Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy


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Editor’s key points
- Persistent pain after cardiac surgery can be a challenging problem to manage.
- To develop strategies to reduce pain, we need to identify preventable risk factors.
- This current study found a dose-dependent association between intraoperative remifentanil and chronic pain after cardiac surgery.
- Further investigation of the long-term effects of remifentanil is needed.

Background. Chronic thoracic pain after cardiac surgery is a serious condition affecting many patients. The aim of this study was to identify predictors for chronic thoracic pain after sternotomy in cardiac surgery patients by analysing patient and perioperative characteristics.

Methods. A follow-up study was performed in 120 patients who participated in a clinical trial on pain levels in the early postoperative period after cardiac surgery. The presence of chronic thoracic pain was evaluated by a questionnaire 1 yr after surgery. Patients with and without chronic thoracic pain were compared. Associations were studied using multivariable logistic regression analysis.

Results. Questionnaires of 90 patients were analysed. Chronic thoracic pain was reported by 18 patients (20%). In the multivariable regression model, remifentanil during cardiac surgery, age below 69 yr, and a body mass index above 28 kg m⁻² were independent predictors for chronic thoracic pain (odds ratios 8.9 [95% confidence interval (CI) 1.6–49.0], 7.0 (95% CI 1.6–31.7), 9.1 (95% CI 2.1–39.1), respectively). No differences were observed in patient and perioperative characteristics between patients receiving remifentanil (58%, n=52) compared with patients not receiving remifentanil (42%, n=38). The association between remifentanil and chronic thoracic pain appeared dose-dependent, both for total dose and for dose corrected for kilogram lean body mass and duration of surgery (P-value for trend: <0.01 and <0.005, respectively).

Conclusions. In this follow-up study in cardiac surgery patients, intraoperative remifentanil was predictive for chronic thoracic pain in a dose-dependent manner. Randomized studies designed to evaluate the influence of intraoperative remifentanil on chronic thoracic pain are needed to confirm these results.

Keywords: anaesthesia, general; cardiac, surgical procedures; chronic pain, remifentanil

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Chronic thoracic pain after cardiac surgery via sternotomy is a serious condition affecting many patients. Recent studies report incidences varying from 11 to 56%,1–6 depending on the definition and the study population.7 Patients suffering from chronic thoracic pain experience a significantly lower physical and mental health status compared with patients without chronic thoracic pain.1 5 8 9 In order to prevent chronic pain, studies are needed to identify factors that may predict an increased likelihood.7

Previous studies recognized younger age,3 5 9 10 increased body mass index (BMI),9 and female gender6 as predictors for chronic thoracic pain. Furthermore, in different studies, severe immediate postoperative pain,6 10 non-elective surgery,6 or a resternotomy in the early postoperative period6 have been suggested. The variety in the identified predictors may result from the different definitions for chronic pain and heterogeneity of the patient populations, and the retrospective design of most studies. The majority of the studies lacked detailed information from the perioperative period, such as pain levels before surgery or the choice and dose of anaesthetics and analgesics used during cardiac surgery. In this respect, it has been shown...
that the anaesthetics used during surgery may have long-term effects regarding chronic pain, as Salengros and colleagues\(^1\) showed for remifentanil in patients who underwent a thoracotomy.

We performed a follow-up study of patients who participated in a clinical trial on pain levels in the early postoperative period in the intensive care unit (ICU) after cardiac surgery. The present study aimed to identify predictors for chronic thoracic pain 1 yr after cardiac surgery via sternotomy by analysing detailed patient and pre-, intra-, and postoperative characteristics.

**Methods**

**Design and patients**

A follow-up study was conducted in 120 patients who participated in a prospective, double-blind randomized clinical trial on procedural analgesia in the ICU after cardiac surgery (ClinicalTrials.gov identifier: NCT00558090). The inclusion criteria for this clinical trial were patient informed consent, admittance to the ICU after cardiac surgery via sternotomy, age between 18 and 85 yr, and body weight between 45 and 140 kg. Exclusion criteria were pregnancy or breast-feeding, an inability to communicate in either Dutch or English, coma or brain death, and a known morphine or acetaminophen (paracetamol) allergy. For the clinical trial, informed consent was given by 135 patients. Four patients were excluded directly after surgery because they were not admitted to the ICU but to the post-anaesthesia care unit (n=3) or did not undergo a sternotomy (n=1). Eleven patients died within 1 yr after surgery, resulting in 120 patients eligible for the follow-up study. The follow-up study was approved by the Ethics Committee (VCMO, Nieuwegein, The Netherlands) as an amendment to the clinical trial. Additional written informed consent was obtained from the patients.

**Preoperative evaluations**

Before operation, patient characteristics were collected and patients were questioned about their pain history, the use of analgesics, and preoperative pain score. For the latter, the Numeric Rating Scale (NRS) (range 0–10, with ‘0’ representing ‘no pain’ and ‘10’ representing ‘the worst pain imaginable’) was used.

**Intraoperative anaesthesia and analgesia**

For induction of anaesthesia, midazolam and propofol bolus injections were administered together with fentanyl. Patients were paralysed with pancuronium. Anaesthesia was primarily maintained with propofol, with an optional use of nitrous oxide. According to local practice, sevoflurane 0.25–1 minimum alveolar concentration was added for cardioprotection until the start of the extracorporeal circulation. For intraoperative analgesia, intermittent fentanyl doses were used, while a remifentanil continuous infusion was initiated directly after induction of anaesthesia at the discretion of the attending anaesthesiologist. The total dose of remifentanil and remifentanil dose corrected for kilogram lean body mass (kg LBM) and duration of surgery in minutes were calculated. LBM was defined for males \((1.1 \times \text{weight (kg)} – 128 \times \text{height}^{-1} (\text{cm}))\) and females \((1.07 \times \text{weight (kg)} – 148 \times \text{height}^{-1} (\text{cm}))\).\(^12\) Perioperative data were registered in the clinical trial registration form. In total, 18 anaesthesiologists and 10 surgeons were involved during surgery. The specific combination of a surgeon and an anaesthesiologist was unique for 43 patients and did not occur more than five times.

**Postoperative pain measurement and analgesia in the ICU**

According to the standard care in our ICU, a patient data management system (PDMS) obliged nurses to ask patients for their pain score three times a day (0:00, 8:00, and 16:00 h).\(^13\) A pain titration protocol was used in all patients as part of standard care, consisting of intermittent acetaminophen (paracetamol) 4 g daily and a continuous i.v. infusion of morphine, which was started directly upon admittance to the ICU. According to the pain titration protocol, in the case of an NRS score of more than 3, an extra bolus of morphine, an increase in morphine continuous infusion, or both were applied. Pain scores were registered in the PDMS.

**Follow-up study 1 yr after cardiac surgery**

A questionnaire enquiring after the presence of chronic thoracic pain was sent to the patients 1 yr [13 months (SD 0.6)] after cardiac surgery. This previously used questionnaire\(^6\) was based on the McGill Pain Questionnaire.\(^14\) Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS >0), which the patient identified as related to surgery, which was different from angina, and which was present in the 2 weeks preceding the interview.\(^5\)

**Data analysis**

All statistical analyses were performed using IBM SPSS Statistics (version 19.0 for Windows; SPSS, Chicago, IL, USA). Descriptive statistics of patient characteristic and clinical variables were expressed as frequencies with percentages (%), median with inter-quartile range, or mean with standard deviation (SD) where appropriate. Categorical data were analysed by \(\chi^2\) or Fisher’s exact tests and continuous data by Student’s \(t\)-tests or Mann–Whitney \(U\)-tests. In the case of significant differences in frequencies between patients with and without chronic pain in continuous or ordinal variables, receiver operating characteristic (ROC) curves were constructed to identify cut-off points with the most discriminative value. By using these cut-off points (dichotomization) and adding all other associated clinical variables (P<0.10), a backward stepwise logistic regression analysis was performed to identify variables with the most predictive value. Additionally, as a sensitivity analysis, the regression analysis was repeated without dichotomization. Imputation has been applied for 5 data entries (0.3% of all data entries).
A two-tailed $P$-value of $<0.05$ was considered significant for all tests.

**Results**

**Patients and data**

Participant flow is summarized in a flow chart (Fig. 1). Of the 120 questionnaires sent, 96 (80%) were returned. Two were returned blank and three questionnaires were accompanied by a note that these patients were unable to fill in the questionnaire. This resulted in 91 answered questionnaires. Responders of the questionnaire were more often men compared with non-responders [76% (69 out of 91) vs 55% (16 out of 29), respectively ($P=0.03$)]. Otherwise, no differences were observed between responders and non-responders [age [mean 69 (SD 11) vs 70 yr (SD 12), $P=0.69$], European System for Cardiac Operative Risk Evaluation score (EuroSCORE)$^{15}$ [median 7 (range 0–13) vs 6 (2–13), $P=0.39$], or BMI [mean 27 (SD 4) vs 28 (SD 5), $P=0.41$], respectively]. One patient was excluded during the analysis because details of intraoperative anaesthetics and analgesics could not be retrieved. Patient characteristics of the 90 included patients are summarized in Table 1.

**Univariate analysis of patient and pre-, intra-, and postoperative characteristics**

One year after cardiac surgery, 20% of the patients ($n=18$) reported chronic thoracic pain (NRS $>0$). Table 2 compares patient and perioperative characteristics of patients with and without chronic thoracic pain. Patients with chronic thoracic pain were significantly younger [age 63.4 yr (SD 12.4) vs 70.2 yr (SD 9.6)], had a higher BMI [30.2 kg m$^{-2}$ (SD 4.6) vs 26.6 kg m$^{-2}$ (SD 3.3)], a lower EuroSCORE [median 4.5 (IQR 3–7) vs median 7 (IQR 5–9)], and used more preoperative analgesics (27.8% vs 11.1%) compared with patients without chronic thoracic pain. Furthermore, the mean preoperative NRS scores were higher in patients with chronic pain compared with patients without chronic thoracic pain [1.9 (SD 3.1) vs 0.5 (SD 1.3)]. During anaesthesia, patients with chronic thoracic pain received significantly more often remifentanil compared with patients without chronic thoracic pain (83.3% vs 51.4%), yielding a crude odds ratio (OR) of 4.7 (95% CI 1.3–17.8) (power 0.82). The dose of fentanyl during anaesthesia was not different between patients with and without chronic thoracic pain [1.7 mg (SD 0.6) vs 1.7 mg (SD 0.4), $P=0.44$]. Postoperative pain scores in the ICU were not significantly different between patients with chronic thoracic pain and without chronic thoracic pain (Table 2).

Cut-off points identified via ROC curve analysis were 69 yr for age, 28 kg m$^{-2}$ for BMI, and an EuroSCORE of 6. These three variables, together with preoperative pain (NRS $>0$), chronic use of analgesics before surgery, and anaesthesia that included remifentanil, were selected for multivariate logistic regression analysis with stepwise backward elimination.

**Multivariate analysis of patient and pre-, intra-, and postoperative characteristics**

In the multivariate logistic regression analysis, anaesthesia that included remifentanil, age younger than 69 yr, and a
BMI above 28 kg m$^{-2}$ all appeared to be independent predictors for chronic thoracic pain with the corresponding ORs as shown in Table 3. The goodness of fit of the final model was excellent ($P$-value by the Hosmer and Lemeshow test 0.94). Preoperative pain, chronic use of analgesics before surgery, and EuroSCORE were not statistically significant associated with chronic pain in the multivariate analysis. In analysis without dichotomization of continuous variables, remifentanil was confirmed as an independent predictor of chronic thoracic pain (adjusted OR 1.7; 95% CI 1.1–2.8).

Based on these findings, the association between remifentanil and chronic thoracic pain was examined in more detail. In total, 52 patients (58%) received remifentanil during cardiac surgery. Table 4 shows that there were no differences in patient characteristics or perioperative characteristics between patients who received remifentanil and patients who did not receive remifentanil.

Table 5 shows the association between remifentanil dose administered during anaesthesia for cardiac surgery and OR for chronic thoracic pain 1 yr after surgery. Both with increasing total amounts of remifentanil (mg) and with increasing remifentanil dose corrected for kg LBM and duration of surgery, the OR for chronic thoracic pain increased with a

### Table 2

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No chronic pain ($n=72$)</th>
<th>Chronic pain ($n=18$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>53 (74%)</td>
<td>16 (89%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age, yr (so)</td>
<td>70.2 (9.6)</td>
<td>63.4 (12.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, kg m$^{-2}$ (so)</td>
<td>26.6 (3.3)</td>
<td>30.2 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EuroSCORE [median (IQR)]</td>
<td>7 [5–9]</td>
<td>4.5 [3–7]</td>
<td>0.01</td>
</tr>
<tr>
<td>Preoperative NRS [mean (so)]</td>
<td>0.5 (1.3)</td>
<td>1.9 (3.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of chronic pain [n (%)]*</td>
<td>16 (22)</td>
<td>4 (22)</td>
<td>0.98</td>
</tr>
<tr>
<td>Use of analgesics before surgery [%]†</td>
<td>8 (11)</td>
<td>5 (28)</td>
<td>0.08</td>
</tr>
<tr>
<td>Type of surgery [n (%)]</td>
<td>CABG 18 (25)</td>
<td>4 (22)</td>
<td>0.93</td>
</tr>
<tr>
<td>CABG and valve surgery</td>
<td>23 (32)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>Valve surgery</td>
<td>15 (21)</td>
<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>16 (22)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Anaesthesia that included nitrous oxide [n (%)]</td>
<td>46 (64)</td>
<td>13 (72)</td>
<td>0.32</td>
</tr>
<tr>
<td>Anaesthesia that included remifentanil [n (%)]</td>
<td>37 (51)</td>
<td>15 (83)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of surgery [min (so)]</td>
<td>242 (79)</td>
<td>255 (59)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mechanical ventilation [h] [mean (so)]</td>
<td>13.6 (19.6)</td>
<td>14.2 (16.2)</td>
<td>0.93</td>
</tr>
<tr>
<td>Length of stay in the ICU [days] [mean (so)]</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Resternotomy during admittance [n (%)]</td>
<td>7 (10)</td>
<td>3 (17)</td>
<td>0.41</td>
</tr>
<tr>
<td>NRS at 16:00 on the day of surgery [mean (so)]‡</td>
<td>0.9 (0.9)</td>
<td>1.2 (2.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>NRS at 23:59 on the day of surgery [mean (so)]§</td>
<td>1.4 (1.3)</td>
<td>1.8 (1.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>NRS at 8:00 on first postoperative day [mean (so)]</td>
<td>1.6 (1.8)</td>
<td>2.1 (2.0)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthesia that included remifentanil</td>
<td>8.93</td>
<td>1.6–49.0</td>
</tr>
<tr>
<td>Age &lt;69 yr</td>
<td>7.03</td>
<td>1.6–31.7</td>
</tr>
<tr>
<td>BMI ≥28 kg m$^{-2}$</td>
<td>9.05</td>
<td>2.1–39.1</td>
</tr>
</tbody>
</table>
significant $P$-value for trend ($P$-value for trend: <0.01 and <0.005, respectively). This table shows the division of patients into three groups; the first group contains patients who did not receive remifentanil ($n=38$), while the patients who received remifentanil during anaesthesia ($n=52$) were equally divided over the second and third group. This resulted in cut-off points between the second and third group of 1.7 mg for the total dose of remifentanil and 0.12 $\mu$g of remifentanil (kg LBM)$^{-1}$ minute$^{-1}$ of surgery. The $r^2$ between the remifentanil total dose and the dose flow rate related to LBM was 0.82.

**Discussion**

In addition to younger age and increased BMI, remifentanil during cardiac anaesthesia appears to be an independent predictor for chronic thoracic pain 1 yr after sternotomy. To the best of our knowledge, so far, chronic thoracic pain has
Chronic pain after anaesthesia with remifentanil

not been associated with remifentanil in patients after cardiac surgery, although a relation between chronic post-thoracotomy pain and remifentanil has been described. Despite the fact that the current study was not designed to investigate the role of remifentanil in chronic pain after surgery, we found the relation between remifentanil and the OR for chronic thoracic pain to be dose-dependent. There were no other differences in patient and perioperative characteristics between patients who received remifentanil and those who did not. Furthermore, remifentanil was administered in a substantial percentage of patients (58%) and was either started as a continuous infusion directly after the induction of anaesthesia, or not started at all. Therefore, the present study provided a unique possibility to compare patients with and without remifentanil during surgery, possibly leading to the identification of a risk factor for chronic pain that can actually be avoided.

Chronic post-surgical pain related to remifentanil during anaesthesia has so far only been described by Salengros and colleagues in patients after thoracotomy. Remifentanil high dose (0.14–0.26 μg kg⁻¹ min⁻¹) during elective thoracotomy combined with postoperative epidural analgesia was not only associated with a larger area of allodynia around the wound in the first 72 postoperative hours, but also with a significant higher incidence of chronic pain compared with a three times lower dose of remifentanil and epidural analgesia during surgery. In patients after major abdominal surgery, a higher dose of remifentanil [0.3 (SD 0.2) μg kg⁻¹ min⁻¹] has been associated with acute opioid tolerance and opioid-induced hyperalgesia compared with a lower dose of remifentanil [0.1 (SD 0) μg kg⁻¹ min⁻¹], suggested by higher postoperative pain scores in the first postoperative hour and exaggerated postoperative opioid consumption in the first 24 postoperative hours. Similar to other studies upon cardiac surgery, we were not able to evaluate pain scores in the first postoperative hour due to prolonged sedation after cardiac surgery. Therefore, we cannot report on the actual presence of acute opioid tolerance in our patients. Higher doses of remifentanil during cardiac surgery were, however, shown to be associated with hyperalgesia for the first 7 postoperative days compared with a 1.5 times lower dose of remifentanil when applied via target-controlled infusion. Unfortunately, in the aforementioned study populations, the development of chronic pain was not evaluated. It can be anticipated that hyperalgesia is linked to peripheral and central pain sensitization and thereby correlates with the development of postoperative chronic pain. This suggests that hyperalgesia due to remifentanil in the early postoperative period may explain the higher incidence of chronic pain.

In addition to the finding of a dose-dependent association between remifentanil and development of chronic thoracic pain, the present study also confirmed an increased BMI (≥28 kg m⁻²) and a younger age (<69 yr) as risk factors. As surgery may be more difficult in the obese patient, with both a larger surface of tissue damaged and a longer retraction time, this may explain the association between an increased BMI and chronic thoracic pain. For the observed association between younger age and the presence of chronic thoracic pain after surgery, Bruce and colleagues have suggested that younger patients have a lower pain threshold and are less likely to accept and more likely to report pain. Another explanation is that younger patients are more active and more likely to be hampered by pain in their activities, whereas older patients may be more likely to accept their limitations.

We consider some limitations of our study. First, the studied patients participated in a clinical trial on pain levels in the early postoperative period after cardiac surgery. This may have led to a selection bias because patients either may have had a specific reason not to participate or, on the contrary, may have been eager to participate in a study with the expectation of additional attention for pain and analgesia. On the other hand, the fact that the patients participated in this clinical trial, which resulted in a carefully prospectively monitored group of patients with detailed information on patient and perioperative characteristics, could be considered as a strength of the present study. Secondly, despite the high response rate of 75% of the questionnaires, selection bias cannot be excluded, as we have no information about the patients who did not respond. Thirdly, the continuous infusion of remifentanil during cardiac anaesthesia could be initiated after induction of anaesthesia at the discretion of the attending anaesthetist. Surgeons, surgical techniques, and anaesthetists were not randomized or standardized for the study, even though the large number of surgeons (n=10) and anaesthesiologists (n=18) without fixed combinations between the two could be considered a strength. More patients in the remifentanil group underwent a coronary artery bypass grafting (CABG) with the possible use of the left internal mammary artery, which has been associated with chronic pain. Later studies could not confirm this association. Patients with chronic pain did not, however, undergo a CABG more often than patients without chronic pain. These limitations make it impossible to draw more conclusions than the reported association between remifentanil and chronic thoracic pain after cardiac surgery. Unmeasured confounding cannot be ruled out, even though there were no significant differences in patient or other characteristics between the patients who received remifentanil and those who did not. As such, the results of this study, with higher amounts of remifentanil being significantly associated with higher ORs for chronic pain, warrant further blinded, randomized, and prospective studies as this may prevent the development of chronic thoracic pain or at least part of this serious condition. In further research, a follow-up at 3–6 months after cardiac surgery should be considered, thereby identifying chronic pain in an earlier period, which would increase the response rate.

In conclusion, chronic thoracic pain after sternotomy was associated with the use of remifentanil during cardiac surgery, younger patients, and an increased BMI. Higher doses of remifentanil were positively associated with significantly higher ORs for chronic pain. This is the second study
that reports an association between remifentanil and chronic pain. Before this finding should be implemented in clinical practice in cardiac anaesthesia, further research through randomized controlled trials with and without remifentanil during cardiac surgery is called for, to investigate the influence of remifentanil on the development of chronic thoracic pain.

Declaration of interest
None declared.

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References