Identifying risk factors for perioperative decline in right ventricular performance in cardiac surgery patients: a prospective observational study in a tertiary care hospital

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ABSTRACT

Objectives Impaired right ventricular (RV) function after cardiac surgery is associated with morbidity and long-term mortality. The purpose of this study was to identify factors that play a role in the development of RV dysfunction in the perioperative cardiac surgery setting.

Design We performed a prospective, observational, single centre study. Over a 2-year period, baseline and perioperative characteristics were recorded. For analysis, subjects were divided into three groups: patients with a ≥3% absolute increase in postoperative RV ejection fraction (RVEF) in comparison to baseline (RVEF+), patients with a ≥3% absolute decrease in RVEF (RVEF−) and patients with a <3% absolute change in RVEF (RVEF=).

Setting Tertiary care hospital in the Netherlands.

Participants We included all cardiac surgery patients ≥18 years of age equipped with a pulmonary artery catheter and admitted to the ICU in 2015–2016. There were no exclusion criteria. A total number of 267 patients were included (65.5% men).

Outcome measures Risk factors for a perioperative decline in RV function.

Results A reduction in RVEF was observed in 40% of patients. In multivariate analysis, patients with RVEF− were compared with patients with RVEF= (first-mentioned OR) and RVEF+ (second-mentioned OR). Preoperative use of calcium channel blocker (CCB) (OR 3.06, 95% CI 1.24 to 7.54/OR 2.73, 95% CI 1.21 to 6.16 (both p<0.001)), intraoperative fluid balance (FB) (OR 1.45, 95% CI 1.02 to 2.06 (p=0.039)/OR 1.09, 95% CI 0.80 to 1.49 (p=0.575)) and baseline RVEF (OR 1.22; 95% CI 1.14 to 1.30/OR 1.27, 95% CI 1.19 to 1.35 (both p<0.001)) were identified as independent risk factors for a decline in RVEF during surgery.

Conclusion Apart from the impact of the perioperative FB, preoperative use of a CCB as a risk factor for perioperative reduction in RVEF is the most prominent new finding of this study.

INTRODUCTION

Previous studies showed an association between decreased right ventricular (RV) function after cardiac surgery with a higher 2-year mortality and a complicated postoperative intensive care unit (ICU) admission. Patients with a decreased postoperative RV function are in need of more inotropic medication and intravenous fluid administration during ICU admission. Furthermore, decline in renal function occurs more frequently in patients with postoperative RV dysfunction as well as a longer duration of mechanical ventilation and a longer length of stay in ICU. Besides a higher demand for the individual patient, postoperative RV dysfunction has a negative effect on availability of ICU capacity and leads to higher costs.

However, risk factors for the decline of RV function during the surgical procedure are not well documented. Based on physiology, the development of RV dysfunction may be related to changes in preload, afterload and contractility. Since cardiovascular medication plays a major role in the treatment of cardiac dysfunction, we hypothesised that preoperative use of cardiovascular medication might protect against the development of perioperative RV dysfunction. Data about the effect of cardiovascular medication on RV function are scarce. In patients with heart failure with reduced ejection fraction, a possible positive effect of beta-blockade on RV function has been reported. Also, small studies indicate...
a potential positive effect on RV function of angiotensinconverting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) in patients without cardiac failure.10,11

We conducted this study to identify factors that play a role in the development of RV dysfunction in the perioperative cardiac surgery setting, with a particular interest in the role of preoperative use of cardiovascular medication.

METHODS

Study design and setting

We performed a prospective, observational, single-centre study in a closed format, 20-bed mixed ICU in a tertiary teaching hospital in the Netherlands. By protocol in our hospital, all valve surgery patients and coronary artery bypass grafting (CABG) patients with a poor left ventricular (LV) function are monitored perioperative with a continuous cardiac output pulmonary artery catheter (PAC; 7.5F CCO catheter, model 774F75; Edwards Lifesciences, Edwards, Irvine, CA, USA). This PAC is interfaced with a computerised monitoring system (Vigilance; Edwards Lifesciences; Irvine, California). The PAC enables near-continuous data on cardiac index (CI), mixed venous oxygen saturation (SvO₂), RV end-diastolic volume and RV ejection fraction (RVEF).

Over a 2-year period (2015–2016), we included all cardiac surgery patients ≥18 years of age with available preoperative and postoperative invasive haemodynamic measurements. There were no exclusion criteria. Two dedicated cardiothoracic anaesthesiologists recorded baseline PAC-derived RVEF after induction but before sternotomy, in addition to the routinely recorded RVEF in the postoperative ICU phase.

Data collection

We collected the following baseline parameters: age, sex, height, weight and comorbidities. Preoperative use of cardiovascular medication, divided in ACEi, ARB, beta-blockers, CCB and diuretics, was registered. Collected perioperative parameters were type of surgery, preoperative haemodynamic variables (pulmonary artery pressure (PAP), central venous pressure (CVP), RV end-diastolic volume index (EDVi), CI, RVEF, SvO₂), intraoperative characteristics (cross clamp and cardiopulmonary bypass time, pericard closure, type of cardioplegia, perioperative fluid balance (FB)), CVP peak pressure at end of extracorporeal circulation, presence of stenosis in right coronary artery (RCA), revascularisation of RCA, haemodynamic parameters in first 10 min at ICU (PAP, CVP, EDVi, CI, RVEF, SvO₂). The perioperative echo assessment of LV and RV function, performed by the attending cardiac anaesthesiologist, is reported to the ICU as good, moderate or poor. These data were collected as well. We chose to use the detailed near-continuous PAC measurements for the assessment of perioperative RV function. These measurements corresponded with the global echocardiographic assessment of the cardiac anaesthesiologist in a previous study.12

Sample size

Based on our previous publications, patients were divided into three groups: patients with a ≥3% absolute increase in postoperative RVEF in comparison to baseline (RVEF+), patients with a ≥3% absolute decrease in postoperative RVEF in comparison to baseline (RVEF−) and patients with a <3% absolute change in postoperative RVEF in comparison to baseline (RVEF=).12

In a random sample, 50% of patients had a perioperative decrease in RV function. Since we expected to test a maximum of 10 parameters in multivariate analysis, 300 patients were needed to reach a minimum of 10 patients per parameter per group.

Statistical analysis

The Statistical Package for Social Sciences (SPSS V.25 for Windows, Chicago, Illinois) was used for statistical analysis. Normal distribution of variables was tested with the Kolmogorov-Smirnoff test. Every single parameter was tested for a relationship with perioperative change in RV function using an unpaired t test in case of normal distribution and χ² test for non-normally distributed variables. All preoperative and intraoperative parameters with a p value ≤0.25 in the univariate analysis were included in the multivariate analysis.

Patient and public involvement

None.

RESULTS

During the study period, 286 patients were potentially eligible for inclusion. In 19 patients preoperative or postoperative measurements were not available which made inclusion impossible. The remaining 267 patients were included in the study. Baseline characteristics are provided in table 1. Median age was 70 (IQR 63–77), 65.5% of patients in this study were men. Most patients underwent valve repair/replacement (42.3%) or a combination of valve surgery with CABG (37.8%). Preoperative echocardiographic LV function was good (>50%) in 179 patients (67%), moderate (30–49%) in 49 (18.4%) and poor (<30%) in 38 patients (14.2%). Echocardiographic RV function was good in the majority of patients (n=227, 85%) and poor in only 4 (1.5%) patients. The remaining 28 patients (10.5%) had a moderate preoperative RV function.

107 patients (40%) qualified for the RVEF− group, 64 patients (24%) qualified for the RVEF= group and 96 patients (36%) qualified for the RVEF+ group. Based on the univariate analysis, sex, preoperative use of a CCB, central venous peak pressure at the end of the extracorporeal circulation, perioperative FB, preoperative SvO₂, preoperative echocardiographic LV function and PAC-derived preoperative RVEF were included in

the multivariate analysis (online supplemental table 1). Preoperative use of CCB, perioperative FB and baseline RVEF were identified as independent risk factors for a decline of RVEF during surgery (table 2).

**DISCUSSION**

In this study we observed a reduction in RVEF in 40% of all patients during a cardiosurgical procedure. In a multivariate analysis, perioperative FB, preoperative RVEF and prior use of CCB were identified as independent risk factors.

Although increased preload is a known risk factor for RV dysfunction in general, in our study, a statistically significant association between perioperative FB and reduction in RVEF could only be established when patients with a perioperative decrease in RVEF were compared with...
patients with a stable RV function, and not in comparison to patients with an increase in RVEF. The observed association with baseline RVEF is most likely attributable to a regression-to-mean effect: those with a normal RVEF at baseline are more likely subjected to an absolute reduction of ≥3%.

Surprisingly, the most prominent finding of this study is preoperative use of a CCB as a risk factor for the perioperative reduction in RVEF. CCBs disrupt the movement of calcium through calcium channels, in general, leading to vasodilatation due to a lower contractility of arterial smooth muscle cells and a negative inotropic effect.\textsuperscript{13} CCBs can be divided in dihydropyridines (DHP) and non-dihydropyridines (non-DHP), with some differences in action between these subgroups. DHP CCBs, like amlodipine and nifedipine, are derived from the molecule DHP and they are often used to reduce systemic vascular resistance and arterial pressure. The non-DHP CCB subgroup consists of phenylalkylamines (eg, verapamil), benzothiazepines (eg, diltiazem), non-selective agents and others. Phenylalkylamine CCBs have minimal vasodilation action compared with DHPs. They act relatively selective on the myocardium, leading to a negative inotropic effect. Benzothiazepine CCBs are an intermediate class between phenylalkylamines and DHPs in their selectivity for vascular calcium channels. They have both a negative inotropic and vasodilator effect.\textsuperscript{13–15}

CCBs are indicated for many cardiovascular indications, including hypertension, coronary spasms, angina pectoris, supraventricular arrhythmias, hypertrophic cardiomyopathy and pulmonary arterial hypertension (PAH).\textsuperscript{13} Although CCBs in general have a negative inotropic effect, a subset of patients with idiopathic PAH (IPAH) responding to short-acting vasodilators react to high-dose CCB with a fall in PAP and an increase in cardiac output due to unloading of the RV.\textsuperscript{16} In patients with PAH, most experience is available with the DHP CCB nifedipine and the non-DHP diltiazem.\textsuperscript{16–19}

However, several studies in this specific setting acknowledge unfavourable haemodynamic effects, including exacerbation of RV failure during long-term treatment.\textsuperscript{19–21} The supposed mechanism is unclear, but in an animal model, administration of the non-DHP CCB diltiazem has been shown to impair right atrial contractility, which decreases cardiac output. This effect occurred only in simulated non-responding subjects, where pulmonary vasoconstriction was induced by banding of the pulmonary artery.\textsuperscript{22}

Current guidelines only advise initiation of high-dose CCB therapy for patients with IPAH, heritable PAH or drug-induced PAH who are responders to acute vasoreactivity testing.\textsuperscript{23}

Furthermore, some studies evaluating the effect of CCBs on RV function in patients with chronic obstructive pulmonary disease (COPD) have been performed.\textsuperscript{24–26} In 13 subjects with COPD sublingual administration of nifedipine resulted in decreased RV afterload and an increased RV contractility and compliance.\textsuperscript{24} In patients with COPD with partial or full respiratory insufficiency and reduced baseline RVEF, a single oral dose of nifedipine resulted in a partial recovery in RVEF in 65% of subjects.\textsuperscript{25} Also, short-term treatment with the DHP CCB felodipine in subjects with advanced COPD leads to an increase in RVEF and a decrease in pulmonary vascular resistance.\textsuperscript{26}

To our knowledge, there are no data available in the literature regarding the effect of CCBs on RV function in a mixed cardiac surgery population. Previous studies on CCBs in cardiac surgery patients focused on perioperative mortality and myocardial infarction, mainly in patients undergoing CABG.\textsuperscript{27–31} Three observational studies concluded that CCBs did not reduce perioperative mortality or myocardial ischaemia in cardiac surgery patients.\textsuperscript{28–30} However, a meta-analysis of RCTs suggests that the risk of perioperative myocardial ischaemia in CABG patients is reduced by perioperative CCB use.\textsuperscript{31} This meta-analysis was not powered to detect a difference in perioperative mortality. It is important to notice that only 1 out of 36 included RCTs in CABG patients investigated preoperative use of CCB, all other studies focused on intraoperative and/or postoperative treatment with CCBs. A subsequent prospective observational study on this subject was performed using propensity matching to correct for confounders. In this study, CCBs were found to reduce mortality after cardiac surgery; however, no distinction between subtypes of CCB was made.\textsuperscript{27}

Our seemingly contradictory finding that preoperative CCB use is a risk factor for a perioperative reduction in RVEF might be explained by differences in patient selection. The above-mentioned studies in cardiac surgery

| Table 2 Independent risk factors for a decline in right ventricular ejection fraction during cardiac surgery |
|----------------------------------------------------|-------------|------------------|------------------|
| RVEF−* vs RVEF=† OR 95% CI P value               |
| Cumulative fluid balance (L)                      | 1.45        | 1.02             | 2.06             | 0.039 |
| RVEF (%) preoperative                             | 1.22        | 1.14             | 1.30             | <0.001|
| Use of CCB                                        | 3.06        | 1.24             | 7.54             | 0.015 |
| Nagelkerke R\textsuperscript{2} 0.411            |
| RVEF−* vs RVEF‡ OR 95% CI P value                 |
| Cumulative fluid balance (L)                      | 1.09        | 0.80             | 1.49             | 0.575 |
| RVEF (%) preoperative                             | 1.27        | 1.19             | 1.35             | <0.001|
| Use of CCB                                        | 2.73        | 1.21             | 6.16             | 0.015 |
| Nagelkerke R\textsuperscript{2} 0.396            |

*Patients with a ≥3% absolute decrease in postoperative right ventricular ejection fraction compared with baseline. †Patients with a <3% absolute change in postoperative right ventricular ejection fraction compared with baseline. ‡Patients with a ≥3% absolute increase in postoperative right ventricular ejection fraction compared with baseline. CCB, calcium channel blocker; RVEF, right ventricular ejection fraction.
patients mainly included CABG patients, while in our cohort, only patients who were monitored with a PAC-based computer were included. By protocol, these were patients undergoing valve surgery and patients with a poor LV function.

It is conceivable that there is a subset of patients in which CCB therapy is potentially beneficial and another subset of patients in whom preoperative use of CCB might be more harmful. Since the mechanism of action differs between subtypes of CCBs, it is possible that the prescribed type of CCB plays a role in perioperative risk of a decline in RV function.

In our hospital, calcium gluconate is administered after weaning from cardiopulmonary bypass as is common practice in cardiac surgery. Calcium is administered independent of preoperative use of cardiovascular medication and the anticipated consequence of calcium administration is a positive inotropic effect. Therefore, we consider it unlikely that intraoperative calcium administration is responsible for the finding that preoperative CCB use is a risk factor for a decline in RV function.

On the day of surgery, all antihypertensive drugs except beta blockers are interrupted. Given the long half-life of the CCBs used in the outpatient setting, it is likely that the effect of this medication is not completely disappeared at the time of surgery.

We performed the first study that focused on factors that play a role in development of a perioperative decline in RV function in cardiac surgery patients. A strength of this study is the availability of precise preoperative and postoperative invasive haemodynamic measurements in a large consecutive cohort of selected cardiac surgery patients.

This study is limited by its observational and explorative character. In particular, data on subtype of CCB preoperatively used are lacking. Further studies are needed to elaborate on the potential interaction between preoperative use of CCB and perioperative decline in RV function.

CONCLUSION

A reduction in RVEF was observed in 40% of a selected group of cardiosurgical patients. Apart from the impact of the perioperative FB, the acknowledgement of preoperative use of a CCB as a risk factor for perioperative reduction in RVEF is the most prominent new finding of this study. The observed association with baseline RVEF is most likely attributable to a regression-to-mean effect. We suggest further research to the potential interaction between CCB and RV function.

REFERENCES
Calcium channel blockers have been extensively studied in various clinical settings. Here are some key references:


19 Packer M. Therapeutic application of calcium-channel antagonists for pulmonary hypertension. *Am J Cardiol* 1985;55:196B-201B.


