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ORIGINAL ARTICLE

Short- and long-term impact of remifentanil on thermal detection and pain thresholds after cardiac surgery

A randomised controlled trial

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BACKGROUND The clinical relevance of the suggested hyperalgesic effects of remifentanil is still unclear, especially in the long term.

OBJECTIVE The current study evaluated the impact of remifentanil on thermal thresholds 3 days and 12 months after surgery, measured with Quantitative Sensory Testing.

DESIGN A single-blind, randomised controlled trial.

SETTING A tertiary care teaching hospital in The Netherlands, from 2014 to 2016.

PATIENTS A total of 126 patients aged between 18 and 85 years, undergoing cardiothoracic surgery via sternotomy (coronary artery bypass grafts and/or valve replacement) were included. Exclusion criteria were BMI above 35 kg m^{-2}, history of cardiac surgery, chronic pain conditions, neurological conditions, allergy to opioids or paracetamol, language barrier and pregnancy.

INTERVENTIONS Patients were allocated randomly to receive intra-operatively either a continuous remifentanil infusion or intermittent intra-operative fentanyl as needed in addition to standardised anaesthesia with propofol and intermittent intravenous fentanyl at predetermined time points.

MAIN OUTCOME MEASURES Warm and cold detection and pain thresholds 3 days and 12 months after surgery. In addition the use of remifentanil, presence of postoperative chronic pain, age, opioid consumption and pre-operative quality of life were tested as a predictor for altered pain sensitivity 12 months after surgery.

RESULTS Both warm and cold detection, and pain thresholds, were not significantly different between the remifentanil and fentanyl groups 3 days and 12 months after surgery ($P > 0.05$). No significant predictors for altered pain sensitivity were identified.

CONCLUSION Earlier reports of increased pain sensitivity 1 year after the use of remifentanil could not be confirmed in this randomised study using Quantitative Sensory Testing. This indicates that remifentanil plays a minor role in the development of chronic thoracic pain. Still, the relatively high incidence of chronic thoracic pain and its accompanying impact on quality of life remain challenging problems.

TRIAL REGISTRATION The study was registered at EudraCT (ref: 2013-000201-23) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02031016).

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Introduction

Chronic postsurgical pain – defined as the persistence of pain at least 3 months after a surgical procedure – has been reported to occur in 25 to 55% of patients after cardiac surgery.[1–4] It is known to have a negative impact on quality of life (QoL) and daily activities, contributing to increasing public health costs and lost productivity.[5–7] Chronic postsurgical pain is considered to be mostly neuropathic and associated with sensory abnormalities.[8]

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Altered pain sensitivity in patients can be identified using Quantitative Sensory Testing (QST)[9,10] by exposing patients to external stimuli and thereby mapping their pain and detection thresholds.[11] Studies report a predictive value of increased pain sensitivity measured with QST for the development of acute postoperative pain[12] in contrast to no predictive value of response to analgesic treatment.[13] Lundblad *et al.*[14] showed that pre-operative lower electrical pain threshold predicted higher pain intensity 18 months after total knee replacement. A recent cohort study revealed that lower pain pressure thresholds with heightened widespread pain sensitivity before surgery were associated with significantly higher pain severity at 12 months after total hip replacement.[15]

Evidence is growing for opioid-induced hyperalgesia being another external factor besides surgery itself that could influence pain perception.[16] Remifentanil is a fast-acting opioid and favoured for its pharmacokinetic profile, but is also associated with postoperative hyperalgesia.[16–18] A retrospective study in cardiac patients suggested that remifentanil use was associated with chronic postoperative pain 12 months after surgery.[19] A recent randomised controlled trial (REFLECT trial) showed no significant difference in the incidence of chronic thoracic pain 1 year after surgery between patients receiving either intra-operative remifentanil or fentanyl [11 (17.5%) vs. 12 (19.7%), $P = 0.817$].[20] However, a significant difference was found at 3-month follow-up, when patients treated with remifentanil reported postoperative pain significantly more often compared with the control group [32 (50.8%) vs. 21 (33.3%), $P = 0.049$]. These patients also consumed significantly more opioids compared with the remifentanil group 48 h after surgery ($P = 0.047$).[20]

As part of the REFLECT trial, thermal detection and pain thresholds were measured before surgery, and 3 days after and 12 months after surgery. This study aims to investigate the effect of remifentanil on these thermal detection and pain thresholds, and to identify whether altered thresholds predict the development of chronic postsurgical pain after cardiac surgery.

Methods

The prospective and randomised controlled REFLECT trial was approved by the local research ethics committee (VCMO St. Antonius Hospital, Chairperson V. Deneer, ref: R13.013) on 8 August 2013, and registered with EudraCT (ref: 2013-000201-23). Written informed consent was obtained from all patients before the cardiothoracic surgical procedure.

Patients aged 18 to 85 years were eligible if they were scheduled for elective cardiac surgery via sternotomy (coronary artery bypass grafting and/or valve replacement). Exclusion criteria were: pregnancy or breastfeeding; language barrier; history of drug abuse; neurological conditions such as peripheral neuropathy or fibromyalgia; known remifentanil, fentanyl, morphine or paracetamol allergy; BMI above 35 $kg\,m^{-2}$; prior cardiac surgery (re-operations); and chronic pain condition. Patients with a BMI above 35 $kg\,m^{-2}$ were excluded because altered sensory thresholds have been reported compared with nonobese patients.[21]

The study protocol has been published previously.[22] All patients were scheduled for cardiac surgery with a classical full sternotomy approach, so no minimally invasive surgery was performed. After a standardised induction protocol, both groups received a continuous infusion of propofol (starting dose 200 to 300 $mg\,h^{-1}$) and intermittent intravenous fentanyl (200 to 500 μg) at predetermined times (before incision, at sternotomy, at aortic cannulation and at opening of the pericardium). Patients were allocated randomly to either a remifentanil or a fentanyl study arm and were blinded to treatment group allocation. The remifentanil arm received a continuous remifentanil infusion based on ideal body weight starting at 0.15 $\mu g\,kg^{-1}\,min^{-1}$. The fentanyl arm received additional fentanyl boluses (200 to 500 μg) as needed.

Thirty minutes before the anticipated end of surgery, each patient received a fixed dose of intravenous morphine of 10 mg, or, when indicated 5 mg. Immediately after surgery, paracetamol (1 g orally or intravenously) was given four times a day together with a continuous infusion of morphine (starting dose 2 $mg\,h^{-1}$), which was adapted individually on the guidance of the patient's numerical rating scale (NRS) pain scores according to the standard pain protocol of the hospital with a target NRS value of less than 4.[23] On the ward, the continuous infusion of morphine was replaced by 2.5 to 10 mg of intravenous morphine as needed as per protocol.

One day before surgery, 3 days after surgery and 12 months after surgery, patients underwent Quantitative Sensory Testing (QST) in a quiet room pre-operatively and on the ward postoperatively. Thermal detection and pain thresholds were assessed with the Thermal Sensory Analyser (TSA; Type II Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) using previously published protocols.[24,25] The thermode (30 × 30 mm) stimulating surface was placed on the volar side of the nondominant forearm. The applied temperature ranged from 0 to 50 °C, which is safe and nondamaging to the skin. First, the subject's visual motor reaction time was measured with open-source software (http://delphiforfun.org/Programs/Reaction_times.htm). Next, detection and pain thresholds for cold and heat were determined with the method of limits.[26] The detection thresholds for cold and heat were examined by gradually decreasing or increasing, respectively, the baseline temperature of 32 °C at a rate of 1 $°C\,s^{-1}$. The subject was instructed

to press the button as soon as the cold or heat stimulus was felt, after which the temperature normalised to baseline temperature. Then, the subject was instructed to press the button if the thermode started to feel painful – either for cold or heat. For the determination of pain thresholds, the temperature was reversed at a rate of 10 °C s^{-1} after the button was pressed. A minimum of two tests served as rehearsals. Detection and pain thresholds were calculated as the means of the four following tests. If the button was not pressed before 0 or 50 °C was reached, the test was automatically terminated. In this case, the pain thresholds were set at 0 and 50 °C, respectively. All QST tests in this study were performed by the same researcher.

Postoperatively, a nurse on the ICU/Post Anaesthesia Care Unit or the ward recorded pain scores using the visual analogue scale three times daily and opioid consumption during the first 72 h.

After discharge from the hospital, subjects were asked to complete a questionnaire 3, 6 and 12 months after surgery. This questionnaire has been described previously[27] and is based on the Brief Pain Inventory[28] containing questions about pain (perception, location, intensity). In addition, QoL was self-reported with the short form-12 health status instrument at the same time points.

Statistical analysis

Continuous data are presented as median [interquartile range] and analysed using the Mann–Whitney *U* test, or as mean ± SD and analysed using Student's *t* test, where appropriate. Normal distribution of the variables was assessed with the Kolmogorov–Smirnov test and histograms. Categorical data were compared between treatment groups using χ^2 tests. Independent of treatment group, the QST outcomes and reaction times at the follow-up time points were compared with baseline using the Wilcoxon signed-rank test. In a multivariate analysis of the QST data, the following independent variables were included for warm and cold detection and pain thresholds: treatment condition (remifentanil vs. fentanyl), baseline QST measurement, age, opioid consumption in the first 72 h, chronic pain 12 months after surgery, pre-operative QoL. Reaction time was only included in the analysis of the reaction time-dependent thresholds for detection of heat and cold. A robust regression analysis with MM estimation was used to account for the fact that the model residuals were not normally distributed. The weight function was the Tukey bisquare estimator. *P* values (two-sided) of less than 0.05 were considered statistically significant. Data were analysed in IBM SPSS Statistics version 24 (Chicago, Illinois, USA) and R-statistics version 3.0.1 (Vienna, Austria).

Power

A sample size calculation was performed for the primary endpoint, chronic thoracic pain and based on the findings of a previous study.[19] This study found, 1 year after cardiac surgery, an incidence of chronic pain of approximately 10% in the fentanyl study arm and 30% in the remifentanil arm. This resulted in a total number of patients of 117, with a power of 0.80 and a two-sided significance level of 0.05. Taking into account a mortality rate of 8% 1 year after surgery,[19] the total number of patients is 126, which results in 63 subjects per arm.

Results

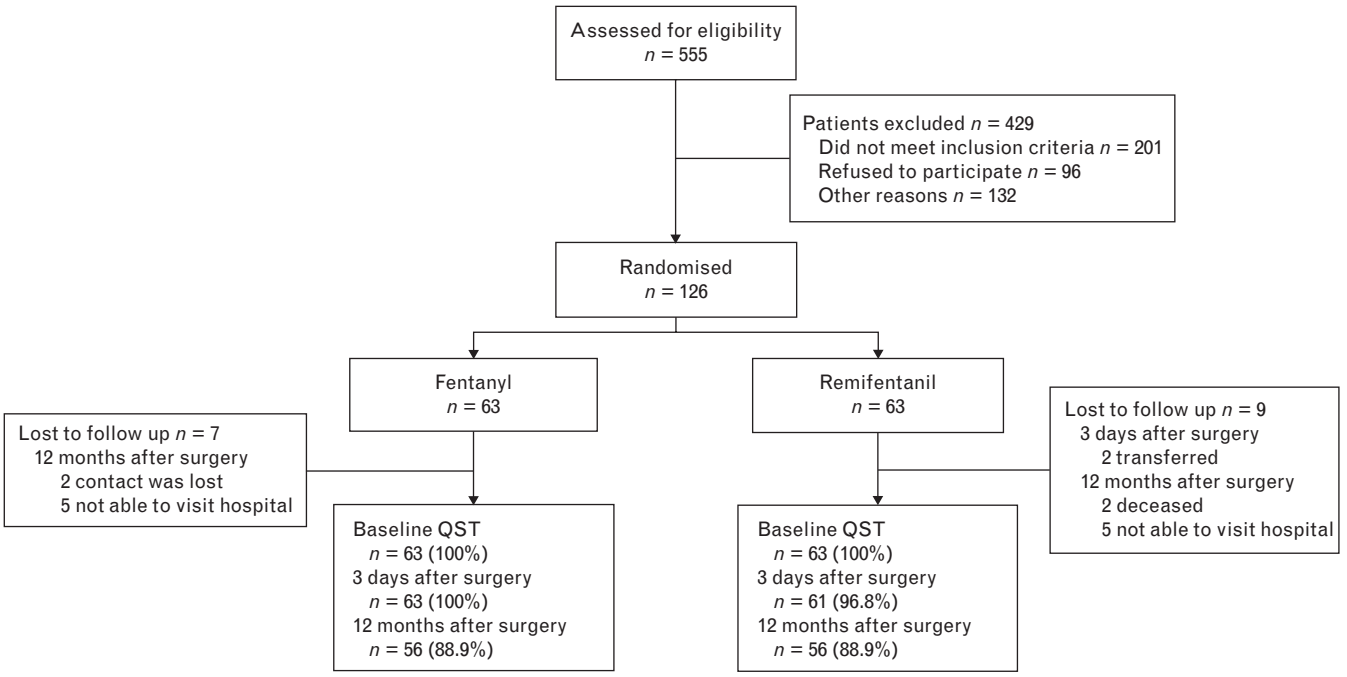
A total of 555 patients were screened for eligibility; 201 patients did not meet the inclusion criteria, 96 patients refused to participate and 132 patients were excluded for other reasons (n=127 logistic reasons and n=5 unknown). In total, 126 patients were included (Fig. 1). Detection thresholds and pain thresholds were measured in all 126 patients one day before surgery. After surgery, 124 subjects were tested (two had been transferred to other hospitals). One year after surgery, QST measurements were taken in 112 patients. Two patients had died, other patients were not able to visit the hospital again or contact was lost (Fig. 1). An overview of patient characteristics is shown in Table 1. More details on the primary outcome of the study can be found in the original article.[20]

Three days after surgery, no significant differences in detection thresholds were found between the groups (warm median °C [IQR] 30.2 [29.6 to 30.7] vs. 29.8 [28.6 to 30.7] $P = 0.320$; cold: 35.2 [34.6 to 36.5] vs. 35.7 [34.6 to 36.9], $P = 0.31$). Pain thresholds were not significantly different between groups (heat pain median °C [IQR] 47.0 [44.2 to 48.6] vs. 46.8 [43.7 to 49.0], $P = 0.87$; cold pain median °C [IQR] 10.1 [2.8 to 18.4] vs. 8.6 [1.3 to 20.1], $P = 0.86$). Twelve months after surgery, no significant differences in detection and pain thresholds (median °C [IQR]) were found between the groups (warm detection: 35.2 [34.5 to 36.3] vs. 35.3 [34.5 to 36.9], $P = 0.91$; cold detection: 30.4 [29.4 to 30.7] vs. 30.3 [29.5 to 30.7], $P = 0.70$; heat pain: 47.7 [45.4 to 49.2] vs. 48.1 [45.7 to 49.4], $P = 0.88$; cold pain: 6.6 [1.7 to 18.3] vs. 4.8 [1.6 to 13.5], $P = 0.65$) (Fig. 2).

Independent of group allocation, three days after surgery pain thresholds for heat and cold (median °C [IQR]) were lower than baseline values (heat: 46.9 [43.8 to 48.7] vs. 48.1 [46.4 to 49.1], $P < 0.001$; cold: 9.5 [1.8 to 19.2] vs. 5.6 [1.5 to 15.3]; $P = 0.002$). This could not be explained by the reaction time, as this was significantly higher 3 days postsurgery compared with baseline (0.308 ± 0.1 vs. 0.380 ± 0.1; $P < 0.001$). Pain thresholds returned back to baseline levels 12 months after surgery (heat baseline: 48.1 [46.4 to 49.1] vs. 12 months: 48.0 [45.7 to 49.3], $P = 0.782$; cold baseline: 5.7 [1.5 to 15.2] vs. 12 months: 4.9 [1.7 to 15.5], $P = 0.588$) (Supplemental data content Table S1, http://links.lww.com/EJA/A173).

Twelve months after surgery, detection thresholds for heat and cold (median °°C [IQR]) were lower than

Fig. 1



Flow chart of study.

baseline values (heat: 35.2 [34.5 to 36.4] vs. 35.8 [34.7 to 37.3]; $P = 0.047$; cold: 30.4 [29.4 to 30.7] vs. 29.9 [28.9 to 30.6]; $P = 0.045$) (Supplemental data content Table S1, http://links.lww.com/EJA/A173).

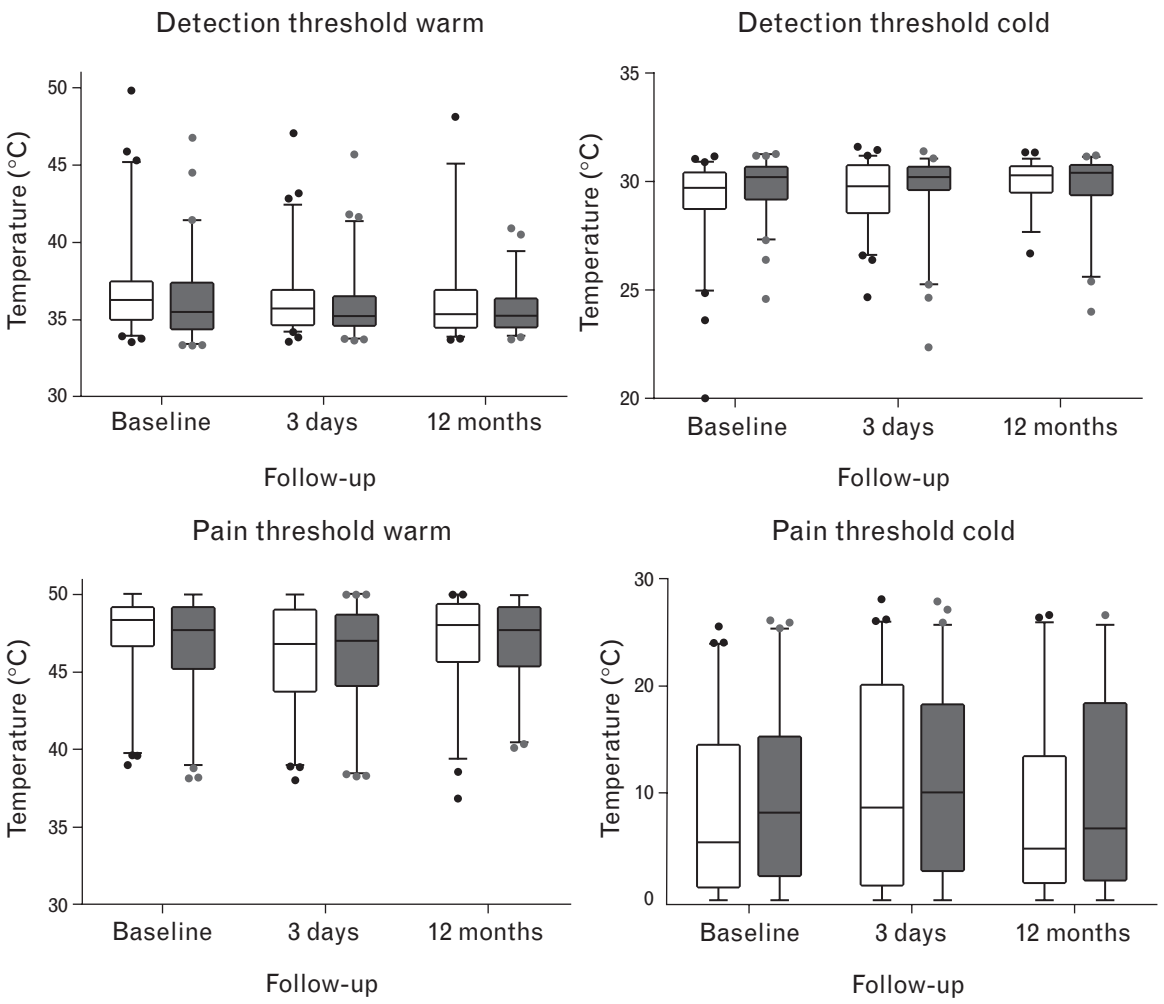
Regression estimates for the four QST modalities measured 12 months after surgery are shown in Table 2. In the model, treatment condition (remifentanil or fentanyl), presence of chronic pain 12 months after surgery, age, opioid consumption and pre-operative QoL were not significantly associated with altered pain sensitivity measured with QST. Baseline values were associated with the follow-up values for cold detection and pain thresholds 12 months after surgery. The regression estimates for detection and pain thresholds measured 3 days after surgery also revealed no significant

Table 1 **Patient and peri-operative characteristics**

	Fentanyl, *n*=63	Remifentanil, *n*=63	*P*
Male sex	57 (90)	58 (92)	0.752
Age (years)	66 ± 7.6	62 ± 9.0	0.006
BMI (kg m^{-2})	28.0 ± 3.1	27.5 ± 3.6	0.471
Pre-operative NRS	0 [0 to 0]	0 [0 to 0]	0.765
Pre-operative quality of life			
PCS	49.3 [43.3 to 53.1]	47.6 [39.6 to 54.3]	0.666
MCS	51.3 [46.1 to 57.2]	50.4 [46.8 to 54.3]	0.212
Type of surgery			0.389
CABG	51 (81.0)	49 (77.8)	
Valve	9 (14.3)	7 (11.1)	
Combination	3 (4.8)	7 (11.1)	
EuroSCORE	3 [2 to 4]	2 [0 to 4]	0.035
Intra-operative characteristics			
Duration of general anaesthesia (min)	218.6 ± 49.0	233.4 ± 72.1	0.179
Duration of surgery (min)	187.4 ± 46.7	198.1 ± 70.8	0.317
Cross-clamp time (min)	51.4 ± 21.3	59.6 ± 32.5	0.095
Propofol (mg kg^{-1})	12.0 [9.7 to 16.6]	12.6 [9.5 to 15.4]	0.913
Fentanyl (μg kg^{-1})	26.1 [19.4 to 31.4]	19.4[15.4 to 27.2]	0.003
Remifentanil (μg kg^{-1})	NA	22.9 [18.1 to 30.9]	NA

Continuous data are presented as mean ± SD or median [interquartile range], and categorical data are presented as number (%). CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; MCS, mental composite score; NA, nonapplicable; NRS, numerical rating scale; PCS, physical composite score.

Fig. 2



Detection and pain thresholds at baseline (n=126), 3 days after surgery (n=124) and 12 months after surgery (n=121). Whiskers represent the 5th to 95th percentiles. Black, fentanyl group; grey, remifentanil group.

predictors for altered pain sensitivity. For all four modalities, baseline measurements showed significant correlation with the measurement 3 days after surgery after adjustment for other variables (Supplemental data content Table S2, http://links.lww.com/EJA/A173).

Discussion

Several studies of widely different design found that remifentanil use during surgery correlated with more postoperative pain and higher opioid consumption in the short term.[16,18] The aim of this study was to determine whether the intra-operative use of remifentanil would have any effect on thermal detection and pain thresholds in the short and longer term after surgery. Statistical analysis showed no significant differences in detection and pain thresholds in patients treated with remifentanil or fentanyl 3 days and 1 year after cardiac surgery. In a regression analysis, no other significant predictors for altered pain sensitivity 1 year after surgery were present.

The primary analysis of the REFLECT trial showed that patients receiving remifentanil during cardiac surgery needed more opioids after surgery to reach adequately low pain scores. In addition, 3 months after surgery, these patients also reported more pain related to the surgery, a difference that was not found 1 year after surgery.[20] These potential short-term effects of remifentanil did not result in significant differences in pain and detection thresholds 3 days after surgery. In line with the reported pain scores, sensory thresholds 1 year after surgery were also not significantly different between the two groups.

Regarding the effect of remifentanil on QST modalities directly after surgery, one study showed an increase in pain sensitivity to tactile stimuli in the high-dose remifentanil group during 2 days after surgery.[29] Another study found a decrease in pressure pain tolerance

Table 2 Robust regression estimates of remifentanil, with adjustment for different covariates detection and pain thresholds 12 months after surgery

Modality	Estimate	95% CI	P
Detection threshold for cold			
Intercept	25.6	23.8 to 27.5	<0.001
Remifentanil	0.01	−0.26 to 0.27	0.955
Baseline detection threshold cold (°C)	0.15	0.12 to 0.18	<0.001
Age (years)	0.00	−0.02 to 0.01	0.667
Opioid consumption first 72 h (mg)	0.00	−0.01 to 0.01	0.897
Chronic pain after 1 year	0.09	−0.27 to 0.46	0.612
QoL pre-operative	0.01	−0.03 to 0.04	0.737
Reaction time (s)	0.44	−1.26 to 2.13	0.611
Detection threshold for heat			
Intercept	26.5	20.6 to 32.3	<0.001
Remifentanil	0.36	−0.16 to 0.88	0.178
Baseline detection threshold heat (°C)	0.23	0.09 to 0.38	0.002
Age (years)	−0.001	−0.03 to 0.03	0.932
Opioid consumption first 72 h (mg)	0.01	0.00 to 0.02	0.259
Chronic pain after 1 year	0.30	−0.40 to 0.99	0.401
QoL pre-operative	0.003	−0.04 to 0.05	0.897
Reaction time (s)	−0.09	−3.96 to 3.78	0.964
Pain threshold for cold			
Intercept	−0.23	−10.6 to 10.1	0.965
Remifentanil	−1.06	−3.70 to 1.58	0.427
Baseline pain threshold cold (°C)	0.82	0.57 to 1.07	<0.001
Age (years)	−0.01	−0.16 to 0.13	0.853
Opioid consumption first 72 h (mg)	−0.01	−0.06 to 0.03	0.591
Chronic pain after 1 year	0.56	−2.78 to 3.90	0.741
QoL pre-operative	0.07	−0.09 to 0.24	0.363
Pain threshold for heat			
Intercept	22.9	8.5 to 37.3	0.002
Remifentanil	−0.11	−0.92 to 0.70	0.791
Baseline pain threshold heat (°C)	0.53	0.22 to 0.84	0.001
Age (years)	0.01	−0.05 to 0.06	0.746
Opioid consumption first 72 h (mg)	0.004	−0.01 to 1.02	0.615
Chronic pain after 1 year	−0.25	−1.51 to 1.02	0.702
QoL pre-operative	−0.02	0.07 to 0.03	0.422

QoL, quality of life questionnaire.

thresholds directly after eye surgery in the high-dose remifentanil group, whereas thermal thresholds showed no effect.[30] In the current study, thermal pain thresholds 3 days after surgery had significantly decreased from baseline values in both treatment groups. This could indicate higher sensitivity for heat and cold sensation 3 days after the surgery, despite the administration of analgesics. A confounding factor is that patients in the remifentanil group received more opioids in the first 48 h compared with the fentanyl group. However, patients in both groups had received opioids and decreased thresholds were found in both groups. One year after surgery, pain thresholds had returned to baseline values. No significant differences in detection and pain thresholds were found between the remifentanil and fentanyl groups.

To our knowledge, no data is available regarding the intra-operative use of remifentanil and its effect on hyperalgesia measured with QST in the longer term. Despite being another concept than hyperalgesia, with different definition and mechanism, one study measured allodynia (i.e. pain due to a stimulus that does not usually provoke pain) 1 month after remifentanil administration. In 38 cardiac surgery patients, an increased area of mechanical allodynia around the incisional site was found in the patients receiving high dose remifentanil and postsurgical epidural analgesia.[31] This study illustrates that remifentanil use during surgery can have an impact on sensory thresholds in the longer term. Our study assessed only secondary hyperalgesia, which is thought to derive from central sensitisation to pain.[32] No differences in thermal thresholds were found before and 12 months after surgery. As patients in the remifentanil group directly after surgery had an increased need for opioids and reported more thoracic pain 3 months after surgery, it was encouraging to find that after 12 months there were no significant differences in patient-reported outcomes or in sensory thresholds. This implies that the clinical relevance of remifentanil-induced (secondary) hyperalgesia on sensory perception in the longer term is minimal or possibly self-limiting.

The possible mechanisms of remifentanil-induced hyperalgesia are still controversial. The ultrashort half-life of remifentanil together with inadequate and timely administration of long-acting analgesics could be an explanation for the increase in pain scores and in the use of postoperative opioids after the use of remifentanil. However, in our and other studies in which long-acting opioids were administered in a timely manner for bridging the possible opioid gap, increases in pain parameters directly after surgery have been reported.[17,18] This suggests that there are more potential causes of hyperalgesia.

On a molecular level, it has been suggested that changes in neuroplasticity in the peripheral and central nervous system may lead to central sensitisation of nociceptive pathways, resulting in reduced nociceptive thresholds.[33] Although multiple mechanisms are postulated, the *N*-methyl-D-aspartate (NMDA) receptor appears to play a key role in the development of opioid-induced hyperalgesia. This receptor is involved in neuroplasticity and long-term potentiation, and affected by remifentanil through multiple pathways.[34–36] It is unknown what the mechanism is regarding a prolonged remifentanil effect, but animal data showed a potential role of protein kinase C zeta (PRCKZ), which appears to plays a role in the development of prolonged remifentanil-induced hyperalgesia. PRCKZ is involved in long-term potentiation and pain memory, peaks 2 days after cessation of remifentanil infusion and returns to baseline level after 7 days. Blockade of this substance reversed postinfusion hyperalgesia induced by remifentanil.[37] The involvement of the NMDA receptor and its role in neuroplasticity could possibly explain the transient negative impact of remifentanil 3 months after surgery. This is only hypothesising, and more research is needed to identify the complex pathways that are involved in the acute and prolonged effects of remifentanil.

The reported incidence of chronic thoracic pain 1 year after surgery in this study is 18.9% overall and not significantly different between study groups. Previous studies have reported 1-year incidences around 25%.[2–4] Pharmacological interventions for preventing chronic pain are still not convincing, with a modest effect of ketamine as most promising.[38] Other drugs, for example pregabalin, seem to have no added value.[39]

QST is widely used to diagnose and monitor chronic and neuropathic pain disorders.[11] However, in routine clinical practice, QST is not well established in relation to postoperative pain because results are conflicting or not convincing, and measurements are time-consuming. As mentioned above, some studies report a predictive value of pre-operative QST measurements, whereas others find no such association.[40,41] Our study shows no distinctive added value of measuring thermal detection and pain thresholds for evaluating chronic postsurgical pain in patients 1 year after cardiac surgery. In addition to thermal thresholds, other methods have been used to study chronic postoperative pain. Measurement of diffuse inhibitory noxious control (DNIC) gives a dynamic view of the pain processing system.[42] Patients with impaired conditioned pain modulation or DNIC were found to have a greater likelihood of developing chronic postoperative pain.[11,43] Pre-operative DNIC explained around 25% of the variability in chronic postoperative pain intensity, whereas the numbers of static thresholds were below 6%. It is possible that the use of multiple modalities of QST, such as pressure, electrical thresholds or measuring DNIC, provides more information, but the more extensive and time-consuming, the more difficult is the use of QST protocols in daily practice. In addition, static QST thresholds such as detection and pain thresholds appear to have sufficient test–retest reliability.[44] Our study measured thermal detection and pain thresholds 3 days and 12 months after surgery and was performed to assess the potential of QST for application in clinical practice. After all, it takes only 16 to 18 min per measurement. Still, gathering pieces of evidence of the complicated puzzle of postoperative pain management adds to the final goal of reducing incidences of short-term and chronic postoperative pains. Recently, it has been suggested that patients with peripheral neuropathic pain can be divided into subgroups on the basis of sensory profiles, potentially increasing the response to pharmacological treatment.[45] Whether QST can also play a role in the management of postoperative pain is a field for future research.

Limitations

First, the ideal study design should be double-blind and contain no other opioid besides remifentanil. Patients in the remifentanil group also received fentanyl during surgery as this was standard care in our hospital and it is not, in our opinion, in patients' best interest to use a high-dose remifentanil as the single analgesic during this prolonged procedure because of the risk of increased immediate postoperative pain. Of note, an earlier observational study using the same regimens suggested that remifentanil was predictive for chronic thoracic pain 1 year after the study.[19] However, it has to be taken into account that patients in the remifentanil group also received fentanyl during surgery and the possibility that fentanyl does not contribute to the outcome of this study cannot be excluded.

Second, the design of this study is single-blind. In our opinion, blinding only patients to study treatment was enough to ensure a valid outcome of the primary and secondary outcomes because patients self-reported pain scores and were in control of QST measurements.

Third, the QST-battery was limited to thermal stimuli, whereas multiple modalities (e.g. electrical, pressure) can give more information about pain perception of the individual patient. Conclusions can be drawn only for the development of secondary hyperalgesia 1 year after remifentanil administration measured with thermal thresholds. For instance, no data are available about mechanical or electrical tests around the wound.

Conclusion

Despite the unfavourable effects of remifentanil vs. fentanyl on chronic thoracic pain after 3 months, it is positive that no significant effect of remifentanil on thermal pain sensitivity and chronic thoracic pain was found 1 year after cardiac surgery. Additional predictors of altered pain sensitivity could not be identified. Again, this study contributes to the body of literature that concludes that chronic postoperative pain is multimodal and it remains difficult to predict which patients are at risk for chronic postoperative pain. However, this study showed again a high incidence of chronic thoracic pain after cardiac surgery, which is known to have a considerable impact on QoL. Investing in the prevention and early detection of chronic postsurgical pain is the next logical step.

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Presentation: none.

References

1 Macrae WA. Chronic postsurgical pain: 10 years on. *Br J Anaesth* 2008; **101**:77–86.

2 Bruce J, Drury N, Poobalan AS, *et al.* The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 2003; **104**:265–273.
3 Ho SC, Royse CF, Royse AG, *et al.* Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. *Anesth Analg* 2002; **95**:820–823.
4 Meyerson J, Thelin S, Gordh T, *et al.* The incidence of chronic poststernotomy pain after cardiac surgery – a prospective study. *Acta Anaesthesiol Scand* 2001; **45**:940–944.
5 Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004; **5**:143–149.
6 Leadley RM, Armstrong N, Reid KJ, *et al.* Healthy aging in relation to chronic pain and quality of life in Europe. *Pain Pract* 2014; **14**:547–558.
7 Andrew R, Derry S, Taylor RS, *et al.* The costs and consequences of adequately managed chronic noncancer pain and chronic neuropathic pain. *Pain Pract* 2014; **14**:79–94.
8 Haroutiunian S, Nikolajsen L, Finnerup NB, *et al.* The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013; **154**:95–102.
9 Rolke R, Baron R, Maier C, *et al.* Quantitative sensory testing in the German research network on neuropathic pain (DFNS): standardized protocol and reference values. *Pain* 2006; **123**:231–243.
10 Zaslansky R, Yarnitsky D. Clinical applications of quantitative sensory testing (QST). *J Neurol Sci* 1998; **153**:215–238.
11 Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain* 2009; **10**:556–572.
12 Werner MU, Mjobo HN, Nielsen PR, *et al.* Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology* 2010; **112**:1494–1502.
13 Grosen K, Fischer IW, Olesen AE, *et al.* Can quantitative sensory testing predict responses to analgesic treatment? *Eur J Pain* 2013; **17**:1267–1280.
14 Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg Br* 2008; **90**:166–171.
15 Wylde V, Sayers A, Lenguerrand E, *et al.* Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. *Pain* 2015; **156**:47–54.
16 Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014; **112**:991–1004.
17 Yu EH, Tran DH, Lam SW, *et al.* Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia* 2016; **71**:1347–1362.
18 de Hoogd S, Ahlers SJ, van Dongen EP, *et al.* Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clin J Pain* 2016; **32**:726–735.
19 van Gulik L, Ahlers SJ, van de Garde EM, *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br J Anaesth* 2012; **109**:616–622.
20 de Hoogd S, Ahlers SJGM, van Dongen EPA, *et al.* Randomized controlled trial on the influence of intraoperative remifentanil versus fentanyl on acute and chronic pain after cardiac surgery. *Pain Pract* 2018; **18**:443–451.
21 Torensma B, Thomassen I, van Velzen M, *et al.* Pain experience and perception in the obese subject systematic review (revised version). *Obes Surg* 2016; **26**:631–639.
22 de Hoogd S, Ahlers SJ, van Dongen EP, *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 2014; **15**:466.
23 Ahlers SJ, van Gulik L, van Dongen EP, *et al.* Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth Intensive Care* 2012; **40**:417–426.
24 van den Bosch GE, van Dijk M, Tibboel D, *et al.* Thermal quantitative sensory testing in healthy Dutch children and adolescents standardized test paradigm and Dutch reference values. *BMC Pediatr* 2017; **17**:77.
25 Valkenburg AJ, van den Bosch GE, de Graaf J, *et al.* Long-term effects of neonatal morphine infusion on pain sensitivity: follow-up of a randomized controlled trial. *J Pain* 2015; **16**:926–933.
26 Rolke R, Magerl W, Campbell KA, *et al.* Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* 2006; **10**:77–88.
27 van Gulik L, Janssen LI, Ahlers SJ, *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur J Cardiothorac Surg* 2011; **40**:1309–1313.
28 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994; **23**:129–138.
29 Joly V, Richebe P, Guignard B, *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**:147–155.
30 Schmidt S, Bethge C, Forster MH, *et al.* Enhanced postoperative sensitivity to painful pressure stimulation after intraoperative high dose remifentanil in patients without significant surgical site pain. *Clin J Pain* 2007; **23**:605–611.
31 Salengros JC, Huybrechts I, Ducart A, *et al.* Different anesthetic techniques associated with different incidences of chronic postthoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J Cardiothorac Vasc Anesth* 2010; **24**:608–616.
32 Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurol* 2014; **13**:924–935.
33 Lee M, Silverman SM, Hansen H, *et al.* A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; **14**:145–161.
34 Li Y, Wang H, Xie K, *et al.* Inhibition of glycogen synthase kinase-3beta prevents remifentanil-induced hyperalgesia via regulating the expression and function of spinal *N*-methyl-D-aspartate receptors in vivo and vitro. *PLoS One* 2013; **8**:e77790.
35 Yuan Y, Wang JY, Yuan F, *et al.* Glycogen synthase kinase-3β contributes to remifentanil-induced postoperative hyperalgesia via regulating *N*-methyl-D-aspartate receptor trafficking. *Anesth Analg* 2013; **116**:473–481.
36 Arout CA, Edens E, Petrakis IL, *et al.* Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. *CNS Drugs* 2015; **29**:465–486.
37 Zhao Q, Zhang L, Shu R, *et al.* Involvement of spinal PKMzeta expression and phosphorylation in remifentanil-induced long-term hyperalgesia in rats. *Cell Mol Neurobiol* 2017; **37**:643–653.
38 Chaparro LE, Smith SA, Moore RA, *et al.* Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev* 2013;CD008307.
39 Martinez V, Pichard X, Fletcher D. Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a meta-analysis of randomized trials. *Pain* 2017; **158**:775–783.
40 Granot M. Can we predict persistent postoperative pain by testing preoperative experimental pain? *Curr Opin Anaesthesiol* 2009; **22**:425–430.
41 Marcuzzi A, Dean CM, Wrigley PJ, *et al.* Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J Pain Res* 2016; **9**:599–607.
42 Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol* 2010; **23**:611–615.
43 Yarnitsky D, Crispel Y, Eisenberg E, *et al.* Prediction of chronic postoperative pain: preoperative DNIC testing identifies patients at risk. *Pain* 2008; **138**:22–28.
44 Nothnagel H, Puta C, Lehmann T, *et al.* How stable are quantitative sensory testing measurements over time? Report on 10-week reliability and agreement of results in healthy volunteers. *J Pain Res* 2017; **10**:2067–2078.
45 Baron R, Maier C, Attal N, *et al.* Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain* 2017; **158**:261–272.