Remifentanil and Sufentanil Preserve Left Ventricular Systolic and Diastolic Function in Patients with Ischemic Heart Disease-A Randomised Comparative Study

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Abstract

Although the impact of drugs on cardiac function seems unchanged by standard haemodynamic measurements, it may be followed by injurious stress and deterioration of myocardial function as stable conventional monitoring not necessarily represent unaffected function. The aim of the study was to assess changes in global haemodynamic measures, primarily by changes in cardiac index, and contemporary indices of LV systolic and diastolic function during induction of anaesthesia with remifentanil compared to sufentanil. The aim was to compare the effects of sufentanil and remifentanil with primary focus on the opioids given as a single drug and secondary in conjunction with propofol.

Methods: Thirty patients with ischaemic heart disease scheduled for elective cardiac surgery were randomized to receive either remifentanil or sufentanil as basic opioid. Cardiac function was evaluated with invasive haemodynamic measures established before administration of the opioids, combined with echocardiographic left ventricular systolic (longitudinal peak systolic strain) and diastolic function (tissue Doppler-index, E/e').

Results: In single drug administration, no differences were found in cardiac index (CI), stroke volume index (SVI) and heart rate (HR) between the opioids. A minor fall was seen in mean arterial blood pressure (MAP) after remifentanil (104 ± 14 to 91 ± 15 mmHg; P=0.001) and sufentanil (107 ± 21 to 94 ± 24 mmHg; P=0.003), with no difference between groups (P=0.933). Central venous pressure (CVP) increased after sufentanil (P=0.022) and mean pulmonary artery pressure (mPAP) in both groups. No changes were observed for cardiac index, stroke volume index and heart rate or in longitudinal peak strain (remifentanil -14.3 ± 4.0 to -16.3 ± 4.6; P=0.059 and sufentanil -14.5 ± 2.8 to -15.1 ± 2.3; P=0.469). After initiation of propofol all parameters declined over time. Remifentanil patients had lower MAP (P=0.001) and CVP (P=0.003), while heart rate (P=0.025) was higher. No other statistically significant differences between the groups.

Conclusions: In a single drug setting, the haemodynamic effects of remifentanil are comparable to sufentanil in ischaemic patients. Combined with propofol, identical greater changes are seen in especially MAP, HR and SVI in both groups, likely designated to propofol and its combination with opioids.

Keywords: Remifentanil, Sufentanil; Echocardiography; Cardiac function; Ischemic heart disease

Introduction

In cardiac anaesthesia, opioids are frequently administered in high doses due to their ability to maintain stable haemodynamic conditions in critically ill patients [1]. Sufentanil has shown superior peroperative haemodynamic stability [2-3] and reduced need for postoperative analgesia compared to fentanyl and remifentanil [4]. In a recent study, it was found that a single high dose of sufentanil, without the influence of intermittent positive pressure ventilation, sedatives and muscle relaxants, had no adverse effects on haemodynamics and left ventricular (LV) function in patients with ischaemic heart disease (IHD) [5]. Remifentanil has gained increased attention due to its possible fast-track potential with shorter ventilation time, shorter admission in the ICU [6,7] and improved postoperative quality [8]. However, some studies have shown less haemodynamic stability after remifentanil compared to other opioids [9-12].

Most studies describing the impact of pharmacological agents on cardiac function have used standard invasive haemodynamic parameters. These parameters may appear stable or even improved, but at the cost of injurious stress to the heart due to i.e. higher oxygen consumption and possible deteriorated myocardial function [13]. Hence, stable haemodynamic parameters may therefore not necessarily represent unaffected myocardial function. Furthermore, few studies have investigated the influence of opioids alone. In that respect the combination of invasive haemodynamic monitoring and echocardiographic measurements has proven feasible [5,13]. Conventional 2-dimensional grey scale echocardiography is relative dependent on optimal image quality. Tissue Doppler imaging (TDI) allows for quantitative determination of myocardial function [14,15] and correlates closely with the LV ejection fraction measured by 2-dimensional echocardiography. A relatively new modality, speckle tracking ultrasonography (STU), enables tracking of the radial, longitudinal and circumferential myocardial deformations or strains.
that are independent of tethering forces [16]. Studies have found STU to be in good agreement with sonomicrometry, tagged computerised magnetic resonance imaging and independent of insonation angle [17]. Myocardial relaxation may be evaluated by calculating and comparing the ratios of mitral annular diastolic early (e') and atrial (a') tissue Doppler velocities and corresponding transmural pulsed wave Doppler velocities (E & A) [18,19].

Using invasive measures of global haemodynamics supplemented with echocardiographic indices of LV systolic and diastolic function, we hypothesised that remifentanil is equivalent to sufentanil during induction of cardiac surgery in patients with IHD, both given as a single drug and in combination with propofol.

We hypothesised that remifentanil is equivalent to sufentanil during induction of cardiac surgery in patients with IHD, both given as a single drug and in combination with propofol. The aim of the study was to assess changes in global haemodynamic measures (primary outcome variable) and contemporary indices of LV systolic and diastolic function (secondary outcome variable) during induction of anaesthesia with remifentanil compared to sufentanil.

Methods

Patients, inclusion and exclusion

The study was randomised and performed in accordance with the Helsinki declaration. Written informed consent was obtained from all patients. The study is registered in the EudraCT trial database (2010-022428-58, https://eudract.ema.europa.eu/), clinical trials (NCT02053818, http://clinicaltrials.gov/) and was approved by The Central Region Committees on Health Research Ethics (No 20100160).

Power calculations (type I error <0.05, type II error <0.20) was based on a previous study [5]. Aiming on a clinical relevant 25% difference in cardiac output with standard deviations of 22% revealed the need for 26 patients. To compensate for missing data, 30 patients were included. All cardiac patients were routinely hospitalised the day before surgery and identification of the patients was done consecutively. Preoperative echocardiography was performed the day before surgery. Subjects were randomly assigned at a 1:1 allocation ratio to receive either sufentanil or remifentanil treatment using sealed envelope technique. The anaesthetist handling the procedure was informed of the result of the randomisation 30 minutes before surgery. The research nurse followed the patient during the entire data collection period to ensure strict compliance with patient blinding. The consort flow diagram of patient inclusion is shown in Figure 1.

Inclusion criteria were patients aged 60 to 80 years scheduled for elective coronary bypass surgery with or without aortic valve replacement. An acceptable image quality during transthoracic echocardiography of preoperative examination was a requirement to include patients. Exclusion criteria were arrhythmia, ejection fraction <30%, systolic blood pressure ≥ 180 mmHg, known pulmonary hypertension (mean pulmonary artery pressure (mPAP) ≥ 33% of MAP) and diabetes mellitus (all types) together with signs of ongoing angina or acute myocardial infarction within the last 30 days. Patients were screened for optimal echocardiographic image quality and difficult airway anatomy the day before surgery and patients with a simplified airway risk index [20]>3 were excluded. Patients continued ordinary medical treatment until the morning of surgery, except for platelet inhibitors which were stopped five days in advance. Premedication consisting of 5-10 mg diazepam and 2 g paracetamol Omit retard was administered 1-2 hours before surgery.

Haemodynamic monitoring

Upon arrival in the operating room, monitoring with continuous five-lead electrocardiogram and peripheral saturation was established. Invasive catheter were inserted under local anaesthesia for haemodynamic monitoring including systolic blood pressure, diastolic blood pressure, central venous pressure (CVP) and pulmonary artery pressures. Continuous cardiac index (CI) and mixed venous saturation (SvO₂) were measured with a thermistor-tipped, flow-directed...
pulmonary artery catheter (PAC) (744 HF75, Edwards Life sciences, Germany) and a Vigilance monitor (VGS 2, Edwards Critical-care, Irvine, USA). The data collection started when obtained measurements were considered stable. All measurements were stored electronically in our patient data management system every minute for later analysis.

**Monitoring protocol**

After establishment of haemodynamic monitoring, pre-oxygenation was initiated followed by the first echocardiographic examination. Immediately afterwards, sufentanil or remifentanil was administered intravenously. Patients in the sufentanil group received 1-2 µg/kg sufentanil administered within 1-2 minutes. After allowing two minutes for circulation, the second set of haemodynamic data was recorded and the second echocardiographic examination was performed. Total dose before cardiopulmonary bypass (CPB) was 3.0-3.5 µg/kg. After completion of the second examination, propofol at an infusion rate of 100-200 mg/h (according to the patients demand as ascertained by the anaesthetist) was initiated followed by a bolus of 0.6 mg/kg rocuronium to facilitate tracheal intubation.

Patients in the remifentanil group received 0.5-0.6 µg/kg/min remifentanil for 6-8 minutes, followed by the second echocardiographic examination. After a completed second examination, infusion of propofol (100-200 mg/h) was initiated, followed by a remifentanil bolus (60 µg) and a rocuronium bolus (0.6 mg/kg) to facilitate tracheal intubation. Remifentanil infusion was continued with 0.2-0.4 µg/kg/min until start of surgery after which the maintenance dose was 0.4-0.6 µg/kg/min until CPB.

Propofol was used for maintenance of anaesthesia in both groups. Each echocardiographic examination lasted approximately two minutes. During the study examination, patients were breathing spontaneously via a facemask with 6-8 L/min of 100% oxygen.

**Echocardiography**

Transthoracic echocardiography was performed with a M5S 1.5-4.6 MHz phased-array matrix transducer connected to a Vivid E9 ultrasound system (GE Healthcare, Horten, Norway). The patient was placed slightly in the left lateral position. The apical 4-chamber view was obtained in all cases and cine-loops were digitally stored for off-line analysis in dedicated software (EchoPac, GE Healthcare, Horten, Norway).

**LV systolic function**

Left ventricular ejection fraction (LVEF) was calculated using the method of discs and LV deformation was assessed by STU based on the apical 4-chamber view. This method relies on natural acoustic markers in tissues and is expressed as a percentage change in tissue length during the cardiac cycle, as the myocardial tissue shortens during contraction; longitudinal strain is expressed as negative values. The software processing was semi-automatic and based on manually placed regions of interest including timing of the end of systole. Deformation can be expressed as strain from a single imaging plane or as global strain calculated as the average value from the three apical imaging planes. All strain measurements in the current study were calculated as longitudinal strain. In addition, peak systolic velocity (′v′) was measured in the septal and lateral region of the mitral annulus by means of TDI. These values correspond to longitudinal systolic function in the LV and are closely related to global LV function [16].

**LV diastolic function**

Pulsed wave Doppler was used for measuring mitral inflow blood velocities. The first peak in blood flow velocity early in the diastole was designated E and the late or atrial peak was designated A. Tissue Doppler imaging of the septal and lateral mitral annulus was used for measuring tissue velocities throughout the cardiac cycle with e′ and a′ corresponding to the above mentioned mitral inflow velocities. In order to quantify overall diastolic function, a surrogate marker of LV filling pressure was calculated as a ratio between E and e′. The E/e′ ratio considers not only the blood flow, but also the tissue movement and is well validated as an indicator of LV filling pressure [18,19]. All echocardiographic measures were averaged from three consecutive cine-loops obtained at end-expiration.

**Predefined outcome variables**

The primary outcome variable was firstly the change in cardiac index and mean arterial pressure caused by remifentanil as compared to sufentanil, when both drugs administered as single drugs and secondly measurements when drugs was given together with propofol.

Secondary outcomes were other invasive measurements including CVP, mPAP, SvO2, along with echocardiographic indices of left ventricular systolic function (LVEF, longitudinal strain and s′) and left ventricular diastolic function (e′, e′/a′, E/e′)

**Statistical analyses**

The analysis of all haemodynamic data was done off-line after complication of the study. All off-line analyses were performed by an experienced echocardiographic technician blinded with respect to opioid administration. Normality of data was checked by D’Agostino-Pearson test for Normal distribution. Study results are presented as mean ± SD or median (interquartile range) according to type of distribution. A paired samples t-test or a Wilcoxon test was used for all in-patient comparisons (before and after opioid administration) according to normality. For inter-group comparisons, continuous data were analysed with an independent samples t-test or Mann-Whitney test and categorical data with a χ²-test. Haemodynamic changes over time were analysed with two-way ANOVA or ANOVA for repeated measurements where appropriate. Analyses were performed with MedCalc® software version 12.3 (Mariakerke, Belgium). A probability value of <0.05 was used to define statistical significance.
Results

Thirty patients were included in the study. Two patients were excluded just before surgery; one due to an unanticipated need for rapid-sequence induction due to increased spasticity and stiffness, and one due to cancellation of surgery, thus leaving 28 patients for analysis (Figure 1). Selected patient characteristics are shown in Table 1. There was no difference between opioid groups in preoperative demographic and echocardiographic data. Pulse oximetry measurements before (97.2% ± 2.6%) and after induction with opioids (97.7% ± 3.5%) showed no significant difference (P=0.542).

No difference was seen in primary outcome parameters. The change in cardiac index after single drug administration was -0.34 ± 0.80 after remifentanil and 0.01 ± 0.50 after sufentanil (P=0.180; t-test). Table 2 demonstrates haemodynamic and echocardiographic data before and after remifentanil and sufentanil administration. Both groups presented an identical, substantial fall in mean arterial pressure (MAP), the remifentanil group from 104 ± 13 to 91 ± 15 mmHg (P=0.001) and the sufentanil group from 107 ± 21 to 94 ± 24 mmHg (P=0.003; paired samples t-test). There was no difference between groups in the MAP fall (-12.8 vs. -13.1; P=0.933; independent samples t-test). Furthermore, an increase in CVP was seen in the sufentanil group (P=0.022) and increases in mean pulmonary artery pressure (mPAP) were seen in both groups (remifentanil group (P=0.020) and sufentanil group (P=0.036) (Table 2).

Overall, the echocardiographic parameters did not change significantly after opioid induction. Except for an statistically insignificant and minor improved longitudinal peak systolic strain (P=0.068) in the remifentanil group there was no differences in peak velocities, measures of filling pressure (E/e') or other indicators of diastolic function (E'/a' and e') remained unchanged in both groups (Table 2).

Overall there was no statistical or clinical significant differences of haemodynamic impact between remifentanil and sufentanil patients, demonstrated as delta-values (After values-Before values) in table 2.

There were no statistically significant differences between groups in time from anasthesia induction to CPB with regard to invasive measurements (77 minutes ± 18 for sufentanil versus 69 minutes ± 13 for remifentanil, P=0.209). The mean amount of propofol in the pre-CPB period was 49.2 ± 24.5 µg/kg/min in the sufentanil group vs. 50.5 ± 18.9 µg/kg/min in the remifentanil group (P=0.877, independent samples t-test).

Figure 2 shows invasive haemodynamic measurements from the baseline values and the first 60 minutes after infusion of propofol. All parameters declined over time. Patients receiving remifentanil had lower MAP (P<0.001), CVP (P=0.003) and systemic vascular resistance index (SVRI) (P=0.005) throughout the study period, while heart rate (P=0.025) was higher compared with the sufentanil group. No statistically significant differences between the two groups concerning CI, stroke volume index (SVI), mPAP or mixed venous saturation (SvO2). The response to propofol infusion was similar in the two groups with regard to all invasively measured parameters (All P-values >0.234, univariate ANOVA for repeated measurements). None of the patients received continued infusion of inotropes, while two patients (one in each group) received vasoconstrictors in the observation period. Additional patients receiving vasoconstrictor bolus dose (≥ 3 doses of 1-5 µg noradrenaline) was 4 in the remifentanil group and 2 in sufentanil group (P=0.418; χ2-test). All, except one bolus dose was given after start of propofol.

Discussion

This study demonstrates that almost all the haemodynamic parameters and advanced indices of LV systolic and diastolic function were preserved after both single drug remifentanil infusion and sufentanil bolus dose in patients with IHD. However, after initiating full anaesthesia when adding propofol, a decrease in MAP, CVP, SVI and CI was seen en both groups.

Both groups showed a minor fall in HR after single drug administration. After combination with propofol, the HR was higher in the remifentanil group contrary to earlier reports describing severe bradycardia after administration of remifentanil [10]. The findings of the single drug administration of sufentanil are in agreement with our earlier reports, but in the present study the fall in MAP was higher than in the previous study [5]. We also observed a higher increase in CVP in the sufentanil group, possibly explaining the reason for the insignificant increase in SVI as seen in other studies with increased CVP [21]. However, as the delta-values (Table 2) showed no differences between the groups, the haemodynamic impact of the two opioids is

Table 2: Haemodynamic and echocardiographic data before and after opioid administration. Statistics: #) Paired samples t-test; *) Wilcoxon test; !) Independent samples t-test; *) Mann-Whitney test. TD: Tissue Doppler.

<table>
<thead>
<tr>
<th>Echocardiographic measurements</th>
<th>Remifentanil</th>
<th>Sufentanil</th>
<th>Δ-values (After–Before)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index (L/m²/minute)</td>
<td>3.5 ± 0.8</td>
<td>3.2 ± 0.6</td>
<td>0.137*</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>72.8 ± 6</td>
<td>69.1 ± 10</td>
<td>0.151*</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>104 ± 13</td>
<td>91 ± 15</td>
<td>0.001*</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>6 ± 7</td>
<td>7 ± 7</td>
<td>0.366*</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>17 ± 4</td>
<td>21 ± 7</td>
<td>0.020*</td>
</tr>
<tr>
<td>Central venous oxygenation (%)</td>
<td>74 ± 6</td>
<td>77 ± 9</td>
<td>0.221*</td>
</tr>
<tr>
<td>Peripheral saturation (%)</td>
<td>97 ± 3</td>
<td>98 ± 3</td>
<td>0.236*</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²/beat)</td>
<td>48.8 ± 13.3</td>
<td>45.6 ± 7.9</td>
<td>0.399*</td>
</tr>
</tbody>
</table>
considered to be of equal magnitude. Overall the found impact was of little clinical importance. That the findings likely are due to primary drugs is further supported by the very little use of vasoconstrictors in the observation period.

Although the standard measures of LV systolic function were statistically unchanged, our data indicated a slight increase in myocardial systolic function as 75% of the patients in the sufentanil group improved longitudinal peak systolic strain as well as a small increase in SVI. Patients in the remifentanil group showed an almost statistically significant increase in longitudinal peak systolic strain, which is in contrast to earlier reports describing cardiac depression after remifentanil [9].

The changes observed are most likely multifactorial. Decreased afterload with concomitant fall in MAP and an increase in right ventricular preload facilitated by a higher CVP are similar to the effects found in high thoracic epidural anaesthesia [21,22]. This mechanism
of interaction between afterload and preload is supported further by the fact that in the remifentanil group, where the increase in CVP was less and thus most likely causing a lower increase in right ventricular preload, the resulting SVI and CI showed trends towards lower values. Pulmonary artery pressures increased with opioids in both groups. As CI remained unchanged, this increase was caused by an increase in pulmonary resistance. The echocardiographic index of left ventricular filling pressure, E/e’, did not change significantly and actually showed a decreasing trend in the remifentanil group. This supports the fact that measurement and control of preload and afterload is very complex.

After propofol infusion, the haemodynamic differences between remifentanil and sufentanil were marginal. The amount of propofol was equal in the two groups and thus the haemodynamic variables measured in the first 60 minutes were measured under the same conditions despite differences in the administration procedure. Although some overall minor differences were found in haemodynamic parameters between the groups, we could not demonstrate any differences in changes of absolute values between groups from pre-induction values to 60 minutes after induction. This indicates that the identical fall in both the remifentanil and the sufentanil group must primarily be attributed to propofol or the combination of propofol and an opioid. This is in accordance with a previous study where we showed that propofol anaesthesia resulted in lower MAP and decreases in echocardiographic indices of cardiac contractility [22].

Limitations of the Study

Generally, opioids are administered together with sedatives and/or relaxants. The purpose of this study was to evaluate the LV function without the influence of other drugs, IPPV and airway manipulation. The preoperative administration of diazepam, and paracetamol may, at least theoretically, have affected the essential circulatory effects of opioids, but any overall marginal result should be the same in the two groups.

When comparing drugs with so great differences in distribution, pharmacokinetics and excretion half-time makes it difficult to give fully equipotent doses of the drugs involved. The sufentanil dose used has been described in previous studies as moderate to high dose [5,21]. From the literature doses of remifentanil are given as 0.01 µg/kg/min [23] over 0.05 µg/kg/min [24] to 0.1 µg/kg/min in shorter periods [25]. In another way of comparing, it has been suggested that remifentanil should be given as 10:1 compared to Sufentanil [26]. Although debatable, we calculated backward from 60 minutes of remifentanil infusion, and found that infusion rates of 0.4-0.6 µg/kg/min (moderate to high rate) would result in a total of 20-30 µg/kg compared to 2-3 µg/kg in the sufentanil group. As the infusion rates were in the moderate to high end we assumed equipotent dosages. Some of the haemodynamic parameters showed clinically relevant, although statistically insignificant, differences which may be contributed to the relatively small sample size. However, the trend with lower values after remifentanil given alone or in combination with propofol does not discourage the use of remifentanil in cardiac surgery.

Conclusion

In a single drug setting, the haemodynamic effects of remifentanil and sufentanil were comparable in IHD surgery patients. When combined with propofol, greater circulatory changes were seen for both groups, especially with regard to MAP, HR and SVI and thus the major haemodynamic changes were most likely caused by propofol administered in combination with the opioids.

References


