Pressure reflection in the pulmonary circulation in patients with severe mitral regurgitation indicates adverse postoperative outcome

Odd Bech-Hanssena,b,*, Carl-Johan Malmc, Lena Nguyend, Anders Jeppssonc,e, Henrik Schersténc,e and Sven-Erik Rickstenc

a Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden  
b Heart Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia  
c Department of Cardiovascular Surgery and Anesthesia, Sahlgrenska University Hospital, Gothenburg, Sweden  
d Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden  
e Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

* Corresponding author. Heart Centre, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Kingdom of Saudi Arabia.  
E-mail: odd.bech-hanssen@klinfys.gu.se (O. Bech-Hanssen).

Received 8 December 2012; received in revised form 4 February 2013; accepted 13 February 2013

Abstract

OBJECTIVES: Severe pulmonary hypertension (PH) is a known risk factor in valvular surgery. In the present study, we hypothesized that the assessment of pressure reflection (PR) in the pulmonary circulation, indicating increased pulmonary vascular resistance, might improve the identification of patients with increased morbidity and mortality following surgery for severe mitral regurgitation.

METHODS: A total of 103 patients without atrial fibrillation were divided into three groups: Group 1 (n = 48), patients without PR; Group 2 (n = 36), patients with PR and pulmonary artery systolic pressure (PASP) ≤ 60 mmHg and Group 3 (n = 19), patients with PR and PASP > 60 mmHg. Three variables related to PR were selected: the acceleration time in the right ventricular outflow tract (RVOT), the interval between peak velocity in the RVOT and peak tricuspid regurgitant jet velocity and the right ventricular pressure increase after peak RVOT velocity.

RESULTS: There were no differences between groups in age, ejection fraction, need for coronary bypass grafting or creatinine. Patients with PR (Groups 2 and 3) had more use of vasoactive drugs (overall P < 0.0001, Group 1 vs Group 2 P = 0.018). The proportion of patients with > 24 h in the intensive care unit was 27% in Group 1, 54% in Group 2 and 84% in Group 3 (overall P < 0.0001, Group 1 vs Group 2 P = 0.006). The in-hospital mortality in patients without PR (n = 49) was 0% compared with 10.9% in patients with PR (P = 0.029).

CONCLUSIONS: Echocardiography assessment of PR in the pulmonary circulation and severe PH may identify patients with adverse outcome following mitral surgery.

Keywords: Echocardiography • Pressure reflection • Pulmonary hypertension • Mitral regurgitation • Pulmonary vascular resistance

INTRODUCTION

The possible outcome following cardiac surgery in terms of morbidity and mortality is of interest for both the patient and the health providers. Several preoperative risk status models have been developed to predict outcome after coronary artery bypass surgery [1–4]. Pulmonary hypertension (PH) is not a common finding in patients with coronary artery disease and it is included in only one of these models [4]. In patients with valvular heart disease, particularly that affecting the mitral valve, PH is a relatively frequent finding [5]. PH might be due to increased pressure in the left atrium (venous PH, passive PH), increased pulmonary vascular resistance (PVR, reactive PH) or both. The reason for increased PVR can be structural changes in the distal pulmonary arteries, increased vascular tone, or both.

In patients with PH, the increased right ventricular (RV) afterload can lead to preoperative incipient or overt RV failure that may negatively affect the outcome of surgery in terms of morbidity and mortality. However, in patients in whom venous PH dominates, we can expect immediate decrease of pulmonary pressure following mitral valve surgery. On the contrary, in patients with preoperatively increased PVR and reactive PH, there might be a significant residual increase in pulmonary artery pressure after surgery [6]. It is, therefore, conceivable that patients with reactive PH are at higher risk following surgery compared with those with passive PH.

To calculate PVR, it is necessary to perform a right heart catheterization to obtain pulmonary artery mean pressure, pulmonary capillary wedge pressure (PCWP) and cardiac output. In a recent study, we described a new echocardiography method to
identify patients with increased PVR (>3 Wood Units) [7]. The normal pulmonary circulation is characterized by low PVR and compliant arteries with no reflection of the pressure wave. We found that echocardiography signs of pressure reflection (PR) in the pulmonary circulation were associated with high PVR, while there was no significant relation between PCWP and PR.

In the present study, we tested the hypothesis that the presence of echocardiography signs of PR, indicating high PVR, is associated with adverse postoperative outcome in patients with severe mitral regurgitation undergoing mitral valve surgery.

METHODS

Study population

The study was approved by the ethics committee at the University of Gothenburg (448-10). This retrospective study comprised 103 patients with severe mitral regurgitation undergoing mitral valve surgery at Sahlgrenska University Hospital between January 2008 and March 2011. The inclusion criteria were: (1) normal sinus rhythm, (2) pulsed Doppler recordings in the RV outflow tract (RVOT), (3) a tricuspid regurgitation that enabled Doppler assessment of right ventricle peak systolic pressure and (4) no RVOT obstruction. An echocardiography investigation is part of the routine prior to operation and in most patients it is done the day before surgery. Experienced technicians perform the investigation using two different echocardiography systems (iE33, Philips Healthcare, Netherlands or Vivid E9, GE Healthcare, USA).

Pressure reflection in the pulmonary circulation

In the normal pulmonary circulation, the pressure and flow waves generated by the right ventricle are almost completely dampened and display similar contours (Fig. 1) [8, 9]. In individuals without obstruction in the RVOT, the shape of the pressure waveforms in the right ventricle and pulmonary artery (including the timing of peak pressure) are similar. An increase in the pre-capillary properties, such as reduced compliance and increased resistance, causes a reflection of pressure and flow waves, with marked changes in wave contours. The reflected pressure wave will add on to the forward travelling wave and there will be an increase in pressure in the right ventricle and pulmonary artery while the flow is decreasing (Fig. 1). The site and magnitude of PR influence the timing of peak velocity in the RVOT, the timing of peak velocity in relation to peak pressure in the right ventricle and the magnitude of pressure increase in the right ventricle after peak velocity in the RVOT (Fig. 1).

Doppler echocardiography

In the present study, we assessed the following three variables to identify PR, described below and in Fig. 2:

(i) The time interval from opening of the pulmonary valve to peak velocity, the so-called acceleration time (AcT).
(ii) The time interval from peak velocity in the RVOT to peak velocity in the tricuspid regurgitation jet (=peak pressure in the right ventricle) (tPV – PP).
(iii) The pressure increase (augmentation) in the right ventricle after peak velocity in the RVOT, or the so-called augmented pressure (AP).

The assessment of PR requires continuous Doppler recording of the tricuspid regurgitant jet and pulsed Doppler recording of the RVOT flow. We used multiple windows guided by colour Doppler to obtain the highest tricuspid regurgitation jet velocity. Most often the highest velocity was found in a projection that shows the right ventricle somewhere between a standard four-chamber and parasternal short-axis view. The flow velocity was recorded by placing a 5 mm sample volume in the RVOT below the pulmonary valve. The time intervals between QRS and pulmonary valve opening (a) and peak velocity (b) were determined (Fig. 2). The timing of the RV peak systolic pressure was

Figure 1: Schematic drawings of the pulmonary artery pressure and flow in a subject with normal PVR (left) and one with increased PVR and PR. Observe the increase in pulmonary artery pressure after the peak flow velocity in the patient with increased PVR.
determined as the time from QRS using the same QRS reference as in the RVOT, to the peak velocity of the tricuspid regurgitant jet (c) recording. In subjects where the peak velocity in the RVOT preceded the peak velocity (b < c) in the tricuspid regurgitant jet, the time interval (c) was superimposed onto the velocity spectrum of the tricuspid regurgitant jet in order to calculate the right ventricle pressure corresponding to the peak velocity in the RVOT. The velocity of the tricuspid regurgitant jet at this point was measured and the pressure gradient between the right ventricle and the right atrium was calculated (pressure gradient = 4 x velocity2). The time from peak velocity in the RVOT to peak pressure in the right ventricle (tPV–PP) was calculated as (c–b). The time from onset of flow in the RVOT to peak velocity (AcT) was calculated as (b–a). The AP was calculated as the difference between peak pressure in the right ventricle and the pressure corresponding to peak velocity in the RVOT. The mean right atrial pressure was estimated using the inferior vena cava dimension and collapsibility with inspiration [10].

A patient was considered to have PR if AcT was <103 ms or the tPV–PP time was >89 ms or if AP was >8 mmHg, as previously described [7]. The patients were divided into three groups: Group 1: patients with no signs of PR in the pulmonary circulation, Group 2: patients with PR and a pulmonary artery systolic pressure (PASP) ≤60 mmHg and Group 3: patients with PR and a PASP >60 mmHg.

Other echocardiographic variables

The left ventricular ejection fraction and left ventricular volume were measured using Simpsons method. The RV area in diastole (RVd area) and systole (RVs area) were determined using planimetry. The RV area ejection fraction (RVEF) was calculated from \[ \frac{\text{RVd area} - \text{RVs area}}{\text{RVd area}} \times 100 \]. The right and left atrial area was determined by planimetry in end-systole. The stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral (VTI). Cardiac index was calculated as \((\text{stroke volume} \times \text{heart rate})/\text{body surface area}\). The assessment of the severity of mitral and tricuspid regurgitation was done according to the recommendations of the American Society of Echocardiography [11]. The ratio between the VTI of pulsed Doppler at the tip of the mitral valve (MV) and in the left ventricular outflow tract (LVOT) was used as a continuous variable describing the severity of mitral regurgitation [12]. The mitral valve VTI was used as a surrogate for the total left ventricular stroke volume and the left outflow tract integral was used as a surrogate for net stroke volume. A ratio >1.4 indicates severe regurgitation. All Doppler measurements were performed off-line with a sweep speed of 100–200 mm/s and the investigator was blinded to the results from the intensive care unit (ICU) records.

Cleveland Clinic intensive care unit admission score and outcome variables

In the present study, we determined the Cleveland Clinic ICU admission score [13], and the following clinical outcome variables were used: the duration of postoperative heart failure treatment, assessed as the number of days with the use of ≥two inotropic agents, and the length of stay in ICU. The ICU admission score takes into consideration preoperative risk factors, intraoperative events and physiological variables at admission to the ICU [13]. This score increases the possibility of identifying patients with high risk of mortality and morbidity based on postoperative status when compared with preoperative scoring alone. In the present study, the total ICU admission score as well as its three components (preoperative, intraoperative and admission physiology) are reported. The ‘preoperative’ variables with their score in parenthesis are: Body surface area <1.72 m² (1), one prior heart operation (1), two or more heart operations (2), operation or angioplasty for peripheral vascular disease (3), age ≥70 years, preoperative creatinine >167 mmol/l (4) and preoperative albumin <35 g/l (5). The ‘intraoperative’ factors are: Cardiopulmonary bypass time ≥160 min (3) and use of intra-aortic balloon pump or left ventricular assist (7). The ‘ICU admission physiology’ variables are: Alveolar-arterial O₂ gradient ≥33 kPa (2), heart rate >100 beats/min (3), total O₂-extraction ratio >0.50 (3), central venous pressure >17 mmHg (4) and base excess less than –4 mmol/l (4).

Statistical methods

Continuous variables with normal distribution are expressed as the mean ± SD and median (25 and 75 percentile) when the distribution is not normal. To compare multiple groups, we used one-way ANOVA test when the distribution was normal, Kruskal-Wallis test when the distribution was not normal and the χ² test for proportions. In cases where the null-hypothesis was rejected (P < 0.05 considered statistically significant) we continued with a post-hoc analysis using the independent-sample t-test or
The age was 65 ± 11 years and the percentage of males was 72%. Mitral repair was performed in 83%. The median time interval between preoperative echocardiography and operation was 2 days (the 25th and 75th percentile were 1 and 5 days, respectively). Five percent had severe, 7% had moderately severe, 16% moderate and 71% mild tricuspid regurgitation. Twenty-three percent had concomitant coronary bypass grafting.

Forty-eight patients (47%) did not have signs of PR (Group 1). PR was present in 55 patients, 36 had PASP ≤60 mmHg (Group 2) and 19 had severe PH with PASP >60 mmHg (Group 3) (Fig. 3).

The diagnosis of PR was based on three criteria in 40%, two in 33% and one in 27% of the patients. All the patients with severe PH (Group 3) had PR (Fig. 3). Mild-to-moderate PH (PASP 40–60 mmHg) was present in 77% of the remaining patients with PR and in 33% of the patients without PR.

Table 1 shows the clinical and echocardiography data for patients without PR (Group 1), with PR and moderate (Group 2) and severe (Group 3) PH, respectively. There was no significant difference in clinical background data and LVEF between the three groups except the EuroSCORE. Patients with severe PH (Group 3) had significantly higher risk compared with patients without PH (Group 1). The difference between Group 1 and Group 2 did not reach statistical significance. Patients with PR (Groups 2 and 3) had more severe regurgitation assessed by the VTI ratio MV/LVOT, lower cardiac index and more pronounced tricuspid regurgitation, while RVEF did not differ between Groups 1 and 2. The patients with severe PH (Group 3) had lower RVEF and higher RA pressure compared with those in Group 2, while the degree of mitral and tricuspid regurgitation and cardiac index did not differ between Groups 2 and 3.

The ICU admission score was significantly higher in patients with PR (Groups 2 and 3) compared with those without PR (Group 1) (Fig. 4). There was no difference between patients with PR and moderate or severe PH, respectively (Groups 2 and 3).

The duration of postoperative heart failure (=days with >2 vasoactive drugs) was significantly longer in patients with PR (Groups 2 and 3) compared those without PR (Group 1) (Fig. 5), while...
postoperative heart failure duration did not differ between Groups 2 and 3. Patients with PR had significantly longer stay in the ICU (Fig. 6A) compared with those without PR, particularly in Group 3. The proportion with >24 h at the ICU was 27% in Group 1, 54% in Group 2 and 84% in Group 3 (Fig. 6B).

Six patients died in hospital (5.8%). The in-hospital mortality in Group 1 was 0% (0/48), 11.1% (4/35) in Group 2 and 10.5% in Group 3 (2/19). The mortality in patients with PR was 10.9%. There was a significant difference in in-hospital mortality between patients with and without PR ($P = 0.029$).

**DISCUSSION**

The main findings of the present study were that preoperative echocardiography signs of PR in the pulmonary circulation were associated with a higher postoperative mortality rate and increased morbidity, as demonstrated by a higher ICU admission risk score, more advanced heart failure and a longer ICU length of stay compared with patients with no signs of PR.

It is well known that severe PH (>60 mmHg) is associated with an adverse outcome in valve surgery [14–17]. PH in a patient with severe mitral regurgitation can be explained by increased pressure in the left atrium and venous PH or by increased precapillary PVR. The presence of signs of PR, suggesting elevated PVR, in all patients in Group 3 with advanced PH, indicates that these two mechanisms often coexist. The increased PVR might be due to structural vascular changes with intima-media thickening [18] or increased vascular tone. In most patients undergoing valve surgery will the pressure in the left atrium decrease markedly immediately after the operation? Marked decrease in pulmonary artery pressure and PVR ≥2 months following surgery

**Figure 4:** Box plots show the overall ICU admission score (A), the preoperative score (B), the preoperative score (C) and the ICU admission physiology score (D).
has been reported in patients with mitral regurgitation or stenosis and increased preoperative PVR [19]. The short-term effect of decreased left atrial pressure on increased PVR has not been well studied. In a recent study on patients with preoperative PH, 46% had residual PH, caused by elevated PVR, 24 h following surgery [6]. This residual PH was an independent risk factor for increased postoperative mortality, morbidity and prolonged stay in ICU [6].

The most important finding of the present study was that we identified a group of patients with echocardiography signs of PR, with only mild-to-moderate PH (Group 2). These patients would not be regarded as having reactive or 'out-of-proportion' PH [20], and their moderately elevated pulmonary artery pressure would have been regarded as due to venous PH, expected to normalize after surgery. The mild-to-moderate PH in these patients, together with their preserved preoperative RV systolic function, would indicate that no major postoperative morbidity would occur [6]. However, postoperative morbidity was higher also in this group of patients, when compared with patients with no PR (Group 1), suggesting that PR is associated with adverse outcome also in patients with mild-to-moderate PH. In fact, postoperative morbidity in Group 2 was comparable with that in patients with severe PH (Group 3), suggesting that PR and not only pulmonary artery pressure per se, is an important preoperative variable when predicting postoperative outcome. Thirty-three percent of patients without PR had mild-to-moderate PH. It is conceivable that this was venous PH with normal PVR. Indeed, the postoperative period was relatively uncomplicated in this group as 73% had <24 h stay in the ICU and 78% did not require any vasoactive treatment.

Eight patients in Group 2 (22%) with echocardiography signs of PR did not have PH (PASP <40 mmHg). This can be explained by the fact that pulmonary artery pressure is dependent on blood flow. The pulmonary artery pressure as well as the transpulmonary gradients will be reduced in patients with left ventricular forward failure. In this context, the PR variables, therefore, offer a relatively flow-independent PVR estimation that has the potential to detect patients at risk for postoperative morbidity with no or only moderately elevated pulmonary artery pressure. The absence or presence of PR together with other known clinical and echocardiography variables associated with increased postoperative risk might help in further risk stratification of the patients.

The outcome of valve surgery is dependent on several factors including the preoperative status and intraoperative and postoperative events. We believe that preoperative PR is a signal for postoperative residual PH caused by elevated PVR leading to RV failure following surgery. This was supported by our findings of prolonged treatment of severe postoperative heart failure in patients with preoperative PR, and also in patients with no or mild-to-moderate PH. Strategies to reduce the negative effect of increased PVR on RV function should aim at optimal intraoperative RV preservation and pulmonary vasodilatation immediately after weaning from bypass. In this respect, inhaled NO and sildenafil alone or in combination are possible treatment options [21–23].

Figure 5: Box plots show the days with ≥2 vasoactive drugs at the ICU.

Figure 6: Box plots show (A) hours stay at the ICU and (B) the proportion of patients with >24 h stay.
There are several possible limitations of the present study. Only patients with pulsed Doppler in the RVOT were included. This has probably introduced a selection bias towards patients with higher pulmonary artery pressure and more advanced disease. This selection bias explains the relatively high in-hospital mortality in our study population (5.8%). The overall in-hospital mortality in patients undergoing mitral surgery in the study period 2008–11 was 2.7%. However, this should not importantly influence the main findings of the study. Our definition of severe heart failure was the use of two or more inotropic agents, but we have no information on whether the patients suffered from RV, left ventricular or biventricular failure. The data presented indicate differences in the occurrence of heart failure between patients with and without PR. The study was retrospective. A prospective design would have made it possible to describe with more certainty the presence, or not, of RV failure and to evaluate the diagnostic performance of the PR variables regarding increased postoperative morbidity. The study population was relatively small. There was an increase in in-hospital mortality in patients with signs of PR. However, a larger study population will be needed to establish whether the presence of PR preoperatively has implications for mortality. The haemodynamic data presented in the study are solely based on echocardiography. Invasive measurements of pressure and assessment of PVR are not a part of the preoperative work-up or postoperative monitoring in patients undergoing mitral valve surgery. A prospective study including invasive assessments of pressure and PVR is needed to establish the relation between PR and PVR in patients with severe mitral regurgitation.

REFERENCES


