericardial opening. 4 After weaning of cardiopulmonary bypass (i.e. 5 minutes after removal of cannulas) 5 After pericardial approximation or closure. 6. After sternal closure. None of the variables were considered as absolute reference value (gold standard).

PULMONARY ARTERY CATHETER

Hemodynamic variables were derived from a PAC (7.5F CCO/SvO₂/CEDV-Pulmonary Artery Catheter, model 774F75, Edwards Lifesciences Corporation, Irvine, USA), which interfaced with a computerized monitoring system (Vigilance® CCO/SvO₂/CEDV monitor, Edwards Lifesciences Corporation, Irvine, USA). This catheter is equipped with a thermal filament which generates heat pulses in a random on-off pattern for continuous thermodilution cardiac output measurements, which is repeated every 60 seconds. The change in blood temperature is measured downstream throughout the entire respiratory cycle. Based on this pattern, a relaxation thermodilution waveform is generated. The RVEF is computed by the exponential slope of this thermodilution waveform curve and the continuous averaged heart rate.²² In addition to the RVEF, this catheter enables continuous measurements of the cardiac output and cardiac index, mixed venous oxygen saturation (SvO₂), end-diastolic volume index (EDVi), pulmonary artery pressures (PAP), and central venous pressure (CVP). The PAC was placed immediately after induction of anesthesia via the right jugular vein. Positioning of the PAC was performed according to instructions of the manufacturer based on waveforms and pressure characteristics. Measurements started directly after placement of the PAC. During cardiopulmonary bypass (CPB), measurements were paused and restarted immediately after weaning from CPB.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Two-dimensional TEE measurements were performed with the Philips IE33® transesophageal echocardiography system (Philips Medical Systems, Eindhoven, the Netherlands) with a X7-2t TEE probe (Philips Medical Systems, Andover, MA, USA). Following induction of general anesthesia and PAC placement, the TEE probe was placed and data were acquired directly after placement. All subjects were in zero degrees supine

position. All measurements of the RV were performed with the probe in the modified (deep) transgastric position (dTG) at 0°. ^{23,24}

Image acquisition was obtained by a single echo cardiographer. In each acquired image, three cardiac cycles were recorded. The RV function was analyzed using M-mode and pulsed wave tissue doppler imaging (TDI). The ultrasound line was aligned at the RV free wall at the level of the lateral tricuspid annulus to measure both TAPSE and velocities with pulsed wave tissue doppler imaging (PW TDI). PW TDI represents the time to peak velocity of the systolic myocardial contraction (S'), the early diastolic myocardial relaxation (E'), and active atrial contraction in late diastole (A'). Myocardial performance index (MPI) as a global index of myocardial function was measured with PW TDI. M-mode is defined as a mono-dimensional view of the ultrasound wave along a chosen ultrasound line. The ultrasound line was aligned at the lateral annulus of the tricuspid valve to measure TAPSE. All images were analyzed using Philips IntelliSpace Cardiovascular 2.3 software. Criteria for readability of the images were defined as a clear delineation of the lateral tricuspid annulus and traceable envelopes of PW TDI. The reliability of the TEE measurements was evaluated by calculating intra- and interobserver variability. Offline post-processing data analysis of measurements was done post-operatively by two experienced operators in a blinded manner and in random order to test the inter-observer variability. The second operator was not directly involved in the image acquisition and is American Society of Echocardiography Board Certified. For assessment of intra-observer variability, offline analysis of all measurements was repeated by the same observer in a blinded manner and in random order.

PERI-OPERATIVE DETAILS

All patients were anesthetized in the same manner according to local protocol. Induction of anesthesia was established with sufentanil 3-7 µg/kg, rocuronium 0.6 mg/kg, and midazolam 0.1 mg/kg. For maintenance sevoflurane and sufentanil was used. All patients received tranexamic acid 2g, and if below 75 years of age also 1 mg kg⁻¹ of dexamethasone was administered. Cardiopulmonary bypass was performed at a continuous blood flow (2.2-3.0 l/min/m²) during normo- or mild hypothermia (>34°C). The CPB hardware consisted of a HL-30 heart-lung machine and HCU-30 heater-cooler and inline blood analysis monitor (CDI 500 Terumo Cardiovascular Systems Corporation, Ann Arbor, Michigan, USA). The CPB circuit consisted of a Rotaflow centrifugal pump, a Quadrox-D membrane oxygenator a Quart arterial filter, a JVR1900 collapsible venous reservoir and a BCR 3500 cardiotomy-reservoir. The components are Bioline-coated, except for the venous reservoir which has a Safeline-coating (MAQUET Cardiopulmonary AG, Hirrlingen, Germany). Heparinization started with an initial bolus of 300 IU/kg heparin (LEO Pharma BV, Amsterdam, the Netherlands), which was replenished until the Celite activated clotting

time (ACT) test exceeded 480 seconds (Hemochron® Response, Edison, NJ, USA). The CPB priming solution (1400 ml) contained 7500 IU heparin. After termination of the extracorporeal circulation heparin was reversed with protamine sulphate (Meda Pharma BV, Amstelveen, the Netherlands). A cell saver was used during full heparinization of the patient. Surgical procedures were performed per local protocol. Cardioplegia was administered continuously (blood) or intermittently (St Thomas) every 45 min, by surgical preference.

By protocol, all patients received temporary pacemaker leads and were subsequently paced 90 beats per minute. The pacing wires were placed on the atrial and ventricular epicardial surface before weaning from cardiopulmonary bypass. Preferably, pacemakers were programmed in the AAI mode. In case of an abnormal supraventricular rhythm, the pacemaker was set to VVI mode. Patients in VVI mode were excluded from assessment of E'/A' and MPI. Throughout the procedure, patients were ventilated in a pressure regulated volume-controlled mode and PEEP settings remained unaltered.

STATISTICAL ANALYSIS

Statistical analyses were performed using the statistical package for social science (SPSS 25 for Windows; SPSS Inc, Chicago, IL). Data are described as median with interquartile range [IQR] unless stated otherwise. Due to small sample size, non-parametric tests were applicable. Comparison between two measurements in time of a single variable were performed by Wilcoxon Signed Rank Test. Correlation coefficients were expressed as Spearman Rs. All results were considered significantly different in case the p-value was <0.05. Due to the explorative nature of the study, a power calculation was impossible. In accordance with similar studies a sample size of 20 patients was deemed sufficient. Bland-Altman analysis was used to obtain inter- and intra-observer variability between echocardiographic measurements. For both intra- and inter observer variability, the intraclass correlation coefficient was calculated, using the two-way random model and absolute agreement between measurements.

RESULTS

Between July 2017 and July 2018, 121 patients underwent AVR with or without CABG in our institution. Major reason for exclusion were significant right coronary artery stenosis (N=41), logistical reasons (N=30), and atrial fibrillation (N=6). Baseline characteristics are listed in Table 1. Pre-operative LVEF was above 55% in all patients. In six patients, the postoperative quality of the PW TDI signal was either insufficient or VVI pacing rendered the measurement of MPI impossible. None of the patients had a mitral regurgitation exceeding grade 1 out of 4.

RIGHT VENTRICULAR FUNCTION MEASUREMENTS

TEE measurements of all subjects during surgical procedure are shown in Table 2. TAPSE was significantly reduced from between the time before surgical procedure to sternal closure (from 20.8 [16.6-23.4] to 9.1 [5.6-15.5] mm, $p<0.001$, Fig 1). Representation over time shows that this reduction was not limited to the pericardial opening, but appeared to be a gradual reduction, even after partial pericardial closure (Fig 2A). In addition, S' also decreased over time. (from 8.7 [7.9-10.7], to 7.2 [5.7-8.6] cm/s, $p=0.041$, Fig 3A). The overall reduction in TAPSE and S' was not accompanied by a reduction in actual RV performance: MPI remained constant before and after the procedure (from 0.52 [0.43-0.58] to 0.50 [0.42-0.88], $p=0.278$, Fig 3B). In addition, PAC-derived RVEF was also unaltered after the procedure (from 27 [22-32] to 26 [22-28]%, $p=0.294$, Fig 2B and Fig 3C). Simultaneously, continuous cardiac index (CCI) increased over time (from 2.4 [1.7-2.8] to 2.9 [2.4-3.4] l/min/m², $p=0.009$, Fig 3D). There was no change in central venous pressure (CVP) and pulmonary artery pressure (Table 2). The correlation coefficient between the change in TAPSE over time and the change in RVEF over time was insignificant. (Fig 4; $r_s^2=0.02$, $p=0.37$) The inter- and intra-observer variability showed a very good reproducibility for all echocardiographic measurements (Supplemental materials; Table S1, Figure S1, and Figure S2)

Table 1: Perioperative characteristics

Demographic characteristics (N=20)	
Age (years)	69 [65-76]
Male (%)	45
Comorbidities (%)	
Diabetes mellitus	15
Vessel disease	30
COPD	0
Cardiac status	
Recent myocardial infarction (<90days) (%)	0
Previous cardiac surgery (%)	0
Unstable Angina (%)	0
NYHA class III or IV (%)	45
euroSCORE II	1.4 [1.1-1.8]
Left ventricular function (%)	
Preoperative LVEF >55%	100
Postoperative LVEF >55%	95
Moderate or severe LV hypertrophy	12
Dilated LV	0
Preoperative status	
Preoperative serum creatinine	79 [69-92]
Preoperative pulmonary hypertension (%)	4
Intraoperative characteristics	
Aortic cross-clamp time (min)	78 [60-94]
ECC time (min)	100 [82-121]
Use of norepinephrine after CPB (%)	15
Use of phenylephrine after CPB (%)	75
Use of dobutamine after CPB (%)	0
Procedure (%)	
CABG+AVR	20
Isolated AVR	80
Postoperative characteristics (%)	
Myocardial infarction	5
Reoperation	10
Tamponade	5
Bleeding	5
Ischemic Cerebrovascular accident	5

Data are presented as median [IQR] unless stated otherwise. Abbreviations: COPD: Chronic obstructive pulmonary disease; NYHA: New York Heart Association; euroSCORE European System for Cardiac Operative Risk Evaluation; LVEF: Left Ventricular Ejection Fraction; LV: Left Ventricle ECC: Extracorporeal circulation; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; AVR Aortic Valve Replacement.

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Figure 1: Individual measurements of tricuspid annular plane systolic excursion (TAPSE), measured with transesophageal echocardiography before sternal opening (1) and after sternal closure (6).

Figure 2: Evaluation of right ventricular function

Measurement points: 1: after general anesthesia. 2: After sternal opening. 3 After pericardial opening. 4: After weaning from cardiopulmonary bypass. 5: After pericardial approximation or closure. 6. After sternal closure.

* $p < 0.05$. P-values were calculated over the difference between time point 1 and 6.

Figure 2A: Tricuspid annular systolic plane excursion (TAPSE) measured with transesophageal echocardiography.

Figure 2B: Right ventricular ejection fraction measured with pulmonary artery catheter.

Figure 3: Comparison between pre-operative measurements before sternal opening (point 1) and postoperative measurement after sternal closure (point 6). Systolic excursion velocity (S') was measured with transesophageal pulsed wave tissue doppler (Fig 3A), Myocardial performance index (MPI) with transesophageal echocardiography (Fig 3B), right ventricular ejection fraction (RVEF) was measured with a pulmonary artery catheter (Fig 3C), and continuous cardiac index (CCI) was measured with a pulmonary artery catheter (Fig 3D). * $p < 0.05$. NS = non-significant.

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Figure 4: Correlation between the change in TAPSE over time and the change in RVEF over time. Measurement points: 1: after general anesthesia. 2: After sternal opening. 3 After pericardial opening. 4: After weaning of cardiopulmonary bypass. 5: After pericardial approximation or closure. 6. After sternal closure.

Table 2: Transesophageal and hemodynamic measurements of all subjects during surgical procedure

Time point	1	2	3	4	5	6	P-value
Transesophageal measurements							
TAPSE (mm)	20.8 [16.6-23.4]	20.4 [13.8-24.0]	15.4 [13.5-18.9]	13.5 [9.6-16.8]	10.0 [8.9-13.1]	9.1 [5.6-15.5]	<0.001
S' (cm/s)	8.7 [7.9-10.7]	9.4 [8.3-10.3]	9.3 [8.1-10.2]	8.5 [7.3-10.6]	6.7 [5.9-8.4]	7.2 [5.7-8.6]	0.041
E' (cm/s)	7.4 [6.3-9.3]	7.6 [6.6-9.3]	6.2 [5.7-8.1]	6.9 [5.7-8.1]	5.3 [4.3-5.9]	5.1 [4.2-5.9]	0.023
A' (cm/s)	10.2 [8.1-13.0]	10.9 [9.1-12.5]	11.9 [8.8-13.9]	9.9 [8.9-12.0]	8.3 [6.9-10.6]	6.9 [5.5-9.9]	0.023
E'/A'	0.71 [0.58-0.90]	0.72 [0.58-0.84]	0.55 [0.48-0.6]	0.64 [0.49-0.84]	0.63 [0.54-0.69]	0.75 [0.57-0.89]	0.442
MPI	0.52 [0.43-0.58]	0.44 [0.36-0.55]	0.49 [0.37-0.58]	0.63 [0.45-0.82]	0.71 [0.49-0.84]	0.50 [0.42-0.88]	0.278
Hemodynamic measurements							
SvO ₂ (%)	77 [76-79]	77 [75-81]	79 [76-82]	76 [72-82]	74 [69-80]	73 [69-79]	0.040
CCI (l·min ⁻¹ ·(m ²) ⁻¹)	2.4 [1.7-2.8]	2.1 [2.0-2.5]	2.4 [2.1-2.8]	3.1 [2.8-3.5]	3.2 [2.7-3.4]	2.9 [2.4-3.4]	0.009
EDVi (ml/m ²)	136 [112-153]	134 [119-150]	125 [113-146]	122 [107-154]	135 [118-148]	129 [110-137]	0.444
RVEF (%)	27 [22-32]	24 [19-27]	26 [22-33]	29 [25-34]	27 [25-29]	26 [22-28]	0.294
SVi (mL·beat ⁻¹ ·(m ²) ⁻¹)	37 [31-42]	31 [28-37]	31 [28-35]	35 [33-41]	36 [31-41]	34 [28-40]	0.024
HR (beats per minute)	60 [55-67]	66 [60-70]	65 [60-79]	90 [86-90]	90 [90-90]	90 [90-90]	<0.001
Mean ABP (mmHg)	69 [62-78]	71 [66-82]	62 [55-66]	59 [54-66]	61 [56-69]	66 [60-70]	0.350
CVP (mmHg)	13 [9-14]	9 [8-11]	8 [6-11]	8 [7-13]	11 [8-14]	13 [10-15]	0.775
Mean PAP (mmHg)	22 [19-24]	21 [20-23]	19 [18-21]	20 [17-26]	21 [18-23]	23 [21-24]	0.812
sPAP (mmHg)	32 [27-36]	29 [25-32]	29 [23-33]	29 [23-34]	28 [23-32]	30 [28-32]	0.150
dPAP (mmHg)	16 [13-19]	15 [13-17]	14 [12-17]	16 [12-20]	16 [14-19]	18 [15-20]	0.268

Data are presented as median [IQR]. Measurement points: 1: after general anesthesia, before sternal opening. 2. After sternal opening. 3. After pericardial opening. 4. After weaning from cardiopulmonary bypass. 5. After pericardial approximation or closure. 6. After sternal closure. P-values were calculated over the difference between the individual time points 1 and 6. Abbreviations: TAPSE tricuspid annular plane systolic excursion; S' systolic excursion velocity. E' early diastolic excursion velocity; A' late diastolic excursion velocity; MPI myocardial performance index. SvO₂ mixed venous oxygen saturation; CCI continuous cardiac index; EDVi end-diastolic volume index; RVEF right ventricular ejection fraction; SVi Stroke Volume Index; HR heartrate; ABP arterial blood pressure; CVP central venous pressure; PAP pulmonary artery pressure; sPAP systolic pulmonary artery pressure; dPAP diastolic pulmonary artery pressure.

DISCUSSION

From this study it becomes clear that longitudinal parameters of RV contraction, i.e. TAPSE and S', were significantly reduced between the time point prior to and after cardiothoracic surgery. This reduction was not limited to the opening of the pericardium. However, the decline in longitudinal parameters in RV function was not accompanied by a decrease in global RV performance, as expressed by TEE-derived MPI, and PAC-derived RVEF and CI. Consequently, a correlation could not be established between the change over time in TAPSE and RVEF. Assessment of the multiple changes of RV performance during cardiac surgery should therefore not be limited to a single measurement. Whether that includes a combination of ultrasound derived longitudinal parameters and PAC, or a more complex echocardiographic evaluation seems to be setting and operator dependent.

Several studies reported a significant reduction in TAPSE and/or S' after cardiothoracic surgery.^{8,17,18,25,26} In general, opening of the pericardium and weaning from cardiopulmonary bypass have been identified as pivotal time points for this reduction.^{14,17,19,27,28} In addition, we were unable to confirm this previously reported critical influence of the opening of the pericardium on RV function. This is in accordance to on-pump CABG patients without valve repair.²⁹ Data on the change of RVEF during cardiothoracic surgery are not fully unequivocal. In accordance with our data, a significant reduction in TAPSE was not accompanied by a reduction in 3D TTE or PAC-derived RVEF in patients with CABG surgery³⁰ or mitral valve repair.^{15,19,31} Similarly, both PAC-derived and 3D TEE-derived RVEF remained unaltered during CABG procedure, but simultaneously measurement of TAPSE and S' were lacking in that study.³²

In addition, in a recent study with TEE-derived 3D echocardiography among CABG patients, RVEF remained unchanged while peak longitudinal strain of the RV lateral and inferior wall, TAPSE, and S' declined significantly after procedure.³³ Yet, our data seem to be conflicting with the establishment of a significant correlation between ultrasound-derived TAPSE and PAC-derived RVEF in a mixed group of cardiothoracic patients.²⁵ Despite the use of an identical method to assess RVEF, the referred study was restricted to a single postoperative measurement. Moreover, a comparison between pre- and postoperative performance of the RV was not included. In other words, the observed correlation between TAPSE and RVEF suggests that both variables reflect RV function to some extent. This is also illustrated by the observed relationship between adverse outcome and variables.^{34,35} Yet, our observations indicate that they are not interchangeable and clearly markers of different processes. A reduction in RV longitudinal contractions, as reflected by TAPSE and S', may be compensated for by radial shortening of the RV, enabling preservation of global RV performance.²¹ Vice-versa, in long-term exercise-induced changes of RV mechanics, longitudinal

contractions are more profoundly involved with a concomitant decreased importance of free wall radial motion, underlining the non-interchangeable contribution of the two contractile mechanisms in various conditions.³⁶ Clearly, the design of the study does not allow to explore the underlying mechanisms of changes in RV performance. However, from our results it becomes clear that preload (as reflected by EDVi) as well as afterload (as reflected by mean PAP and PEEP settings) did not change over time. This was accompanied by a reduction in SVi, compensated for by an increase in heartrate.

Our study has several limitations. We specifically selected patients scheduled for aortic valve surgery with a preserved LV function, in the absence of significant RCA stenosis, in order to avoid the influence of LV systolic impairment and RV ischemia on our results. Whether our data are thus applicable to different settings of cardiothoracic surgery remains a topic for future studies. It becomes clear that the type of assessment of RV parameters may be of substantial influence on the results. TEE and TTE both deal with specific challenges to obtain reliable measurements of RV performance. Even the positioning of TEE probe may be of influence on measurements of the same parameters.³⁷ Guidelines on echocardiography of the RV focus on TTE, whereas TEE is predominantly used in the perioperative setting. Due to lack of normal values and validation studies, extrapolation to TEE measurements from the TTE methods remains cumbersome.^{38,39,40,41} Since we did not change our method throughout our study protocol, we believe that the changes over time are represented adequately. This is especially true since our transgastric view allowed to reproduce TAPSE and S' with minimum change in angle. This is of particular importance since there seems to be a lack of consistency in the echocardiographic assessment of the RV and the definition of RV dysfunction in the current guidelines.^{38,39,42,43} Unlike the LV, the complex anatomy of the RV does not allow any geometrical assumptions, which makes a reliable echocardiographic assessment of size and volume difficult.³⁸ The most recent guideline for chamber quantification recommends to include RV and right atrial size and a measure of RV systolic function, as assessed by at least one or a combination of the following: fractional area change (FAC), S', TAPSE, and MPI, each with their own advantages and limitations.⁴² In a large worldwide survey, TAPSE appeared to be the most commonly used parameter in daily practice, followed by S'.⁴⁴ Although both parameters seem to correlate well with RV function in both normal subjects and in different disease states, validated against radionuclide angiography and MRI, the current study underlines the complexity of a full assessment of RV function in specific settings.³⁴ In particular, the assessment of MPI appeared to be cumbersome. In six out of twenty patients we were unable to perform MPI measurements with the potential of bias.

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In addition to echocardiography, the PAC might play an important role in the bedside evaluation of the RV function as well, despite its invasive character.^{40,45,46} The latest version of the PAC, as used in this study, enables continuous bedside assessment of the RVEF, EDVi, cardiac index, and SvO₂.

Assessment of thermodilution-derived RVEF correlates well with MRI- and angiography-derived RVEF.^{35,47,48} Furthermore, RVEF is associated with survival in different clinical settings, including cardiac surgery.^{4,49} Notwithstanding the criticism on the use of PAC, the device is still widely used in the perioperative setting during cardiac surgery and measurements are not operator-dependent.^{46,50}

CONCLUSION

During aortic valve surgery, the reduction of echocardiographic parameters of RV longitudinal contraction (TAPSE and S') is generally not accompanied by a reduction in global RV performance, as established with TEE and PAC. Such reduction may rather serve as a marker of geometrical adaption. Solely relying on a single RV parameter as a marker for global RV performance may not be adequate to assess the complex adaptation of the RV to aortic valve replacement. In addition, we were unable to confirm the previously reported critical influence of the opening of the pericardium on RV function.

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SUPPLEMENTAL MATERIALS

Table S1: Intraclass correlation coefficients (ICC) with 95% confidence interval (CI) of intra- and interobserver variability.

	Intra-observer variation ICC (95%CI)	Inter-observer variation ICC (95%CI)
TAPSE	0.97 (0.95-0.98)	0.97 (0.96-0.98)
S'	0.98 (0.97-0.99)	0.97 (0.95-0.98)
E'	0.99 (0.98-0.99)	0.98 (0.97-0.99)
A'	0.95 (0.91-0.97)	0.98 (0.97-0.98)
E'/A'	0.93 (0.88-0.96)	0.95 (0.92-0.97)
MPI	0.88 (0.79-0.93)	0.90 (0.86 -0.93)

Abbreviations: TAPSE tricuspid annular plane systolic excursion; S' systolic excursion velocity. E' early diastolic excursion velocity; A' late diastolic excursion velocity; MPI myocardial performance index.

Figure S1: Bland-Altman plots of all transthoracic measurements to illustrate inter-observer variability of TAPSE (A), S' (B), E' (C), A' (D), E'/A' (E), and MPI (F). Average of the difference (red line) with 95% limits of agreement are shown. TAPSE tricuspid annular plane systolic excursion; S' systolic excursion velocity. E' early diastolic excursion velocity; A' late diastolic excursion velocity; MPI myocardial performance index.

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Figure S2: Bland-Altman plots of all transesophageal measurements to illustrate intra-observer variability of TAPSE (A), S' (B), E' (C), A' (D), E'/A' (E), and MPI (F). Average of the difference (red line) with 95% limits of agreement are shown. TAPSE tricuspid annular plane systolic excursion; S' systolic excursion velocity. E' early diastolic excursion velocity; A' late diastolic excursion velocity; MPI myocardial performance index.

Chapter 6

High versus Normal Blood-Pressure Targets in Relation to Right Ventricular Dysfunction after Cardiac Surgery: a Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: Management of right ventricular (RV) dysfunction is challenging. Current practice is predominantly based on data from experimental and small uncontrolled studies and includes augmentation of blood pressure. However, whether such intervention is effective in the clinical setting of cardiac surgery is unknown.

DESIGN: Randomized controlled trial

Setting: Single-center study in a tertiary teaching hospital

Participants: 78 patients equipped with a pulmonary artery catheter (PAC), classified according to PAC-derived right ventricular ejection fraction (RVEF): 44 patients with an RVEF of <20% and 34 patients with an RVEF of $\geq 20\%$ and <30%.

INTERVENTIONS: Patients were randomly assigned to either a normal-target group (mean arterial pressure (MAP) 65 mmHg) or a high-target group (MAP 85 mmHg). Primary endpoint was the change in RVEF over a one-hour study period.

MEASUREMENTS AND MAIN RESULTS:

RVEF <20%: There was no significant between-group difference in change of RVEF (-1% [-3.3-1.8] in the normal-target group vs. 0.5% [-1-4] in the high-target group, $p=0.159$).

RVEF 20-30%: There was no significant between-group difference in change in RVEF (-1% [-3 -0] in the normal-target group vs. 1% [-1 -3] in the high-target group, $p=0.074$).

These results were in line with the simultaneous observation that echocardiographic variables of RV and LV function also remained unaltered over time, irrespective of either baseline RVEF and treatment protocol.

CONCLUSION: In a mixed cardiac surgery population with RV dysfunction, norepinephrine-mediated high blood pressure targets did not result in an increase in PAC-derived RVEF, as compared to normal blood pressure targets.

INTRODUCTION

Right ventricular impairment has been an underestimated clinical entity. Recent studies have shown that RV dysfunction is associated with low cardiac output syndrome^{1,2} and increased mortality in a variety of clinical settings, including sepsis³, cardiac arrest⁴, and post cardiac surgery⁵, thus highlighting its' importance. Since RV dysfunction generally responds poorly to treatment, managing these patients is challenging.

The RV and the left ventricle (LV) share the interventricular septum, muscle fibers, and the pericardium.⁶ In combination with a high pericardial resistance to distention this results in a substantial ventricular interdependence. Volume- or pressure loading of the RV can cause a septal shift leftwards into the LV, resulting in diminished LV filling.⁷⁻¹² Commonly, this septal shift is caused by the dilated RV with a supranormal RV systolic pressure, in combination with a decreased LV systolic pressure, which alters the trans-septal gradient and hence movement of the septum to the left.¹³ In addition, high RV pressures result in a diminished RV coronary perfusion due to altered filling, high RV wall tension and low systemic blood pressure.^{14,15} Alternatively, volume overload in the absence of elevated RV pressures may cause a diastolic septal shift towards the LV, but the septal shape normalizes in systole.

One of the cornerstones of the treatment of acute RV dysfunction or failure is the re-establishment of the trans-septal gradient by increasing systemic aortic pressure, and thus the subsequent LV pressure.^{13,16-19} Animal experiments have shown that vasoconstriction by banding of the aorta can be helpful in order to shift the septum back in place and to restore flow in the right coronary artery.^{20,21} Since aortic banding is not feasible in the clinical setting, stimulation of α -receptors by vasoactive drugs seems to be a clinically applicable alternative.^{20,22} In addition, higher blood pressures will increase RV coronary perfusion and this might be beneficial if compromised. Also, a direct inotropic effect of NE on the RV is conceivable.”

This current practice is predominantly based on data from small, often uncontrolled, experimental studies. However, whether such intervention is effective in the clinical setting of cardiac surgery is unknown. In this randomized controlled trial we studied the norepinephrine (NE)-mediated effect of high versus normal blood pressure targets on right ventricular function in post-cardiac surgery patients with a low (<20%) or moderate (20-30%) RV ejection fraction (RVEF). We hypothesized that a higher blood pressure would improve RV function in this setting.

MATERIAL AND METHODS

STUDY DESIGN

The study was performed between April 2019 and June 2020 and was designed as a single-centre, single-blinded randomized controlled trial. Written informed consent was obtained from all eligible patients prior to surgery. The study complies with the Declaration of Helsinki and was approved by a local ethical and scientific committee. (Regionale Toetsingscommissie Patiëntgebonden Onderzoek Leeuwarden, WMO 1051). The study was registered with ClinicalTrials.gov as NCT03806582.

STUDY POPULATION

According to local protocol, all patients scheduled for heart valve surgery were equipped with a pulmonary artery catheter (PAC) after induction of anesthesia. Patients ≥ 18 years of age with a PAC in place after full sternotomy cardiac surgery were eligible and included in the study within the first post-operative hour in the ICU in case of a postoperative RVEF $< 30\%$, in combination with a mean arterial pressure (MAP) of ≤ 65 mmHg. Exclusion criteria were emergency surgery, off-pump surgery, allergy to (an ingredient of) NE, chronic use of α -blocking medication, severe tricuspid insufficiency (pre- or postoperative), severe hypertrophic left ventricle with (a high risk of) systolic anterior movement of the mitral valve, absence of a regular rhythm, or surgical reasons to maintain normal blood pressure targets.

After arrival in the ICU, eligible patients were classified in two different groups; patients with a low RVEF $< 20\%$, and patients with an moderate RVEF between 20% and 30% . This classification was based on the RVEF as measured by the PAC in the first hour after arrival in the ICU. Such classification was based upon our previous work in the postoperative cardiac surgery setting, in which an RVEF $> 30\%$ was considered normal²³. In each group patients were randomly assigned to either a normal-target blood pressure (MAP 65 mmHg) group or a high-target blood pressure group (MAP 85 mmHg; Fig.1). Allocation concealment was executed in blocks of six patients.

PROTOCOL AND STUDY TREATMENT

After induction of anesthesia in the OR, but before sternal opening, deep transgastric measurements of the RV were obtained from every patient by the attending cardiac anesthesiologist (TAPSE by M-mode and PW TDI). Postoperative transesophageal echocardiography (TEE) image acquisition in the ICU was obtained by a single dedicated echocardiographer. (Philips IE33 transesophageal echocardiography system (Philips Medical Systems; Amsterdam, the Netherlands), with an X7-2t TEE probe (Philips Medical Systems, Amsterdam, the Netherlands). Images were recorded and offline analysis was performed by an observer who was unaware of treatment allocation or hemodynamic status. All images were analyzed using Philips

Figure 1: study protocol. RV right ventricle. RVEF right ventricular ejection fraction. MAP mean arterial pressure. TEE transesophageal echocardiography.

IntelliSpace Cardiovascular 2.3 software. Measurements were obtained in mid-esophageal 2 and 4 chamber views, transgastric, and modified deep transgastric position. RV parameters were measured in the modified deep transgastric position (0°) and included TAPSE by M-mode and PW TDI: peak systolic annular velocity (S'), early diastolic myocardial relaxation (E'), and active atrial contraction in late diastole (A'). Myocardial performance index (MPI), as a global index of myocardial function, was measured with pulsed wave tissue Doppler imaging (PW TDI). LV parameters included LVEF by Simpson's method, tissue doppler imaging (TDI) mitral annulus motion (i.e. S', E', and A'), and transmitral pulsed wave doppler flow (E- and A wave).

After surgery, all patients were admitted to the ICU and remained on mechanical ventilation during the direct postoperative phase. Patients were sedated with propofol and fentanyl. Settings of mechanical ventilation were standardized with a respiratory frequency of 20–25 times per minute, tidal volumes limited up to 6 ml/kg ideal bodyweight, and a postoperative end-expiratory pressure of 10 cm H₂O. Patients were extubated within 3h of ICU admission if hemodynamically stable and in case of an absence of complications (bleeding, infarction). In the ICU, the following data were recorded as baseline: general characteristics, systemic hemodynamic variables, TEE measurements, mid-esophageal 2 and 4 chamber views for Simpson left ventricular ejection fraction (LVEF), modified deep transgastric 0° view for tricuspid annular systolic plane excursion (TAPSE), as well as pulsed wave tissue Doppler imaging (PW TDI) of the RV. Results of standard laboratory tests included blood gas analysis, arterial lactate concentration, cardiac biomarkers (CK & CK-MB), fluid balance, ventilator settings, and surgery characteristics.

Patients were equipped with both an arterial line and a pulmonary artery catheter (PAC; 7.5 F continuous cardiac output/mixed venous oxygen saturation [SvO₂]/continuous end diastolic volume [CEDV]-pulmonary artery catheter, model 774F75; Edwards Lifesciences, Irvine, CA, USA), which interfaced with a computerized monitoring system (Vigilance® continuous cardiac output/SvO₂/CEDV monitor; Edwards Lifesciences, Irvine, CA, USA). This PAC enables near-continuous data on cardiac output/index (CCO/CCI), oxygen supply and-demand balance (SvO₂), as well as on right ventricular end diastolic volume (RVEDV) and right ventricular ejection fraction (RVEF). The correct position of the PAC was confirmed by way of waveform analysis and a chest X-ray upon arrival in the ICU and before the start of the study. Zeroing of the pressure systems was done directly after ICU admittance. Leveling of the pressure systems was checked after every reposition of either the patient or the bed. Details on PAC measurements are provided elsewhere.²⁴ During the study period, PAC-derived data were registered continuously. After enrolment in the ICU, TEE was performed every 15 minutes, starting 15 minutes prior to start study. The final TEE measurement was performed after 60 minutes in the

normal-target group, or in case MAP returned to 65mmHg for the high-target group. Hemodynamic data were collected every minute and were averaged over a period of 15 minutes, starting 30 minutes prior to start study. Final measurements were performed over a 30-minute period after stop study. In line with previous literature, the trans septal gradient (TSG) at baseline and at end study were estimated according to the following formula: $TSG = \text{systolic blood pressure (SBP)} - \text{systolic pulmonary artery pressure (sPAP)}$.¹³

Before start of the study protocol, adequate filling status was obtained. In the high-target group NE was titrated to achieve a MAP of 85mmHg. Dosage was increased every 2 minutes until the target was reached, with a maximum increase in NE administration of $0.24 \mu\text{g.kg}^{-1}.\text{min}^{-1}$ relative to the starting dose or a maximum systolic pressure of 140mmHg. After the 1 hour study period, NE was tapered to a MAP of 65mmHg.

In the normal-target group MAP was titrated to 65mmHg according to local protocol. In case vasopressors were deemed necessary to maintain this MAP, the choice of vasopressors was made prior to the start of study period by the attending physician and remained unaltered during the entirety of the process. During the study period other interventions, including fluid administration, alterations in ventilatory settings, and pacemaker adjustments, were not allowed unless the patient's situation was considered critical.

Primary endpoint was the change in PAC-derived RVEF over a one-hour study period. Secondary endpoints were the change over time in echocardiographic parameters of LV and RV, cardiac index, and TSG.

ANALYSIS

A separate power calculation was performed for each RVEF group. For the RVEF <20% group we anticipated a mean RVEF of 17%, with a standard deviation of 2% based on earlier observations.⁵ We calculated a sample size of 44 patients to detect a relative difference of 10% in a two-sided test with a 0.05 type 1 error and an 80% probability. A relative difference of 10% in this groups is just outside the coefficient of variation of RVEF measurements. For the RVEF 20%-30% group we anticipated a mean RVEF of 25% with a standard deviation of 2.6%.⁵ We calculated a sample size of 34 patients to detect a relative difference of 10% in a two-sided test with a 0.05 type 1 error and an 80% probability.

The Statistical Package for Social Sciences (SPSS 25 for Windows, Chicago, IL, USA) was used for statistical analysis. Data were described as median with interquartile range (IQR) unless stated otherwise. Non-parametric tests were applicable due to the sample size. Comparison between groups was performed using a Mann-Whitney test. For paired data, the Wilcoxon signed rank test was applicable. For nominal or ordinal data, the Chi-square test was used. A two-sided p value of <.05 was considered statistically significant.

RESULTS

Between April 2019 and May 2020, 225 patients were screened prior to surgery, and a total of 191 patients signed informed consent. After cardiac surgery, 78 patients matched the inclusion criteria. 44 patients were assigned to the group with an RVEF of <20%, and 34 patients to the group with an RVEF between 20 to 30%.

BASELINE AND PERIOPERATIVE CHARACTERISTICS

RVEF <20%. There were no differences in baseline and perioperative characteristics between the normal-target and high-target group, with the exception of a difference in type of procedures ($p=0.049$; Tables 1 and 2).

RVEF 20-30%. There were no differences in baseline and perioperative characteristics between the normal-target and high-target group, with the exception of aortic clamp time (100 [82-152] min vs. 78 [64-96] min respectively, $p=0.039$; Table 1 and 2).

STUDY TARGET: MAP

RVEF <20%. At baseline, there were no differences in MAP. No significant increase in MAP was observed in the normal-target group during the study period. The MAP in the high-target group was significantly higher in comparison to normal-target group (64 [62-67] mmHg vs. 85 [83-86] mmHg, $p<0.001$ at stop study, Fig. 2) during the study period.

RVEF 20-30%. At baseline, there were no differences in MAP. No significant increase in MAP was observed in the normal-target group during the study period. The MAP in the high-target group was significantly higher in comparison to the normal-target group (67 [66-70] mmHg vs. 82 [81-87] mmHg, $p<0.001$ at stop study, Fig. 2) during the study period.

PRIMARY ENDPOINT: RVEF

RVEF <20%. Baseline RVEF was not significantly different between the normal-target and high-target group. (19% [17-21.5] vs. 18% [15-20] respectively, $p=0.427$). In addition, there was no significant between-group difference in the change in RVEF (-1% [-3,3-1.8] in the normal-target group vs. 0.5% [-1-4] in the high-target group, $p=0.159$; Fig.3).

RVEF 20-30%. Baseline RVEF was not significantly different between the control and intervention group (25% [23-26] vs. 25% [23-27] respectively, $p=0.702$). In addition, there was no significant between-group difference in the change in RVEF (-1% [-3 - 0] in the normal-target group vs. 1% [-1 - 3] in the high-target group, $p=0.074$; Fig.3).

Table 1: Baseline characteristics of patients with an RVEF 20% and patients with an RVEF ≥20% and <30%.

	RVEF <20%		P-value	RVEF 20-30%		P-value
	Normal target (n=22)	High target (n=22)		Normal target (n=17)	High target (n=17)	
Demographics						
Age (y)	70 [65-78]	73.5 [69-78]	0.180	68 [57-78]	71 [65-77]	0.558
Male (%)	77	90	0.216	65	77	0.452
Body mass index	27 [25-31]	29 [27-31]	0.398	31 [25-32]	27 [25-30]	0.221
Preoperative comorbidities (%)						
DM type 1	0	0		0	0	
DM type 2	23	9	0.216	29	18	0.419
Peripheral vessel disease	9	5	0.550	12	18	0.628
TIA/CVA	14	9	0.635	18	24	0.671
Neurologic dysfunction‡	0	0		0	0	
COPD†	9	5	0.550	0	6	0.310
Pulmonary hypertension‡	41	38	0.852	24	19	0.817
Serum creatinine (µmol/L)	96 [79-123]	93 [77-115]	0.581	84 [72-89]	85 [81-108]	0.241
Cardiac status (%)						
NYHA class III or IV	64	50	0.361	59	47	0.492
Preoperative myocardial infarction	14	9	0.635	18	0	0.287
Previous cardiac surgery	0	5	0.312	0	0	
Previous PCI	5	9	0.550	6	18	0.287
Stenosis RCA	50	50	1.000	18	24	0.671
History with PCI RCA	0	9	0.148	6	18	0.287
Medication prior to surgery (%)						
Beta blocker	55	64	0.226	47	41	0.730
ACE-inhibitor	41	55	0.365	35	18	0.244
Angiotensin-antagonist	27	14	0.262	18	18	1.000
Calcium antagonist	27	14	0.262	29	24	0.697
Diuretics	41	41	1.000	41	30	0.473
Psychiatric drugs	5	5	1.000	6	18	0.287

Data are presented as median [IQR]. Normal-target: mean arterial pressure 65mmHg. High target: mean arterial pressure 85mmHg. † Long term use of bronchodilators or steroids for lung disease. ‡ Disease severely affecting ambulation or day-to-day functioning. ¥ Pulmonary hypertension (mean pulmonary artery pressure ≥25mmHg) measured with pulmonary artery catheter on the operation room prior to surgery. RVEF right ventricular ejection fraction. DM diabetes mellitus. TIA transient ischemic attack. CVA cerebral vascular accident. COPD chronic obstructive pulmonary disease. NYHA New York heart association. PCI Percutaneous Coronary Intervention RCA right coronary artery LVEF left ventricular ejection fraction

Figure 2: Change of mean arterial pressure (MAP) over time

Mean arterial pressures were collected every minute and were averaged over a period of 15 minutes, starting 30 minutes prior to start study (timepoint 1 and 2). Timepoints 3 to 6 indicate the study period. Final measurements were performed over a 30- minute period after stop study (timepoint 7 and 8). *indicates a p-value of <0.001 between groups.

Figure 3: Change of right ventricular ejection fraction (RVEF) over time

Pulmonary artery catheter-derived right ventricular ejection fractions were collected every minute and were averaged over a period of 15 minutes, starting 30 minutes prior to start study (timepoint 1 and 2). Timepoints 3 to 6 indicate the study period. Final measurements were performed over a 30- minute period after stop study (timepoint 7 and 8).

SECONDARY ENDPOINTS

Echocardiographic parameters of the right ventricle are depicted in figure 4. Echocardiographic parameters of the left ventricle are listed in Table 3. We observed no improvement over time in RV and LV parameters irrespective of baseline RVEF. Hemodynamic variables are listed in Table 4.

RVEF <20%. In the high-target group, mean pulmonary artery pressure (mPAP) increased significantly over time (from 19 mmHg [18-25.5] to 25 mmHg [21.0-29.5], $p<0.001$). The estimated TSG increased significantly (from 66[59-73] mmHg to 86[79-100] mmHg, $p<0.001$; Table 4). This was accompanied by an increase in right ventricular stroke work index (RVSWi) in the high-target group between baseline and stop study (from 4.0 g.m⁻¹.beat⁻¹.m⁻² [3.1-5.2] to 4.7 g.m⁻¹.beat⁻¹.m⁻² [4.2-6.9], $p=0.001$; Table 4).

RVEF 20-30%. In the high-target group, mPAP increased significantly over time (from 19 mmHg [18-21.5] to 21 mmHg [18,5-24,5], $p=0.010$). The estimated TSG increased significantly (from 79[66-92] mmHg to 103[90-116] mmHg, $p<0.001$; Table 4). This was accompanied by an increase in RVSWi between baseline and stop study in the high-target group (from 4.5 g.m⁻¹.beat⁻¹.m⁻² [3.6-5.8] to 5.4 g.m⁻¹.beat⁻¹.m⁻² [4.5-5.9], $p=0.049$; Table 4).

Table 2: Peri-operative details of patients with an RVEF <20% and patients with an RVEF ≥20% and <30%.

	RVEF <20%			RVEF 20-30%		
	Normal-target (n=22)	High-target (n=22)	P-value	Normal-target (n=17)	High-target (n=17)	P-value
Hemodynamic characteristics after induction of anesthesia						
CVP (mmHg)	12 [8-13]	10 [8-13]	0.532	11 [8-14]	13 [9-14]	0.279
MAP (mmHg)	65 [63-68]	65 [61-75]	0.842	68 [67-75]	68 [62-75]	0.822
sABP (mmHg)	98 [91-106]	95 [88-104]	0.614	98 [93-106]	94 [89-98]	0.129
dABP (mmHg)	50 [44-56]	53 [46-61]	0.259	56 [52-58]	56 [50-63]	0.654
sPAP (mmHg)	29 [25-36]	32 [25-38]	0.504	28 [23-34]	29 [26-33]	0.504
dPAP (mmHg)	17 [13-21]	15 [13-24]	0.807	17 [14-22]	18 [15-20]	0.828
mPAP (mmHg)	21 [18-26]	21 [17-28]	0.584	21 [18-26]	22 [19-24]	0.651
HR (beats.min ⁻¹)	62 [55-69]	63 [52-79]	0.698	64 [54-76]	63 [55-79]	0.666
CCI (L.min ⁻¹ .m ⁻²)	1.9 [1.4-2.5]	1.9 [1.6-2.1]	0.803	1.8 [1.6-2.2]	1.9 [1.5-2.4]	0.787
EDVi (ml.m ⁻²)	137 [119-157]	149 [121-170]	0.611	106 [101-119]	124 [96-132]	0.419
RVEF (%)	20 [16-33]	18 [13-24]	0.592	29 [22-32]	25 [20-32]	0.336
SvO2 (%)	72 [67-76]	73 [68-78]	0.635	71 [68-75]	72 [67-77]	0.724
SV (ml)	62 [49-77]	57 [44-73]	0.579	61 [52-68]	57 [50-64]	0.430
TEE parameters after induction of anesthesia						
TAPSE (mm)	16.5 [11.2-21.2]	14.2 [8.4-18]	0.241	17 [12-21]	14 [12-20]	0.467
S' (cm/s)	7.2 [5.6-8.5]	7.2 [5.3-8.8]	0.850	8.1 [7.1-9.7]	7.3 [5.5-8.6]	0.273
MPI	0.71 [0.48-0.86]	0.66 [0.42-1.13]	0.988	0.54 [0.43-0.60]	0.62 [0.47-0.76]	0.396
LVEF (%)	52 [36-58]	50 [36-64]	0.325	53 [47-65]	58 [45-63]	0.532
Intraoperative characteristics						
AoX (min)	108 [73-158]	91 [63-118]	0.162	100 [82-152]	78 [64-96]	0.039*
ECC (min)	146 [98-190]	118 [84-154]	0.127	132 [100-180]	112 [93-131]	0.139
RCA graft (%)	41	36	0.757	35	12	0.106
Type of procedure (%)						
CABG + AVR	45	45		59	24	
CABG + MVR/MVP	18	5		0	6	
AVR	5	32	0.049*	17	41	0.093
MVR/MVP	14	5		17	6	
Other	18	13		6	24	
Postoperative Eyeballing RV function by TEE(%)						
Good	68	77		88	81	
Moderate	23	18	0.752	6	19	0.347
Poor	9	5		6	0	
Postoperative Eyeballing LV function by TEE (%)						
Good	68	68		76	75	
Moderate	27	23	0.809	18	13	0.762
Poor	5	9		6	13	

Table 2: Peri-operative details of patients with an RVEF <20% and patients with an RVEF ≥20% and <30%.

Postoperative characteristics						
Bleeding (%)	14	5	0.294	6	6	1.000
MI (%)	14	0	0.073	0	0	
Resubmission (%)	5	0	0.312	0	0	
CVVHD (%)	5	0	0.312	6	0	0.310
Creatinine (μmol/L) [†]	122 [82-167]	96.5 [75-134]	0.064	87 [77-103]	91 [80-127]	0.717
CK (U/L) [†]	957 [406-1613]	615 [454-1273]	0.760	617 [538-977]	450 [289-705]	0.060
CK-MB (U/L) [†]	69 [40-128]	63 [38-80]	0.379	48 [44-74]	42 [26-54]	0.102
Lactate (mmol/L) [†]	2.1 [1.8-3.7]	2.1 [1.5-2.7]	0.254	2.2 [1.7-3]	2.1 [1.7-3.3]	0.822
Fluid balance (ml)	1802 (1050)	1600 [1125-2000]	0.191	1500 [1050-2100]	1800 [1350-2600]	0.406

Data are presented as median [IQR].*Indicates a significant difference across intervention and control group. (p<0.05). Normal-target: mean arterial pressure 65mmHg. High target: mean arterial pressure 85mmHg. Hemodynamic data were obtained with an arterial line and a pulmonary artery catheter. TEE RV measurements were obtained in modified deep transgastric position (0°). LVEF was obtained by Simpson's method. Hemodynamic characteristics and TEE parameters were measured after induction of anesthesia in the operating room, but before sternal opening. [†] Peak value. RVEF right ventricular ejection fraction. CVP central venous pressure. MAP mean arterial pressure. sABP systolic arterial pressure. dABP diastolic arterial pressure. sPAP systolic pulmonary arterial pressure. dPAP diastolic pulmonary arterial pressure. mPAP mean pulmonary arterial pressure. HR heart rate. CCI continuous cardiac index. EDVi End-diastolic volume index. SvO2 mixed venous saturation. SV stroke volume. TEE transesophageal echocardiography. TAPSE tricuspid annular systolic plane excursion. S' systolic myocardial contraction. E' early diastolic myocardial relaxation. A' active atrial contraction in late diastole. MPI Myocardial performance index. LVEF left ventricular ejection fraction. AoX aortic cross-clamp. ECC extracorporeal circulation. CABG coronary-artery bypass grafting. AVR aortic valve replacement. MVR mitral valve replacement. MVP mitral valve repair. MI myocardial insufficiency. LOS ICU length of stay intensive care unit. AF atrial fibrillation. CVVHD continuous veno-venous hemodialysis CK creatine kinase CK-MB creatine kinase-myoglobin binding. RV right ventricular. LV left ventricular.

Figure 4: Change in transesophageal echocardiographic parameters over time

RV parameters were measured in the modified deep transgastric position. After enrolment in the ICU, TEE was performed every 15 minutes, starting with baseline TEE 15 minutes prior to the study period (timepoint 1). The final TEE measurement was performed after 60 minutes in the control group, or in case MAP returned to 65mmHg for the intervention group (timepoint 5). TAPSE tricuspid annular systolic plane excursion. S' systolic myocardial contraction. MPI Myocardial performance index.

Table 3: Echocardiographic transesophageal LV parameters of patients with an RVEF <20% and patients with an RVEF ≥20% and <30%.

LV parameter	RVEF <20%			RVEF 20-30%		
	Normal-target (N=22)			Normal-target (N=17)		
	Baseline	Endpoint	p value	Baseline	Endpoint	p value
S' lateral MV (cm/s)	6.2 [5.1-8.5]	6.7 [4.9-7.2]	0.182	6.3 [5.5-9.1]	6.4 [4.9-8.6]	0.254
E' lateral MV (cm/s)	4.4 [3.9-7.5]	5.3 [4.1-5.3]	0.753	4.4 [3.6-5.1]	4.5 [3.8-5.2]	0.583
E/A	0.8 [0.7-1.0]	0.8 [0.7-0.9]	0.779	0.7 [0.6-0.8]	0.7 [0.6-0.8]	0.346
E/E'	10.5 [9-13.3]	9.7 [8.2-14.3]	0.160	10.7 [8.9-15.5]	10 [8.8-15.5]	0.529
	RVEF <20%			RVEF 20-30%		
	High-target (N=22)			High-target (N=17)		
	Baseline	Endpoint	p value	Baseline	Endpoint	p-value
S' lateral MV (cm/s)	6 [5.2-8.4]	6 [4.8-6.7]	0.306	7.6 [5.6-9.6]	6.6 [5.1-8.5]	0.247
E' lateral MV (cm/s)	5.3 [4.3-6.1]	4.6 [4.0-6.1]	0.734	6.5 [4.5-11.3]	5.2 [4.3-8.0]	0.594
E/A	0.9 [0.7-1.2]	0.8 [0.6-0.9]	0.233	0.8 [0.7-1.1]	0.9 [0.7-1.0]	0.018*
E/E'	8.7 [4.8-15.2]	9 [5.6-13.9]	0.753	9.9 [8-11.9]	10.6 [8.5-17.2]	0.123

Data are presented as median [IQR]. Normal-target: mean arterial pressure 65mmHg. High target: mean arterial pressure 85mmHg. Baseline measurements were obtained in the ICU after enrolment, 15 minutes prior to the study period. The final TEE measurement was performed after 60 minutes of study period in the normal-target group, or in case MAP returned to 65mmHg for the high-target group. Measurements were obtained in mid-esophageal 2 chamber view. LV left ventricle. S' systolic myocardial contraction. MV mitral valve. E' early diastolic myocardial relaxation. E/A ratio of peak velocity blood flow from left ventricular relaxation in early diastole to peak velocity flow in late diastole E/E' ratio between early mitral inflow velocity and mitral annular early diastolic velocity. LVEF left ventricular ejection fraction.

Table 4: Hemodynamic variables during study period

	RVEF <20% Normal-target (N=22)			RVEF 20-30% Normal-target (N=17)		
	Baseline	Endpoint	P-value	Baseline	Endpoint	P-value
CVP (mmHg)	8 [5-11]	7 [5-10]	0.054	9 [6-11]	8 [5-10]	0.150
MAP (mmHg)	68 [62-74]	64 [62-67]	0.008*	68 [63-72]	67 [66-70]	0.722
mPAP (mmHg)	22 [18-26]	22 [18-25]	0.069	19 [15-24]	18 [17-25]	0.541
CCI (L min ⁻¹ . m ⁻²)	1.9 [1.7-2.4]	1.7 [1.6-2.2]	0.010*	2.2 [1.9-2.5]	2.0 [1.8-2.4]	0.010*
TSG (mmHg)	72 [63-80]	63 [53-73]	0.005*	76 [63-92]	72 [67-86]	0.331
EDV _i (ml.m ⁻²)	119 [101-147]	110 [102-141]	0.070	104 [98-112]	101 [93-107]	0.050
RVEF (%)	19 [17-22]	18 [15-20]	0.468	25 [23-26]	23 [21-26]	0.180
SV _i (ml. m ⁻²)	22 [19-27]	19 [17-25]	0.011*	26 [22-28]	23 [20-27]	0.002*
RVSW _i (g.m ⁻¹ .beat ⁻¹ .m ⁻²)	3.9 [3.2-5.1]	4.2 [3.1-4.6]	0.260	3.5 [2.8-5.6]	3.3 [2.8-4.9]	0.408
NE dose (µg.kg ⁻¹ .min ⁻¹)	0.0 [0-0.5]	0.4 [0.0-1.2]	0.028*	0.0 [0.0-0.0]	0.0 [0.0-0.2]	0.144

	RVEF <20% High-target (N=22)			RVEF 20-30% High-target (N=17)		
	Baseline	Endpoint	P-value	Baseline	Endpoint	P-value
CVP (mmHg)	8 [6-9]	8 [6-9]	0.264	7 [5-8]	7 [5-9]	0.590
MAP (mmHg)	67 [61-71]	85 [83-86]	<0.001*	67 [61-71]	82 [81-87]	<0.001*
mPAP (mmHg)	19 [18-24]	25 [21-30]	<0.001*	19 [18-22]	21 [19-25]	0.010
CCI (L min ⁻¹ . m ⁻²)	2 [1.9-2.2]	2.2 [1.9-2.4]	0.534	2.3 [1.9-2.7]	2.3 [2.1-2.5]	0.751
EDV _i (ml.m ⁻²)	122 [107-152]	126 [103-154]	0.881	100 [92-127]	99 [94-117]	0.408
TSG (mmHg)	66 [59-73]	86 [79-100]	<0.001*	79 [66-92]	103 [90-116]	<0.001*
RVEF (%)	18 [15-20]	19 [17-21]	0.337	25 [23-27]	26 [24-29]	0.430
SV _i (ml. m ⁻²)	23 [21-25]	25 [21-26]	0.434	30 [22-34]	27 [24-31]	0.954
RVSW _i (g.m ⁻¹ .beat ⁻¹ .m ⁻²)	4.0 [3.1-5.2]	4.7 [4.2-6.9]	0.001*	4.5 [3.6-5.8]	5.4 [4.5-5.9]	0.049*
NE dose (µg.kg ⁻¹ .min ⁻¹)	0.6 [0.1-0.8]	0.9 [0.6-1.6]	0.003*	0.4 [0.1-0.7]	0.9[0.2-1.5]	0.016*

Data are presented as median [IQR]. During the study period, hemodynamic data were collected with a pulmonary artery catheter which enables near-continuous data collection. Data were averaged over a period of 15 minutes, with baseline measurements starting 15 minutes prior to start study. Endpoint measurements were performed over the last 15 minutes of the 1 hour study period. The trans septal gradient (TSG) at baseline and at end study were estimated according to the following formula: TSG = systolic blood pressure (SBP) – systolic pulmonary artery pressure (sPAP). *Indicates a significant difference between baseline and endpoint. (p<0.05).

CVP central venous pressure. MAP mean arterial pressure. mPAP mean pulmonary arterial pressure. CCI continuous cardiac index. TSG trans septal gradient. EDVi End-diastolic volume index. RVEF right ventricular ejection fraction. SVi stroke volume index. RVSWi right ventricular stroke work index. NE norepinephrine. NA not available.

DISCUSSION

In this study, NE-mediated high blood pressure targets, raising MAP from 65 to 85 mmHg, did not result in an increase in PAC-derived RVEF, as compared to normal blood pressure targets. These observations were in line with the simultaneous observation that there was no improvement in RV echocardiographic parameters (i.e. TAPSE, S' and MPI) in the intervention group.

These results seem to contradict the general paradigm that an increase in blood pressure is likely to improve RV performance as a result of improvement in right coronary artery blood flow and re-establishment of the transeptal gradient, and thus of RV and LV dimensions.^{13,14} Animal experiments suggested the effectiveness of arterial vasoconstriction in the setting of RV dysfunction and failure. In rabbits and dogs, afterload-induced acute RV failure was attenuated by aortic banding due to subsequent restoration of left ventricular pressures.^{20,21} These observations confirmed the relevance of a previously described linear relationship between the maximal RV systolic pressure and the mean femoral artery pressure.²⁵ In rabbits, administration of NE resulted in similar effects.²⁰ In the clinical setting, the administration of epinephrine in a small group of aortic valve surgery patients resulted in a significantly higher PAC-derived RVEF compared to the placebo. However, MAP was the same between groups.²⁶ In order to understand our seemingly contradictory results, it is pivotal to acknowledge the specific setting. First of all, our study was performed in a mixed group of postoperative cardiac surgery patients, not selected for well-known risk factors of RV dysfunction (i.e. pulmonary artery hypertension and LV failure) or a specific cut-off value for the TSG. This is reflected by the fact that the median TSG was only modestly reduced at baseline and during the intervention increased by 20 and 24 mmHg respectively, in patients with a low or moderate RVEF. Apparently, the intervention was accompanied by the anticipated rise in TGS, but not to the extent of previously described hypotensive patients with acute RV pressure overload. In the clinical setting of cardiac surgery, the achieved rise in blood pressure must always be weighed against an additional risk of bleeding, and as such this clinical study reflects only a small margin of the range in blood pressure augmentation that can be achieved in animal experiments.

An alternative explanation for the lack of blood pressure-induced response in RVEF may be provided by the important observation in our study that the rise in blood pressure was accompanied by a rise mPAP during NE administration. It is conceivable that a potential positive effect of the rise in blood pressure on RV function was counteracted by an unintended rise in RV afterload. In this scenario, the maintenance of CI may be achieved by a direct inotropic effect of NE, or via enhancement of right coronary artery blood flow. In this case, PAC-derived RVEF should be combined

with additional variables of RV contractility to fully appreciate the underlying mechanisms. The importance of the rise in afterload during NE administration is illustrated by two conflicting results in the setting of septic shock. Recently, a cohort of 11 septic shock patients was evaluated with the combined use of a PAC and transthoracic echocardiography. NE was used to increase MAP from 60 to 90 mmHg for a period of at least 10 minutes. The authors observed an improved RV function with both PAC and transthoracic echocardiography in the absence of an increase in RV afterload.²⁷ However, in other small uncontrolled studies, the use of NE was accompanied by a significant increase in mPAP, while both RVEF and RV-EDVi remained unchanged.^{28,29} This rise in afterload may be equally important in the setting of cardiac surgery, which was demonstrated by an absence of rise in cardiac index during the use of NE despite a substantial rise in blood pressure.³⁰ Not in every clinical setting the application of an early vasoconstricting approach intended for blood pressure support seems to be the best course of action; in the failing heart, the optimal afterload is narrow and must be tuned carefully.³¹

The application of the findings of this study are limited to the specific setting of cardiac surgery. Controls were well maintained within the generally accepted MAP target for postoperative cardiac surgery patients. Although we cannot rule out that higher MAP targets (with a subsequent impact on the rise in TSG) would have revealed different results, the clinical setting simply does not allow further broadening of the chosen pressure limits. However, this does not reduce the clinical relevance of this study, since the net result in overall cardiac performance is unaltered during the NE-mediated rise in blood pressure. Clearly, the trigger to start a therapeutic intervention depends on the definition of RV dysfunction or failure, which until now remains a topic of debate.^{32,33} The choice to select patients according to the postoperative RVEF clearly characterizes our population, but this is in line with previous publications³⁴ and is supported by its association with long-term survival and ICU morbidity.^{5,35} In addition, the window of observation was limited to one hour. Although the response in RV performance to aortic banding or NE administration in the experimental setting was near-instantaneous²⁰, we cannot rule out unexpected effects of the increase in MAP outside the scope of this study. Also, the limited number of patients in this study has the potential for a type II error, i.e. the unjustified rejection of the hypothesis that NE-mediated increment of blood pressure does improve RV function. However, the study was powered to detect a relative change in RVEF of 10%, representing a small absolute difference, and the data do not suggest any tendency towards a difference in primary endpoint between the normal and high-target groups. Finally, the use of NE may be debated. Compared to the LV, the density of β -receptors in the RV is much lower.³⁶ In an animal study, the effect of NE remained present after administration of a selective β -blocker, indicating that the stimulation of α -receptors is the main therapeutic

target.²⁰ Experimental studies suggest that vasopressin increases systemic vascular resistance in the absence of pulmonary vasoconstriction.^{37,38} Although such characteristics may have potential for the management of RV dysfunction, its effect remains controversial and might even result in a negative performance of the RV.³⁹ Similarly, phenylephrine has been associated with negative inotropic effects.⁴⁰ In our opinion, the choice for NE as a vasopressor seemed appropriate.

CONCLUSION

In a mixed population of patients with RV dysfunction after cardiac surgery, NE-mediated high blood pressure targets, raising MAP from 65mmHg to MAP 85 mmHg, did not result in an increase in PAC-derived RVEF, as compared to normal blood pressure targets.

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Chapter 7

Physician Factors in Utilizing Haemodynamic Data in Patient Care

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ABSTRACT

PURPOSE OF REVIEW

To focus on the missing link between accuracy and precision of monitoring devices and effective implementation of therapeutic strategies

RECENT FINDINGS

Haemodynamic monitoring is generally considered to be an essential part of intensive care medicine. However, randomised controlled trials fail to demonstrate improved outcome unequivocally as a result of hemodynamic monitoring. This absence of solid proof renders doctors to hesitance to apply haemodynamic monitoring in clinical practise. Profound understanding of the underlying mechanisms, adequate patient selection and timing, meaningful representation and software-supported interpretation of data all play an important role. Furthermore, protocol adherence and human behaviour seem to form the often missing link between a solid physiologic principle and clinically relevant outcome. Introduction of haemodynamic monitoring should therefore not be limited to theoretical and practical issues, but also involve integration strategies. By learning from others, we might be able to implement haemodynamic monitoring in such a way that it has potential to modify the course of a disease.

SUMMARY

The clinical success of haemodynamic monitoring goes far beyond accuracy and precision of monitoring devices. Understanding of the factors influencing the effective implementation of therapeutic strategies play an important role in the meaningful introduction of haemodynamic monitoring.

INTRODUCTION

In a recent systematic review an attempt was made to quantify the effect of haemodynamic management in sepsis on clinical outcome.¹ The authors concluded that a set of haemodynamic interventions, including serial lactate measurements, a fluid infusion of 30 mL/kg of body weight, assessment of volume status and tissue perfusion with a focused examination, bedside cardiovascular ultrasonography, or fluid responsiveness testing was not associated with reduction in mortality. Such data are in line with the existing literature on haemodynamic monitoring and highlight an intriguing controversy.

On the one hand haemodynamic monitoring is generally considered to be an essential part of intensive care medicine. And clearly the field has made progress. A better understanding of (patho-) physiology has led us to abandon erroneous endpoints, such as supra-normal values and static pressures as a surrogate for preload.^{2,3} Nowadays, reversible challenges to test the physiological reserve allow us to predict the response of individual patients before an intervention is made.^{4,5} In addition, previously unexplored vascular compartments have now become accessible at the bedside.⁶ Both improvements in technology as well as the introduction of ultrasound enabled less invasive monitoring strategies, thus diminishing the practical limitations of haemodynamic monitoring in clinical reality.⁷ On the other hand, large series of randomised controlled trials (RCTs) failed to unequivocally demonstrate improved outcome as the result of haemodynamic monitoring, irrespective of the type of device, variables or setting.⁸⁻¹⁰ This apparent controversy may be due to many reasons. A common response to explain this perceived discordance is to zoom in on potential flaws of individual studies and to critically appraise the (lack of) high-quality data with respect to statistical solidity.¹¹ And although all of this seems fair, such criticism is unlikely to explain the gap between the intrinsic abilities of haemodynamic monitoring and lack of solid positive patient outcome data to the full extend. A potential 'elephant in the room' in this debate is the absence of integration of the obtained variables into a comprehensible diagnostic and therapeutic process. The way doctors deal with haemodynamic data remains largely outside the scope of the current literature. In this article we review recent publications on haemodynamic monitoring and focus on this potential missing link between accuracy and precision of monitoring devices, and effective implementation of therapeutic strategies.

REVIEW

A PubMed search with the terms 'haemodynamic [TITLE] AND monitoring [TITLE]' revealed 121 articles over the last two years, not restricted to critical care medicine per se. The main focus of these articles is either technology oriented (non-invasive/invasive), a comparison between devices (accuracy and precision) or outcome. None of these papers specifically addresses the issue of the transformation of monitoring data into clinical strategies and the crucial role of the doctor in this perspective. However, the majority of these papers contain bits of information that helps us to open this black box.

KNOWLEDGE

A prerequisite for the success of haemodynamic monitoring is a profound understanding of the meaning and the limitations of the derived variables. In a meta-analysis on non-invasive cardiac output devices in the perioperative setting the authors concluded that these techniques did not reach an acceptable level of agreement.¹² However, a translation of such conclusion to clinical reality is rather complex. Does it mean we should abandon such devices since they provide incorrect information? Or are these devices still capable to track changes over time during an intervention, and valuable as such? In contrast to the general believe that haemodynamic monitoring is simple, there is sufficient literature to suggest otherwise. Analysis of transpulmonary thermodilution data revealed that thermodilution-derived curves are significantly modified during concomitant renal replacement therapy.¹³ But does that mean we can no longer use such device under these conditions? Is the observed change in cardiac index from 6.5 ± 2.5 to 5.4 ± 1.9 L/min/m² also clinically relevant, or is 'extremely high' similar to 'very high' when it comes to decision making? Others observed that the limits of agreement in the assessment of stroke volume between three devices were relatively wide during hypothermia in post-resuscitation patients.¹⁴ But how to guide the confused clinician? Does this imply that one is better than the other under these circumstances? By definition such data are unable to answer these fundamental questions and it is unlikely that the issues raised by these studies will ever be answered in the foreseeable future.

It is not unlikely that such confusion, in the absence of solid proof that haemodynamic monitoring is associated with improved outcome, renders doctors to hesitance and even unwillingness to apply (extended) haemodynamic monitoring in clinical practise. During a one-day survey in one hundred and sixty-one ICU's in Germany, Austria and Switzerland, assessment of cardiac output was only performed in 12.3% of all patients.¹⁵ Such low adherence is not simply explained by restraint towards invasive procedures, since the majority of patients was equipped with an invasive atrial and central venous line. Moreover, the use of (completely non-invasive) ultrasound was restricted to 1.9% of all patients. These data are in

sharp contrast with the common opinion that stroke volume optimisation is the cornerstone for the definition of fluid responsiveness and the rising concern for fluid overload.¹⁶

PATIENT SELECTION AND TIMING

One way to overcome the gap between knowledge and application is to limit its use to those subsets of patients, in which haemodynamic monitoring is most likely to make a difference. Ultimately, all haemodynamic measurements will transform into a trigger to modify haemodynamic management. As such, pre-test likelihood is of much more importance than the accuracy and precision of the device at hand. This implies individualized selection of haemodynamic monitoring strategies.¹⁷ The more complex the disease, the higher the likelihood doctors may not be able to adequately predict the gravity of circulatory derangements.¹⁸ The consistent underestimation of cardiac output by clinicians will most probably influence the therapeutic strategy for the better in the lowest range, as compared to values in the higher end of the spectrum. Vice versa, the improper application of a high-quality device in a setting, unlikely to be attributable to haemodynamic instability, will presumably contribute to confusion instead of solutions. In this respect it seems key to understand that selection of the optimum stage for haemodynamic monitoring on the bases of 'clinical signs of impaired organ perfusion' is virtually impossible, due to lack of specificity.¹⁹⁻²¹ In other words: interpretation of oliguria, tachycardia and high lactate levels as markers of an underlying circulatory problem is far from unambiguous, and thus unsuitable as strict criteria for the initiation of haemodynamic monitoring.

Proper selection of an adequate setting for haemodynamic monitoring also includes timing. Nowadays a four-phase strategy in the fluid management of septic patients has been advocated: resuscitation, optimization, stabilization and evacuation (de-resuscitation).²² Such concept is also helpful in the timing of haemodynamic monitoring. The odds of a positive influence on outcome are higher during the first two phases, as compared to the later stages. Delaying haemodynamic monitoring may unintentionally result in non-specific data, blurring its original extremes. This phenomenon, generally referred to as regression-to-the mean, weakens the potential of haemodynamic monitoring, when initiated only in those who survived the initial phase.^{23,24}

DATA EXTRACTION AND REPRESENTATION

The way haemodynamic monitoring data are collected, gathered and visualized is likely to play a vital role in the ability to convert these data into recognizable patterns that trigger the physician to act. Near-continuous measurements and registration are mandatory to fully value the swift changes in haemodynamic variables. The fact that a change in assessment

of blood pressure from non-invasive to invasive may also affect sampling rate is not always fully appreciated. In a recent randomized controlled trial the continuous non-invasive registration of blood pressure during surgery was associated with a reduction in the number of periods with hypotension, in comparison to intermittent cuff measurements.²⁵ Bland Altman analysis of agreement was acceptable between groups, suggesting that sampling rate was the discriminative denominator.

An additional factor that allows physicians to utilize haemodynamic data to its full potential is a software-derived interface. Graphical displays facilitate the absorption of large amounts of data quickly, since the brain processes pictures all at ones, but processes text in a linear fashion. Simultaneous representation of the target zone helps clinicians guide decision making.²⁶ Future innovations include the ongoing development of automated data integration, serious gaming and the general application of smartphones and other wearable devices, but as of now clinical value needs to be established.²⁷

CONVERSION

In recent times we have come to understand that a measurement in itself is unlikely to make a difference in outcome.²⁸ However, this has not always been the case. Even in this millennium a large randomized controlled trial simply compared the insertion of a monitoring device over a control group without such device, and left the complete haemodynamic management to 'the discretion of the attending physician'.²⁹ Moreover, the effect on fluid management and use of vaso-active drugs was unaccounted for. Sometimes promising and sophisticated monitoring becomes available, based on solid physiological principles. But, as long as it may (not yet) be translated into a clear clinical strategy, clinical application outside the research setting remains limited.^{6,30}

Nowadays, reports on haemodynamic monitoring in combination with a haemodynamic management protocol is usually related to some form of (early) goal-directed therapy (GDT). Such package deals of measurements and actions clearly incorporate well-described strategies, but to differentiate the impact of the individual components is virtually impossible.⁹ Nowadays, the impact of age and gender on normal values becomes more clearly.³¹ Therefore, population-based values do not always represent personal normal values of a patient, highlighting the importance individualized medicine.³² This becomes particularly cumbersome when the amounts of administered fluids are fixed, irrespective from the response in haemodynamic variables.¹ Apparently, a loading dose of 30mL/kg for all does not take the heterogeneity of patients into account, which is the essence of haemodynamic monitoring in the first place. The fact that the actual fluid therapy was outside the scope is reflected by the

absence of report of total mean weight-based fluid administration in all but one study. Such ambiguous attitude towards monitoring and fluid administration was also reported in the setting of sepsis in the emergency department. In an open-label RCT a passive-leg-raise (PLR) guided protocol of fluid administration did neither significantly change lactate clearance, nor mortality, in comparison to the control group.³³ Of note: the control group was treated according to the discretion of the attending physician. However, within the study period of three hours, as well as after 3 days, the authors neither observed a difference in fluid administration, nor in the use in catecholamines. A potential explanation may be that it is conceivable that routine haemodynamic management is already optimal, and that extra monitoring simply is unable to change the course of the disease. However, the reported high incidence of fluid unresponsiveness during PLR suggests an alternative explanation.

PROTOCOL ADHERENCE AND HUMAN BEHAVIOUR

The recent FENICE trial has highlighted a probably most undervalued factor in the success or failure of haemodynamic monitoring.³⁴ In centres all over Europe a substantial proportion of doctors not only defined incorrect endpoints of fluid resuscitation for themselves. But to make matters worse, the test result did not influence their decision to continue or stop fluid administration. Patients received equal amounts of fluids, irrespective of a positive, negative or indifferent result; and irrespective of the type of test. Under such conditions it is hard to imagine any positive outcome as a result of haemodynamic monitoring. Recently, similar experiences have been reported.³⁵ Despite a detailed training programme, the introduction of PLR to assess fluid responsiveness in patients with septic shock did not result in a reduction in fluid administration within the first 48 hours after ICU admission. Evaluation revealed protocol violations after a negative PLR test in two-third of all cases. During a plenary discussion ICU physicians and nurses 'confessed' to consider their gut feeling superior to the test result. Subsequently the team decided in favour of an additional trial period, with a focus on protocol adherence. After intervention in this irrational behaviour the trial was now positive, with a significant and clinically relevant reduction of median fluid balance from 4.8[3.3-7.8] to 3.1[1.5-4.9] L.

Such observations form the often missing link between a solid physiologic principle and clinically relevant outcome.³⁶ It must be stressed however, that these challenges transcend a common implementation plan.³⁷ It involves the fundamental insight that medical personnel are not only driven by reason, but by emotions and habits too. All humans (including doctors!) operate within bounded rationality in order to solve complex problems, beyond and above their rational capacity.³⁸ This form of mental shortcut helps us to make decisions in the very complex setting of the ICU. But it also contributes to our (unaware) rejection of new concepts and ideas, as

long as we deem the old ones sufficient. As a consequence, introduction of haemodynamic monitoring should not be limited to theoretical and practical issues, such as education and training. It also involves integration strategies at the individual level (e.g. motivation, self-efficacy), inner setting (e.g. communication, leadership), as well as the need for constant evaluation at the level of the determinants of integration strategy effectiveness.³⁹ In this respect doctors should no longer be regarded as neutral bystanders, immune to non-rational motivations.⁴⁰ We can learn from others to close this knowledge-to-care gap, and implement haemodynamic monitoring in such a way that it has potential to modify the course of a disease.^{41,42} (figure 1).

We can also improve our strategies by learning from success. Introduction of trans-oesophageal echocardiography (TEE) during cardiac surgery has been adopted as the standard for haemodynamic monitoring in a relatively short period of time.⁴³ Integrating all of the above reveals that profound knowledge on cardiac anatomy and physiology is ubiquitous in the setting of cardiac surgery; all patients go through critical changes during the procedure; the obtained images serve as powerful and integrated feedback to the anaesthesiologist and surgeon; imaging is near-continuous; assessment of critical abnormalities lead to immediate action and can be executed by the same team; and overall success rate is very high. As of now, transfer of TEE as a monitoring device to the ICU setting has not been as successful as in cardiac surgery, due to the fact that critical links seem to be missing.⁴⁴ The absence of continuous availability, heterogeneity of population and lack of clear action protocols hamper the development from (powerful) diagnostic tool to a real monitoring device for the critically ill.

Figure 1. Essential steps in the successful implementation of haemodynamic monitoring

Another success story is the impressive reduction in re-hospitalisation for heart failure, associated with the use of implantable pulmonary artery pressure (PAP) sensors.⁴⁵ Although invasive at the start, a proper understanding of the significance of a rise in PAP in chronic heart failure (as opposed to the former erroneous interpretation of static pressures as a surrogate for preload in ICU setting!); a well-defined high-risk population; longitudinal availability, in combination with strict protocols; and the availability of accessible and uniform (drug)interventions all seem to have contributed to this success. Not only in trials, but also in the real-world setting.

CONCLUSION

Over the years we have progressively come to understand that the clinical success of haemodynamic monitoring depends upon a long chain of events, far beyond accuracy and precision. Profound understanding of the underlying mechanisms, adequate patient selection and timing, meaningful representation and software-supported interpretation of data all play an equally important role. Last but not least the information must be transformed into a concise action plan, both rationally and behaviourally adopted by all members of the ICU team. Meaningful introduction of haemodynamic monitoring has become a science in itself.

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Chapter 8

General Discussion

GENERAL DISCUSSION

In recent years there has been growing acknowledgement that the performance of the right ventricle (RV), which is an essential part of the cardiovascular system, plays a role in clinically relevant endpoints. This fuels the search for a thorough understanding of RV function in different disease states. In this thesis we aimed to improve the understanding of RV performance in the cardiosurgical patient. This chapter discusses our main findings.

ASSESSMENT OF RV FUNCTION IN CARDIAC SURGERY

Most studies assess RV function with echocardiography, either by the transthoracic (TTE) or by the transoesophageal (TOE) route. Although generally accepted as a monitoring device in the surgical setting, the use of TTE and of TOE both face specific challenges. Unlike the left ventricle (LV), the complex shape of the RV does not allow for any geometrical assumptions, which makes it difficult to calculate the size and the volume of the RV. Furthermore, global echocardiographic measurements of RV function require full-chamber imaging, which may be technically demanding and the results may often be limited by poor postoperative image quality.¹⁻³ Therefore, more simple and regional echocardiographic measurements of RV function have been suggested. These include measures of longitudinal RV contraction, such as tricuspid annular plane systolic excursion (TAPSE) and systolic tissue Doppler velocity of the tricuspid valve annulus (S'). Since longitudinal contraction is the main contributor to RV function, these measurements are generally believed to reflect systolic RV function under normal conditions.^{4,5} However, whether this assumption remains true in the specific setting of cardiac surgery seems to be a topic of debate.⁶⁻⁸ Although the use of the (contemporary) pulmonary artery catheter (PAC) clearly comes with its own specific challenges, application of this device has the potential to overcome some of the above-mentioned limitations in the assessment of RV function by perioperative echocardiography. The PAC allows for continuous, operator-independent RV monitoring during surgery as well as in the postoperative patient.

Clearly, the use of PAC is currently debated in the perioperative setting due to a number of large randomized controlled trials that failed to demonstrate any outcome benefit in relation to PAC-use.⁹⁻¹¹ However, for the highly complex link between the use of any monitoring device and clinical outcome to be understood, one requires all of the following: adequate measurements, adequate knowledge about data interpretation, and adequate application of the device and the data in the clinical setting. In relation to the use of PAC there is reason to believe that lack of specific knowledge has played a potential role in the general appreciation of the PAC-device. A thorough understanding of PAC-derived data is essential towards successful clinical application. In **chapter 2** we provided a comprehensive review on the technological characteristics of the contemporary PAC, and

introduce the large spectrum of PAC-derived data, as well as its potential for application within treatment algorithms.

MORBIDITY AND MORTALITY IN RELATION TO RV DYSFUNCTION IN CARDIAC SURGERY

Impaired baseline RV function has been associated with unfavourable outcome in cardiac surgical patients. This was demonstrated in patients having coronary artery bypass surgery with LV failure, mitral valve surgery, or heart transplantation.¹²⁻¹⁵ In addition, a postoperative decline in RV performance appeared to be a predictor of mortality and morbidity, and such a decline may not be volatile but persists up to one year after surgery.^{16,17} However, results are generally derived from small sample sized studies in specific patient populations. Thus the overall prognostic impact of impaired RV function in cardiac surgery remains unclear.

In **chapters 3 and 4** we described a large, heterogeneous group of cardiac surgical patients. In **chapter 3** we demonstrated that postoperative right ventricular ejection fraction (RVEF), as assessed by contemporary PAC, was a strong independent risk factor for long-term mortality. Impaired RVEF was not only associated with mortality directly after the surgical procedure, but its association continued to increase in the two years following the intervention. In **chapter 4**, RVEF was additionally associated with markers of morbidity, such as length of stay in the intensive care unit (ICU), duration of mechanical ventilation, and increased use of inotropic drugs. As anticipated, impaired RV function was associated with morbidity and mortality in combination with well-known risk factors for RV dysfunction, such as LV dysfunction or pulmonary hypertension. However, RVEF by itself remained an independent risk factor after correction for these potential confounders. This underlines the multifactorial aetiology of RV dysfunction in the cardiac surgical patient.

TIMELINE OF CHANGES IN RV FUNCTION DURING CARDIAC SURGERY

The observed association between RVEF and outcome does not allow for conclusions on cause-effect relationship. There are several studies that focused on identifying the time at which impaired RV function appeared after cardiac surgery. TAPSE and S' showed a significant decrease during cardiac surgery, and pericardial incision was suggested as a pivotal moment for the occurrence of this decrease.¹⁸ Since the pericardial support is considered to be fundamental for RV geometry, it has been suggested that the decline in longitudinal parameters reflect a true reduction in global RV function. However, despite the reduction in longitudinal parameters, global RV performance remains unchanged during cardiac surgery as measured with 3D echocardiography or speckle tracking.¹⁹⁻²² In **chapter 5** we combined both invasive haemodynamic PAC-monitoring with TOE in a prospective observational study during cardiac surgery. In this way, we were able to compare both changes in systolic longitudinal contractile

RV function (TAPSE and S') with changes in global myocardial function (TOE-derived myocardial performance index, MPI and PAC-derived RVEF). We observed that the significant reduction in TAPSE and S' was not accompanied by a reduction in global measures of RV function, as assessed by TOE and PAC. Furthermore, we were not able to replicate the previous observation in which pericardial incision was identified as a pivotal time point in the reduction of RV function during cardiac surgery. Instead, we found a gradual reduction in measures of longitudinal contractile RV function throughout the entire surgical procedure, suggesting a multifactorial aetiology. With TAPSE and S' being the most commonly used echocardiographic parameters in daily practice, our data highlight that regional longitudinal RV measurements in the postoperative cardiac surgical setting do not reflect global RV function, and should therefore be interpreted with caution.²³ It is conceivable that current reference values for echocardiographic measurements of TAPSE and S' do not apply to post cardiac surgical patients. They need to be established in this specific setting in order for their prognostic and clinical value to be understood.

MANAGEMENT OF RV DYSFUNCTION IN THE POSTOPERATIVE CARDIAC SURGICAL PATIENT

Impaired RV function can be the cause of postoperative haemodynamic instability and is associated with the development of postoperative organ failure.²⁴⁻²⁷ In case of volume or pressure overload of the RV, the inelastic nature of the pericardium results in the bowing of the intraventricular septum into the LV cavity.²⁸ As a result of this ventricular interdependence, a consecutive fall in cardiac output and systemic blood pressure will deteriorate RV function further by reducing RV coronary perfusion. Dilation of the RV will cause tricuspid annular dilation and further increase in RV preload. The RV enters a vicious circle of increased wall tension, mismatch in myocardial oxygen demand, and delivery and further impairment of contractility and dilatation.^{28,29}

An increase of blood pressure in this setting may re-establish the original configuration of the septum and restore RV coronary blood flow. This intervention is often mentioned as a cornerstone in the treatment of impaired RV function or failure in various disease states.^{30,31} However, data to support such clinical intervention are mainly based on studies in different experimental settings.^{32,33} Whether the increase in blood pressure during impaired RV function is effective in the clinical setting remains to be established. In **chapter 6**, the effect of norepinephrine-mediated high blood pressure targets was investigated in postoperative cardiac surgical patients with impaired RV function. A high blood pressure target (mean arterial pressure of 85 mmHg) did not result in an increase in PAC-derived RVEF or an improvement in RV echocardiographic parameters (TAPSE, S', MPI), as compared to patients with a lower postoperative blood pressure

target (mean arterial pressure of 65 mmHg). These rather unexpected findings warrant further studies that focus on the management of impaired RV function within the boundaries of a clinical setting.

To end this thesis, **chapter 7** provides an in-depth review about the missing links between the monitoring device's accuracy and precision at the one hand, and effective implementation of therapeutic strategies at the other hand. We focus on knowledge, adequate patient selection, adequate timing, data collection and representation, protocol adherence, and human behaviour. This review aims to add to the understanding of the complexity of successful monitoring.

FUTURE PERSPECTIVES

This thesis depicts the pivotal impact of RV function in the perioperative cardiac surgical patient. Since RV function has been traditionally underexposed in comparison to the relevance of LV function, the prognostic impact of the RV perioperative function should be brought to the attention of cardiothoracic surgeons, cardiologists, anaesthesiologists, and intensive care specialists. RV performance provides important prognostic information and has the potential to mitigate cardiac surgical risk factor scores.

For the assessment of RV function after cardiac surgery, it is necessary to define postoperative reference values for both echocardiographic and invasive haemodynamic monitoring measurements. This may improve the understanding and quantification of postoperative RV performance.

In addition, larger studies focussing on the time of occurrence of the reduction in perioperative RV function might unravel aetiology and may fuel the search for alternative management and prevention strategies. Although there are currently many interventions described to optimize RV function in the perioperative period (i.e. fluid management strategies, the use of different vasoactive and/or inotropic drugs, manipulation of heart rate, settings of positive-pressure ventilation), as of now it remains unclear whether these interventions will result in clinically relevant endpoints.

CONCLUSION

The role of the right ventricle remains intriguing in the cardiac surgical setting. This thesis demonstrates that postoperative RVEF provides important information in relation to morbidity and long-term mortality. Assessing the RV function is challenging in the perioperative setting. The reduction in measures of longitudinal contractile RV function was not accompanied by a reduction in global RV measurements as obtained with PAC and TOE. Solely relying on a single measurement of RV function carries the risk of misinterpretation and potentially mismanagement. Aetiology of the reduction of longitudinal parameters of RV function in the cardiac surgical setting is not related to one critical event, such as pericardial incision, but it is rather multifactorial. Although thought to be one of the cornerstones in the treatment of postoperative RV dysfunction, the increase in systemic blood pressure in patients with a moderate or poor RVEF and hypotension was shown to be ineffective in the clinical postoperative setting.

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Chapter 9

Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

DE RECHTER VENTRIKEL ALS ONDERDEEL VAN HET CARDIOVASCULAIR STELSEL

De rechter ventrikel (RV) werd lange tijd gezien als een overbodig onderdeel van het cardiovasculair stelsel van de mens. De enige taak van de RV leek het transport van zuurstofarm bloed vanuit het veneuze vaatsysteem naar de longcirculatie te zijn. Experimentele studies lieten zien dat ernstige schade aan de vrije wand van de RV niet resulteerde in hemodynamische instabiliteit of een vermindering van de conditie bij honden.

Ook patiënten zonder functionele RV, zoals bij een Fontan circulatie, blijken een grotendeels normaal leven te kunnen leiden. Het paradigma was dat als de RV faalt, de linker ventrikel (LV) de functie van de RV ogenschijnlijk gemakkelijk over kon nemen. De afgelopen jaren is steeds duidelijker geworden dat dit paradigma aan vervanging toe is. Steeds meer studies toonden aan dat de RV juist een essentieel onderdeel is van het cardiovasculair systeem. Met deze groeiende erkenning van de functie van de RV, wordt ook steeds meer duidelijk dat de functie van de RV prognostisch van belang kan zijn binnen verschillende patiëntencategorieën. De RV speelt onder andere een belangrijke rol in patiënten met sepsis, aritmogene rechterventrikeldysplasie, en verschillende hartklep ziekten. Daarnaast blijkt ook de functie van de RV van belang te zijn in de cardiochirurgische setting. Er is echter nog veel onduidelijkheid over de incidentie en het in kaart brengen van de RV functie. Ook zijn de etiologie, klinische consequenties en behandeling van RV dysfunctie nog onvoldoende in kaart gebracht. Met dit proefschrift willen we de functie van de RV bij cardiochirurgische patiënten beter in kaart brengen. In hoofdstuk 1 wordt een kort overzicht geschetst van de verschillende onderdelen van dit proefschrift.

HET BEOORDELEN VAN DE RV FUNCTIE BIJ DE CARDIOCHIRURGISCHE PATIËNT

Het beoordelen van de functie van de RV is niet gemakkelijk. MRI is de huidige gouden standaard voor het bepalen van de RV functie, maar is niet klinisch toepasbaar aan bed of tijdens chirurgie. Transthoracale echocardiografie (TTE), transoesophageale echocardiografie (TEE) of een arterie pulmonaliskatheter (PAC) zijn hiervoor een beter alternatief. De meeste onderzoeken gebruiken TTE of TEE voor het evalueren van de RV functie. De vorm van de RV is echter zeer complex, waardoor eenvoudige wiskundige modellen om volume en functie te bepalen niet toepasbaar zijn. Daarnaast vereisen echocardiografische metingen aan de RV vaak goede beeldkwaliteit van de gehele kamer. Dit is technisch lastig en de resultaten worden vaak nadelig beïnvloedt door slechte postoperatieve beeldkwaliteit. Meer eenvoudige metingen zijn metingen van alleen de longitudinale contractie van de RV, zoals tricuspid annular plane systolic excursion (TAPSE) en systolic tissue Doppler velocity of the tricuspid valve annulus (S'). De longitudinale contractie bepaalt voor veruit het grootste gedeelte de functie van de RV en wordt daarom gezien als een goede

weerspiegeling van de algehele RV functie. Of deze aanname een terechte weergave van de werkelijkheid is in de cardiochirurgische patiënt is nog altijd een onderwerp van discussie.

Deze specifieke beperkingen van echocardiografie in de perioperatieve setting kunnen worden overwonnen door het gebruik van de PAC. Met het gebruik van de PAC kunnen er continue, gebruikers-onafhankelijke metingen aan de RV worden verricht. Het gebruik van de PAC staat echter al langere tijd ter discussie. Grote randomized controlled trials tonen geen duidelijke verbetering op patiënt-gerelateerde uitkomstmaten, zoals mortaliteit en morbiditeit. Echter, de complexe verbinding tussen het toepassen van een meetinstrument in de klinische setting en klinisch relevante eindpunten kent vele essentiële schakels, waaronder adequate kennis over het meetsysteem. Een tekort aan specifieke kennis over de PAC heeft mogelijk een rol gespeeld in de waardering van de klinische waarde van de PAC. In **hoofdstuk 2** hebben we een uitgebreid overzicht gegeven van de technologische kenmerken van de hedendaagse PAC. Daarnaast gaan we dieper in op de interpretatie en toepassing van PAC-data in de klinische setting.

MORBIDITEIT EN MORTALITEIT IN RELATIE TOT DE RV FUNCTIE IN DE CARDIOCHIRURGISCHE PATIËNT

Een preoperatief verminderde functie van de RV is geassocieerd met een slechtere klinische uitkomst voor patiënten die een coronary artery bypass grafting (CABG) in combinatie met een slechte LV, mitralisklep chirurgie of een harttransplantatie ondergaan. Daarnaast is ook de postoperatieve RV functie een voorspeller voor morbiditeit en mortaliteit. Dit is echter gebaseerd op onderzoeken met kleine steekproeven in zeer specifieke patiëntpopulaties. De algehele prognostische impact van een verminderde RV functie bij cardiochirurgie blijft onduidelijk. In **hoofdstuk 3 en 4** beschrijven we een grote, heterogene groep cardiochirurgische patiënten. In **hoofdstuk 3** wordt aangetoond dat de postoperatieve rechter ventrikel ejectiefractie (RVEF), gemeten met de PAC, een sterke onafhankelijke risicofactor is voor mortaliteit op de lange termijn. Een lagere RVEF was niet alleen direct na cardiochirurgie geassocieerd met mortaliteit, maar deze associatie bleef zichtbaar in de twee jaar na de ingreep. In **hoofdstuk 4** wordt beschreven dat, naast de eerder gevonden associatie met mortaliteit, er ook een associatie bestaat tussen RVEF en markers van morbiditeit, zoals de verblijfsduur op de Intensive Care (ICU), de beademingsduur en het gebruik van intropica. RVEF was samen met bekende risicofactoren voor het krijgen van een RV dysfunctie (LV dysfunctie en pulmonale hypertensie) geassocieerd met morbiditeit en mortaliteit. Ook na correctie voor deze potentiële confounders bleef een verminderde RVEF een onafhankelijke risicofactor. Dit geeft aan dat RV dysfunctie bij de cardiochirurgische patiënt een multifactoriële etiologie heeft.

CHRONOLOGIE VAN DE VERANDERINGEN IN RV FUNCTIE TIJDENS CARDIOCHIRURGIE

De gevonden associatie tussen de RVEF en klinische uitkomstmaten zeggen echter nog niets over de relatie tussen oorzaak en gevolg. Verschillende studies hebben zich daarom gericht op het identificeren van het moment waarop een verminderde RV functie optrad na cardiochirurgie. TAPSE en S' laten een significante afname zien na cardiochirurgie, waarbij de incisie van het pericard als een cruciaal moment werd aangemerkt. Aangezien het pericard van belang is voor de geometrie van het hart, werd de afname van beide longitudinale parameters gezien als ware vermindering in de functie van de RV. Vervolgonderzoeken met echocardiografie laten echter zien dat, ondanks de afname van de longitudinale parameters, de globale RV functie niet verslechtert.

In **hoofdstuk 5** combineren we RV metingen van de PAC met metingen van de TEE in een prospectieve observationele studie tijdens cardiochirurgie. Longitudinale metingen van de RV (TAPSE en S') konden op deze manier vergeleken worden met globale metingen met de TEE (myocardial performance index, MPI) en de PAC (RVEF). Uit de resultaten blijkt dat de significante reductie in TAPSE en S' niet gepaard gaat met een verslechtering in de globale RV functie zoals gemeten met de PAC en de TEE. De afname in longitudinale parameters bleek verder een geleidelijk proces; een cruciaal moment zoals de incisie van het pericard kon niet gereproduceerd worden in deze studie. Aan de afname van longitudinale parameters lijkt dus een multifactoriële etiologie ten grondslag te liggen. Dit onderzoek laat zien dat TAPSE en S' in de postoperatieve cardiochirurgische setting geen goede maat zijn voor de globale RV functie. Echter, TAPSE en S' zijn de meest gebruikte echocardiografische parameters in de klinische setting. De huidige referentiewaarden voor TAPSE en S' zijn niet toepasbaar op de postoperatieve cardiochirurgische patiënt en zouden voor deze specifieke patiëntenpopulatie opnieuw vastgesteld moeten worden om een beter begrip te krijgen van de prognostische en klinische waarde van deze parameters.

BEHANDELING VAN RV DYSFUNCTIE IN DE POSTOPERATIEVE CARDIOCHIRURGISCHE PATIËNT

De RV en de LV hebben voor een deel gezamenlijke spiervezels, delen het septum en worden omgeven door hetzelfde pericard. Ventriculaire interdependentie beschrijft het concept dat de grootte, vorm en functie van de ene ventrikel wordt beïnvloed door die van de andere ventrikel. Een volume- of drukbelasting van de RV zal resulteren in RV dilatatie. Het pericard is echter erg stug, waardoor het septum zal buigen in de richting van de LV. Dit gaat ten koste van de grootte van de LV, wat weer zorgt voor een afname van de cardiac output en een lagere bloeddruk. Hierdoor ontstaat een verminderde perfusie van de coronairen van de RV. Het RV volume zal nog verder toenemen. Uiteindelijk kan er een vicieuze cirkel van

toegenomen wandspanning en een mismatch in de zuurstofvraag van het myocard en het aanbod ontstaan, wat zal leiden tot verdere achteruitgang van de RV functie. Een verminderde RV functie kan hemodynamische instabiliteit veroorzaken en is geassocieerd met postoperatief orgaanfalen. Het verhogen van de systemische bloeddruk bij RV dysfunctie zou het septum weer in zijn originele positie kunnen terugbrengen en kan bovendien de coronair perfusie van de RV verbeteren. Dit is een veelgenoemde behandeloptie voor RV dysfunctie. Bewijs voor effectiviteit van deze interventie is echter enkel gebaseerd op experimentele studies en de effectiviteit van het verhogen van de bloeddruk in de klinische setting moet nog worden vastgesteld. In **hoofdstuk 6** is het effect van een noradrenaline-gemedieerde verhoging van de bloeddruk op de RV functie onderzocht in de postoperatieve cardiochirurgische patiënt met RV dysfunctie. Een hogere bloeddruk (mean arterial pressure 85 mmHg) resulteerde niet in een verbetering van RVEF gemeten met de PAC of van TEE-parameters (TAPSE, S' en MPI) in vergelijking tot patiënten met een normale postoperatieve bloeddruk (mean arterial pressure 65 mmHg). Deze enigszins onverwachte bevinding suggereert dat er verder onderzoek nodig is naar de behandeling van RV dysfunctie in de klinische setting.

In **hoofdstuk 7** gaan we tot slot dieper in op de missende schakel tussen de nauwkeurigheid en precisie van een meetinstrument enerzijds en de effectieve implementatie van therapeutische strategieën anderzijds. Er wordt ingegaan op de verschillende factoren die hierbij belangrijk zijn: juiste kennis, adequate selectie van patiënten, adequate timing van het toepassen van het meetinstrument, representatie van data, naleving van het protocol en menselijke gedrag. Dit review is bedoeld om een beter begrip te creëren van de complexiteit van succesvolle monitoring en de factoren die hiervan op invloed zijn.

CONCLUSIE

De rol van de RV in cardiochirurgie blijft een intrigerend onderwerp. Een afgenomen postoperatieve RVEF is geassocieerd met morbiditeit en mortaliteit. Het bepalen van de functie van de RV blijft echter een grote uitdaging in de perioperatieve setting. De postoperatieve afname van de longitudinale echocardiografische parameters gaat niet gepaard met een afname van de globale RV functie en vertrouwen op alleen deze parameters kan zorgen voor een verkeerde interpretatie van de RV functie. De vermindering van de postoperatieve longitudinale parameters is een geleidelijk proces en niet gerelateerd aan één cruciaal moment, zoals incisie van het pericard. Ondanks het feit dat bloeddruk verhoging als een hoeksteen van de behandeling van RV dysfunctie wordt beschouwd, bleek het verhogen van de bloeddruk in de postoperatieve cardiochirurgische setting niet effectief bij patiënten met een matige of slechte RVEF.

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“DAT PROMOVEREN IS MEER IETS VOOR ANDERE MENSEN. LAAT MIJ MAAR GEWOON LEKKER DOKTEREN.”

Deze woorden heb ik als co-assistent jaren met volle overtuiging uitgesproken. Maar zoals vaak in het leven loopt het anders en kreeg ik de kans om de wetenschappelijke wereld samen te laten komen met de klinische wereld. Deze ervaring heeft ervoor gezorgd dat ik mij op persoonlijk en professioneel gebied enorm kon ontwikkelen.

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Mijn stage wetenschap tijdens de geneeskunde opleiding bracht mij op de Intensive Care van het Medisch Centrum Leeuwarden. De ontwikkeling van deze stage zien als ‘noodzakelijk om de master Geneeskunde te behalen’ naar ‘ik vind het oprecht leuk en ga er nu een promotietraject van maken’ heb ik te danken aan het enorme enthousiasme van mijn co-promotor **dr. E.C. Boerma**. Beste Christiaan, wat heb ik met veel plezier met je samengewerkt. Niet alleen aan onze onderzoeksprojecten, maar ook in de kliniek. Het is ontzettend fijn dat je deur altijd open stond voor de nieuwste ideeën, maar ook voor een goed gesprek met een lach en soms een traan. Ik heb op zo ontzettend veel fronten van je mogen leren en daarvoor ben ik je heel erg dankbaar.

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Mijn **collega arts-assistenten van de Intensive Care**. Na bijna 5 jaar op de IC heb ik het genoeg gehad om met veel fijne collega's samen te mogen werken. De diensten als jonge dokter op een Intensive Care zijn niet altijd gemakkelijk, maar als assistenten onder elkaar is er altijd oog voor elkaar. Even een kopje koffie of een ijsje halen of juist even hangen op de bank in de assistentenkamer gaf altijd de nodige afleiding wanneer dat nodig was. Dank daarvoor! **Jurgen Winkelhorst** heeft het zelfs aangedurfd om als wetenschapsproject zich ook te richten op de rechter ventrikel. Jurgen, bedankt voor deze leuke en fijne samenwerking.

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CURRICULUM VITAE

Inge Tjitske Bootsma was born on 20 July 1990 in Steggerda (Weststellingwerf), where she grew up with her parents, two brothers, and sister. She graduated high school (Lindecollege, Wolvega) in 2008. After graduation, she studied Movement Science at the University of Groningen. After obtaining her First Year's degree, Inge was admitted by selection to study Medicine at the University of Groningen in 2009.

During her sixth year of Medical School, she started a scientific internship at the Intensive Care of the Medical Center Leeuwarden under the supervision of dr. E.C. Boerma. This project continued after graduation from Medical School in 2015, and resulted in this thesis you are reading right now. Inge combined her PhD with working as a resident at the same Intensive Care Unit. Inge will start as a resident internal medicine in 2021.

Inge is married to Victor Bouwman and together they have a daughter, Elin Bouwman. They live in Leeuwarden.

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