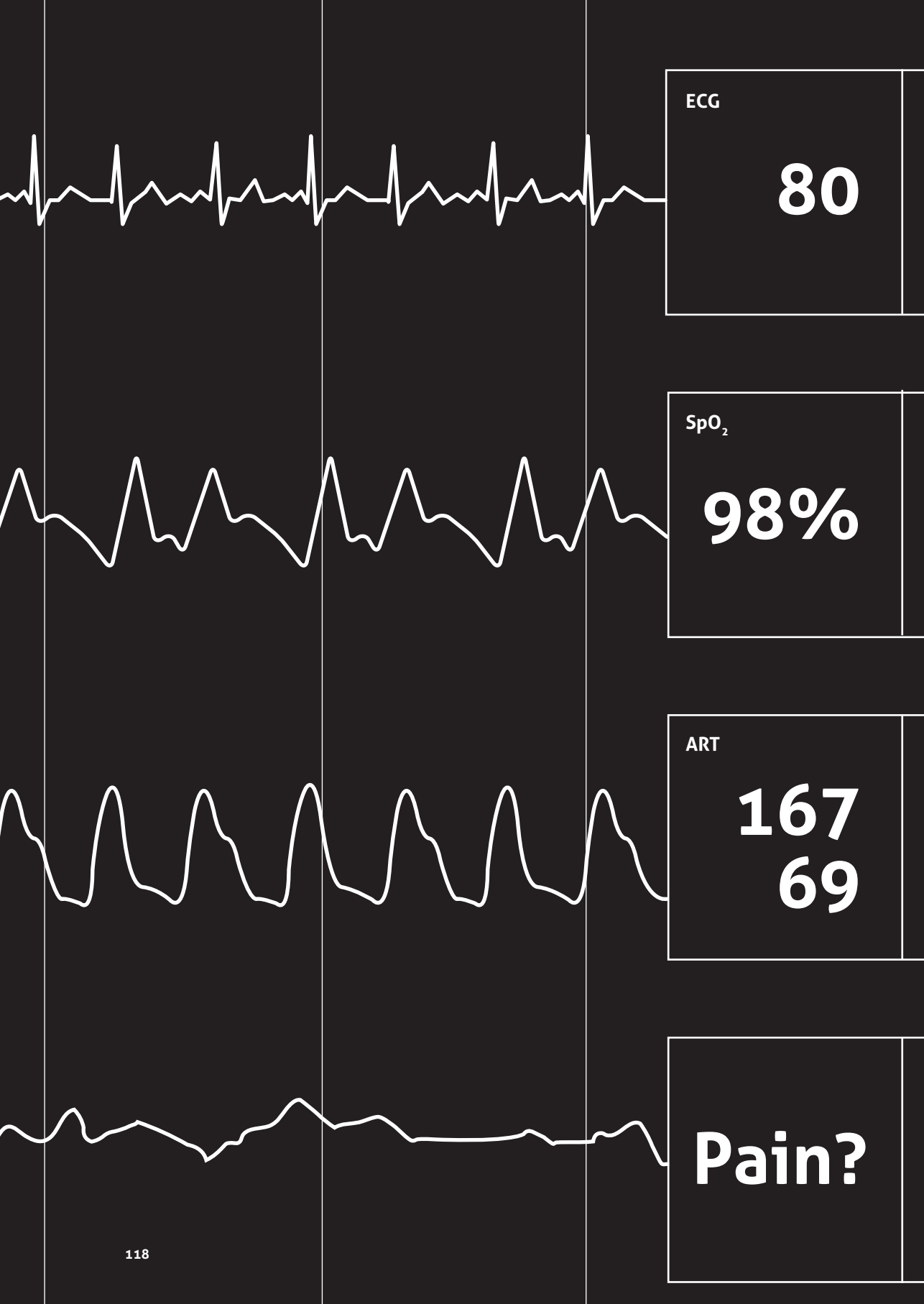
ECG
80
SpO2
98%
ART
167
69
Pain?

# SUMMARY, CONCLUSIONS AND PERSPECTIVES

# CH. 9 section IV

## Summary and conclusions

Even today, many intensive care patients experience pain due to surgery, underlying illness or injury, immobility, medical interventions or pre-existent (chronic) pain. The few studies that focused specifically on pain management in the ICU reported lower pain scores after implementation of systematic pain assessment, as well as shorter durations of ventilator support and ICU-stay, and fewer nosocomial infections [1, 2]. Therefore, international guidelines recommend systematic pain assessment and treatment for all ICU patients. Pain management in the ICU is hampered, however, by heterogeneity in type of illness, patients' medical background and the fact that these patients may not be able of self-report, which is internationally considered the gold standard for pain assessment [3]. The studies presented in this thesis focus on patients in the direct postoperative phase after cardiac surgery, as they represent a relatively homogeneous group and most of them are able to communicate their pain levels after cessation of sedation. Moreover, as acute pain directly after surgery is thought to be a risk factor for the development of chronic pain [4-6], we also evaluated chronic pain after cardiac surgery. Others have reported this phenomenon in 11-56% of patients [6-10].

Routine pain assessment and the implementation of pain management programs are recommended by international (Society of Critical Care Medicine) [11] and national societies (the Netherlands Association for Intensive Care NVIC) [12]. However, effective implementation is not specified. In **Chapter 3** we described the implementation of a pain management program for patients in the ICU after cardiac surgery. The program employed a three-fold strategy; all staff was trained in assessing pain and in providing adequate analgesia, a new patient data management system reminded nurses to ask patients to rate their pain three times a day, and analgesic treatment was optimised. Control patients, who were in the ICU before the pain management program was implemented, reported unacceptable pain (NRS ≥4 on numeric rating scale; NRS) on significantly more occasions than did patients in the intervention group, 41% (26/64) vs. 23% (42/185), respectively, with an odds ratio of 2.54 for unacceptable pain. Patients in the intervention group received significantly more morphine, and doses were higher in patients with higher NRS scores, irrespective of length of stay in the ICU or duration of mechanical ventilation. Even though the quality of pain management at rest had been improved, still 46% of patients experienced at least one painful event (NRS ≥4) during the ICU stay.

We consider the fact that 46% of patients experience at least one painful event a serious problem that needs special attention. Therefore, we focused on the management of procedure-related pain in a following study, described in **Chapter 4.** In this randomized trial patients received either 2.5 or 7.5 mg morphine 30 minutes before a potentially painful intervention (turning in bed or chest drain removal). All 117 patients were treated according to the previously implemented pain titration protocol for pain at rest. At rest, before administration of study medication, the incidence of unacceptable pain (NRS ≥4) in all study patients was 16%, with no significant difference between the two study groups. Five minutes before the intervention, the overall incidence had decreased to 7%, again with no significant

difference between the two groups. Mean NRS during the potentially painful intervention did not differ between the two groups (2.6 [95%CI 2.0-3.2] versus 2.7 [2.0-3.4] in the 2.5 mg and 7.5 mg morphine group, respectively p=0.86). These pain scores were lower than those reported in other studies, i.e. mean NRS scores of 5 and 7 during turning and drain removal, respectively [13, 14]. As such, the pain titration protocol, which is applied during the entire ICU stay, may not affect pain scores at rest alone, but also decrease pain intensity during painful procedures.

The study described in **Chapter 4** provided a good opportunity to study potential objective markers of procedural pain. Therefore, in the sub-study reported in **Chapter 5**, on the morning after surgery, plasma levels of cortisol, adrenalin, and noradrenalin were measured before and after the painful intervention in 59 randomly selected patients. Unacceptable pain (NRS ≥4) was reported by 7 (12%), 26 (44%), and 9 (15%) of patients, before, during, and after the painful procedure, respectively. The occurrence of unacceptable pain was, however, not associated with significant changes in plasma stress hormone levels. We speculate that within 24 hours after surgery, the mixed effects of tissue trauma, surgical stress, hypothermia during surgery and the use of perioperative steroids interfere with the effects of postoperative pain on cortisol and catecholamine levels. Furthermore, the interval between measurements may have been too short to detect changes in cortisol levels. Still, considering that these patients reflect the average population in our ICU, we concluded that cortisol, adrenalin, or noradrenalin levels are not useful to objectify procedural pain.

In **Chapter 6** we evaluated nurses' adherence to the pain protocol for pain at rest in terms of administration of analgesics, the number and timing of pain assessments and interventions initiated upon unacceptably high (NRS ≥4) and low (NRS ≤1) pain scores.
For the patient group described in **Chapter 4**, the protocol consisted of automated prescriptions for intermittent paracetamol and continuous morphine infusion, automated reminders for pain assessments 3 times a day, a flow chart to guide medication adjustment upon specific pain scores, and reassessments after unacceptable pain (NRS ≥4). Overall pain management was adequate with 90% acceptable pain scores and 99% adherence to automated prescribed analgesics and scheduled pain assessments. Non-automated protocol items, i.e. adjustment of continuous infusion of morphine upon pain scores (high and low) and reassessment of pain after unacceptably high pain scores, were poorly adhered to. Neither a pharmacological intervention nor a reassessment was carried out in 30% of unacceptable pain scores. In 273 of the required 303 cases (90%) where morphine should have been tapered, morphine was continued.
Better adherence to these items, possibly via automated reminders within the context of the patient data management system, may further improve pain management. Moreover, registration of reasons to deviate from the protocol could reveal flaws of the protocol.

**Chapter 7** describes a follow-up study of patients from the intervention group after the implementation of a pain management program (**Chapter 3**). The incidence of chronic thoracic pain (NRS >0) associated with the primary surgery was assessed through a questionnaire administered one year after surgery, and possible associations with patient demographics and peri- and postoperative (<7 days) characteristics were examined. One year after surgery, 35% of the responding patients reported chronic thoracic pain. These patients reported more sleep disturbances and more frequent use of analgesics than those without chronic thoracic pain. Non-elective surgery, re-sternotomy, severe pain (NRS >4) on the third postoperative day, and female gender were all independent predictors of chronic thoracic pain.

In **Chapter 8**, 18 of the 90 responding patients (20%) who participated in the randomized clinical trial on procedural pain after cardiac surgery (**Chapter 4**), reported chronic thoracic pain. 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 [1.6–31.7], 9.1 [2.1–39.1], respectively}. 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. Patient and perioperative characteristics (including the amount of administered fentanyl during surgery) did not differ between patients receiving remifentanil (58%) and patients not receiving remifentanil (42%). Remifentanil was either started as a continuous infusion directly after the induction of anaesthesia, or not started at all, depending on the preferences of the attending anaesthesiologist. The results of this study are in line with a previous study reporting an association between remifentanil and chronic pain after thoracic surgery via lateral thoracotomy [15]. Other studies reported hyperalgesia postoperatively after the intraoperative use of remifentanil [16]. Before considering to abandon remifentanil for cardiac anaesthesia, further research through randomized controlled trials with and without remifentanil during cardiac surgery are warranted.

***Perspectives***

This thesis concerns patients admitted to the intensive care after undergoing cardiac surgery. Initially, we aimed to improve pain management in the whole ICU population. However, after a first study comparing the use of different pain scores for ICU patients [17], we concluded this would be hard to realize, for various reasons. First, pain is a subjective experience. The gold standard for pain measurement is what the patient tells us that he/she feels. Regrettably, this gold standard is of little value in many ICU patients who are unconscious or (heavily) sedated. On the other hand, objective parameters that are usually used in anesthesiology as surrogates of pain expression, e.g. heart rate, blood pressure and respiratory rate, can be affected by disease or medication. Second, although pain is universal, the ICU population is very diverse; patients may suffer from pain due to for instance sepsis, mono or multiple organ failure, trauma, elective or emergency surgery, toxins, etcetera. Third, ICUs differ in expertise, number of nurses and doctors per patient and day-night rhythm. Therefore, it may be difficult to compare findings between patient populations. For these reasons, we chose to focus our research on patients admitted

after cardiac surgery. Most patients would be –at some point– able to rate their pain through self-report and they share the same background, i.e. cardiac surgery and cardiopulmonary bypass.

***Pain management in the ICU***

In this thesis, we describe the introduction and implementation of a pain management program for pain at rest after cardiac surgery in the ICU. The program consisted of education of health staff on pain and analgesia, systematic pain measurement and registration, and optimization of the analgesia protocol. The latter implied that paracetamol could be administered intravenously in addition to the rectal and oral routes, and that morphine through continuous intravenous infusion was preferred over morphine subcutaneously and dosing 'when required'. Morphine dosage was to be adjusted upon pain intensity. Analgesics were now started immediately upon arrival at the ICU after surgery, instead of at the first set time point after arrival at the ICU. More morphine was administered to the intervention group compared to the control group, without an increase in adverse events. This showed that morphine is an adequate analgesic for the management of pain in rest in patients in the ICU after cardiac surgery. The change in pain management resulted in fewer cases of unacceptable pain (NRS ≥4) with an odds ratio for unacceptable pain of 2.5 in the control group.

The practical wish to improve the quality of care did not equally match with research purposes, resulting in several methodological limitations that should be considered when interpreting the results. The presence of the researchers on the ward could have influenced our results; notably regarding the control group in **Chapter 3** and in all patients in **Chapter 4**. This presence could have drawn both nurses' and patients' attention towards pain and analgesia more than usual. In addition, in the study described in **Chapter 3**, the control patients provided pain scores in rest situations, whereas patients in the intervention group provided pain scores at preset times, (nurses were reminded by the PDMS), regardless of an intervention at or around that time. Moreover, during the intervention phase, nurses were trained to be more alert of high NRS levels compared to the control phase and they were allowed to rate pain at any other time in addition to the scheduled times. This may have resulted in more frequent registration of high pain scores in the intervention group. Therefore, the actual reduction of high pain scores via the introduction of the pain management program may have been even underestimated. Furthermore, the education sessions were attended by eighty percent of the nurses. The knowledge was not tested, so we cannot be certain that everyone well understood all items of the pain management protocol. A potential other weakness is that we did not reassess NRS inter-rater reliability for the current study, as it was found to be good in a previous study published in 2008 [17]. Repeated quality surveillance should be an integral part of pain management. Another issue can be that patients described in **Chapter 4** were asked to participate in this pain study before they underwent surgery, which may possibly lead to a selection bias, as patients may have had a particular reason (not) to participate in the study. On the other hand, the fact that the patients participated in this clinical trial resulted in a carefully prospectively monitored group of patients with detailed information on patient and perioperative characteristics.

Adherence to systematic pain assessment was evaluated in the patients participating

in the study on procedure-related pain (**Chapter 4**). Reminders via the patient data management system resulted in a 99% performance of scheduled pain assessments (**Chapter 6**). Adherence to unscheduled assessments guided by the flow chart of the pain protocol was not so adequate, however. For example, reassessments after unacceptable high pain scores (NRS ≥4) were recorded in only 15% of occasions of high pain scores. After 29% of high pain scores, neither pharmacological intervention nor reassessment followed. Reassessments may have taken place but remained unrecorded unfortunately. In the current analysis of adherence to the pain protocol, recording particular reasons to deviate were not documented. Future studies should provide space for recording explanations for these deviations as they may explain this apparent non-compliance and may help improve the protocol. Adherence could be enhanced when nurses are reminded by the patient data monitoring system to score pain at pre-set times and to suggest analgesic interventions by introduction of a decision support system, e.g., when an earlier follow-up is needed, when a pain score is higher than acceptable or when analgesia has to be tapered. This may further improve pain management for those who most urgently need it.

After the studies described in **Chapters 3 and 4** had been performed, standardized assessment of delirium using a modified Intensive Care Delirium Screening Checklist [18] has been implemented in the ICU of the St Antonius Hospital, like in many other ICUs. A next step would be an analgesia-based protocol combining the management of pain, delirium and anxiety, assessing pain, delirium and anxiety at least every 4 hours. In this respect, the need for sedation may be superfluous once anxiety due to pain and delirium is treated adequately. Besides, both analgesics and medication for delirium may have sedative effects. Although opioids used to treat pain can be protective against the development of delirium, opioids used at doses high enough to cause sedation, may increase the risk of delirium." [19].

Following the implementation of the pain management system, the outcome in terms of unacceptable pain was still 23% of all measurements (NRS ≥4). Furthermore, 46% of the patients experienced at least one painful event. As the measurement of these unacceptable pain moments may have coincided with a painful procedure, we further focused on the management of procedure-related pain.

***Procedural pain***

In **Chapter 4** the mean NRS scores for turning in bed and drain removal, which are well known painful procedures, were significantly lower than in previous studies [13, 14]. Pain management consisted of administration of morphine and paracetamol starting upon arrival in the ICU, guided by a pain protocol designed to prevent and treat pain at rest. Also the pain scores at rest, obtained before administration of the study medication, were much lower than in other studies. Patients with better baseline analgesia, experienced less pain during the potential painful procedure. Therefore, pain management protocols should cover both adequate analgesia for pain at rest and analgesia for procedural pain.

Still 25% of patients experienced unacceptable pain (NRS ≥4) during the intervention. This may be partly explained by particular aspects of the design of the study.

First, patients received either 2.5 or 7.5 mg morphine before the intervention. Despite randomization, it appeared that patients allocated to morphine 7.5 mg were significantly older and had a higher EURO score than patients assigned to morphine

2.5 mg. Others have shown that older surgical patients need lower doses of analgesics for pain relief than younger patients [20]. And indeed, in the group of patients allocated to morphine 7.5 mg, similar baseline NRS scores could be achieved with a lower baseline morphine consumption than in the patients allocated to morphine 2.5 mg. The administration of 7.5 mg of morphine to prevent procedural pain may have had a better analgesic effect than it would have had on younger and healthier patients. It may have been better to individualize morphine doses not only for pain at rest, but also for procedural pain, taking previous morphine requirements and age into account. The fact that analgesia in rest was well managed via the pain protocol for pain in rest may have prevented finding a difference in effect between morphine dosages. Second, morphine may not have been the optimal choice of drug. We opted for morphine because patients already received morphine in a continuous infusion and nurses in the postoperative wards in our hospital are familiar with morphine for drain removal. On the other hand, the relatively long time to peak effect (potentially more than 0.5 hours) requires advance planning of the procedure, which is not always feasible in an intensive care unit. During our study the median time elapsed between administration of morphine and the intervention was 31 minutes [interquartile range 26-35]. In this context, morphine may not have been the ideal analgesic. Analgesics with shorter time to peak effect such as fentanyl, sufentanil or alfentanil may be preferred over morphine for painful procedures.

An important question therefore is what the ideal treatment for procedural pain within the context of a pain management program for pain in rest would be. Systemic (morphine, fentanyl, sufentanil, remifentanil and ketorolac) [21-24] and locally applied (valdecoxib, bupivacaine) [21, 25, 26] medications have been shown effective during chest drain removal after cardiac surgery. In addition, non-pharmacological interventions, such as locally applied cold packs significantly reduced pain compared to placebo, although pain levels were still high (6.7 (±2.3)) [27]. Pain in the context of other typical ICU procedures, such as endotracheal suctioning, turning and wound care, has hardly been studied. Therefore, future studies comparing analgesics such as fentanyl, sufentanil and alfentanil for procedures that have been proven painful in ICU patients such as wound care and turning are necessary. As pain is currently seen within a biopsychosocial model in which psychological factors and social context are recognized as major modulators of the experience of pain, future studies should also consider the relationship between anxiety and previous experience of pain [24]. As such, studies evaluating anxiety and a combination of analgesics and pharmacological treatment of anxiety –with for example short acting benzodiazepines– during procedural pain may be considered. Non pharmacological approaches such as instruction, music etc can also be considered. Meanwhile, every health care worker should realize that medical and nursing procedures may hurt the patient. Assessment of pain during procedures is recommended by international guidelines [11], but several studies have shown that this in fact was done in less than 25% of cases [28, 29]. ICUs should therefore educate their staff on all aspects of a pain management protocol. Repeated training to guarantee acceptable intra-observer reliability is essential. Individualized treatment, taking into account individual risk factors for adverse effects, previous reactions on treatment and signs of anxiety, should be given before start of a procedure. Care should be taken to ensure sufficient dosing and perform the procedure at a time that corresponds to the drug's peak

effect [24]. Eventually, embedding a protocol for procedural pain within a protocol for the treatment of pain at rest could lead to less procedure-related pain.

***Chronic pain***

As described in **Chapter 7**, more than one third of patients participating in the study described in **Chapter 3** reported chronic thoracic pain one year later. Emergency surgery, emergency re-sternotomy, severe pain (NRS >4) on the third postoperative day, and female gender appeared to be independent predictors of chronic thoracic pain. Speculating on possible explanations, in the case of emergency surgery the central nervous system may not be able to adequately adapt to the new situation, resulting in a sensation of pain persisting beyond the usual healing period. Furthermore, in emergency re-sternotomy the repetitive tissue damage may exert an effect. Severe pain experienced on the third postoperative day may reflect tapering of analgesics in combination with increased strain on the fresh wound through mobilization. Continued stimulation of the sensory transmitting systems would then result in the persistence of pain. Lastly, gender differences in biological and psychosocial mechanisms in the reactions to painful stimuli and differences in response to treatment have been reported [30], but these would not explain why female gender was a predictor of chronic pain.

In the study described in **Chapter 8**, 20% of the patients reported chronic thoracic pain. BMI above 28 kg m2, age below 69 years, and remifentanil during cardiac surgery were independent predictors for chronic thoracic pain. As to possible explanations, surgery in an obese patient may be associated with both a larger damaged tissue area, and a longer retraction time [31]. Regarding the age association, Bruce and colleagues [31] have suggested that younger patients have a lower pain threshold and are less likely to accept pain and more likely to report pain. Older patients may be more likely to accept their limitations including pain as a function of age.

Unexpectedly, the use of remifentanil during surgery was strongly associated with chronic thoracic pain, in a dose-dependent manner. To the best of our knowledge, chronic thoracic pain has so far not been associated with remifentanil for cardiac surgery through sternotomy. Only one study has described a relation between chronic post surgical pain and the use of intraoperative remifentanil [15], but this concerned lung surgery via anterolateral or posterolateral thoracotomy. More literature is available on remifentanil in relation to pain experience or opioid requirement directly after surgery. Intra-operative remifentanil was also shown to be associated with hyperalgesia and acute opioid-tolerance in the direct postoperative period after major abdominal surgery [32]. The authors suggested that remifentanil exerts an effect on anti-analgesia systems and alterations of the N-methyl-D-aspartase (NMDA) receptor, as hyperalgesia was prevented by the administration of ketamine. Another theory suggests that the total amount of administered opioids, including remifentanil, is responsible for opioid-induced hyperalgesia in the acute postoperative period [33]. In our study too, remifentanil was administered in addition to other opioids.

Rauf et al described 20 patients undergoing off-pump coronary artery bypass surgery, receiving additional remifentanil infusion (0.1 μg $kg^{-1}$ $min^{-1}$) from induction until propofol was stopped after surgery [34]. Control patients received equal amounts of fentanyl at induction of anesthesia as well as an additional saline infusion. The study

patients needed more opioids than control patients in the first hour after remifentanil was discontinued, and nurses assigned higher pain to the study patients in the remifentanil group, albeit not significant. In contrast, Lahtinen et al [35] concluded that remifentanil had no effect on postoperative oxycodone consumption and did not enhance pain after cardiac surgery. Unfortunately in their study, chronic pain was not studied. In our study, postoperative pain scores and morphine consumption in the first 48 hours after surgery did not differ between patients who received remifentanil and those who did not.
The outcomes of these studies and our study warrant further research on remifentanil in relation to acute and chronic pain after cardiac surgery. Remifentanil has gained popularity for anesthesia in cardiac surgery and it would be noteworthy to ascertain whether remifentanil is a risk factor for the development of chronic pain.

How to explain the differences in risk factors for chronic pain and incidence of chronic pain between the studies described in **Chapters 7 and 8**? It is likely that to some extent they may be ascribed to differences in study design and inclusion criteria, like in other studies on chronic thoracic pain a (*see Introduction, Table 3*). First, only patients who had been able to communicate adequately while in the ICU after surgery were included in the study on acute and chronic pain (**Chapter 7**). In contrast, patients described in the study in **Chapter 8**, were also sent a questionnaire on chronic pain, even if they had been unable to communicate during the ICU study period. Second, the study described in **Chapter 7** also included patients after non-elective surgery, whereas patients described in **Chapter 8** all underwent elective surgery. Here, selection bias may have occurred as some patients, who were asked to participate in the study before surgery, may have had a specific reason to refuse participation in the study. Others, however, may have been eager to participate in a study expecting additional attention for pain and analgesia. Third, patients studied in the second study on chronic pain (**Chapter 8**) were more likely to receive remifentanil during surgery, included fewer women, were of higher age and underwent more complex surgery, than the patients studied before (**Chapter 7**).Furthermore, in the second study pain scores after discharge from the ICU were not analyzed, so we could not confirm “pain on postoperative day 3” in patients discharged earlier. Future trial designs for chronic pain after surgery should be uniform as suggested by Kehlet and Rathmell [36], enabling to compare studies and to improve understanding of the results. One of the suggestions is to perform procedure-specific prospective studies using pain-related functional impairment scales. The “ideal” study on chronic pain after surgery should include a number of elements, distinguish between preoperative elements, such as presence of pre-existing pain, neurophysiologic and psychological assessments; intraoperative elements, such as details on incision, handling of nerves and muscles); early postoperative elements, such as intensity, character and treatment of pain, neurophysiologic assessment; and late postoperative elements, such as pain intensity and character, psychological consequences and neurophysiologic assessment. In view of our findings in **Chapter 8**, we recommend that perioperative information should also include all administered medication and anaesthetics.
In our studies we used a questionnaire to be informed on the presence of chronic thoracic pain one year after surgery. The answers may have reflected just one point

in time, although we asked for the presence of pain in the two weeks preceding the questionnaire. In the second study in **Chapter 8**, we aimed to gain more information on the presence of chronic pain by asking patients to maintain a pain diary for two weeks one year after surgery. Unfortunately, only 5 out 18 patients with chronic pain (27%) actually kept this diary, so we could not use this information. To limit the time needed to complete the questionnaires we did not include all questions that may be of relevance for research on the development of chronic pain. This, we hoped, would ensure an acceptable response rate. And indeed, response rates were as high as 80%, whereas few patients kept diaries in the second study.

The time frame of one year after surgery was chosen to be able to compare our results with various other studies with incidences of chronic pain between 11 and18% [6, 9, 10, 37]. Future studies should consider earlier assessments, repeatedly for example at 3 month intervals, which would permit both to study the development of chronic pain and to intervene, if necessary, in the early postoperative phase.

Moreover, chronic pain after cardiac surgery deserves more attention in the whole perioperative process. Patients at risk for the development of chronic pain, such as younger patients, females and those with a high BMI should be identified and informed before surgery. Research on the prevention and treatment of chronic pain is warranted via clinical trials, starting with these high risk patients. The value of Quantitative Sensory Testing may be explored as a tool to objectively evaluate pain thresholds/sensitivity and its relation to the development of chronic pain. Moreover, the role of specific analgesics used during surgery, especially remifentanil, should be investigated via randomized clinical trials. A randomized clinical trial randomizing between remifentanil and fentanyl during cardiac surgery in the St. Antonius Hospital in Nieuwegein has started to enroll patients (EudraCT number 2013-000201-23). In the U.S. National Institutes of Health clinical trials registry (www.clinicaltrials.gov), various studies on the possible preemptive effects of perioperative pregabaline, which may show possibilities for prevention of chronic pain after cardiac surgery, are listed. Furthermore, pain should also be monitored after discharge from the ICU to the ward, when increased mobilization or tapering of analgesics may be contributing factors, and later in the outpatient setting at follow up. Thus, nurses and doctors taking care of patients after cardiac surgery should be informed on pain, pain management and the potential short and long term sequelae and further cooperation between anesthesiologists, cardiac surgeons, cardiologists and clinical pharmacologists is warranted.

## Take home messages and recommendations

Acute postoperative pain and chronic pain are, unfortunately, still important issues after cardiac surgery. Concerning acute postoperative pain, this thesis described that the implementation of a pain management program for pain *at rest* in patients in the ICU after cardiac surgery resulted in fewer periods of unacceptable pain – from 41% to 23%. At the same time this may have contributed to the relatively low *procedure-related* pain scores observed in our study. Pain management in our ICU may be refined by improving adherence to the protocol items, especially non-automated ones such as adjusting morphine upon low and high pain scores and reassessing the effects. It also appeared that cortisol, adrenalin and noradrenalin levels are not useful as markers to objectify procedure-related pain in patients in the ICU after cardiac surgery.

Furthermore, this thesis showed that *chronic* thoracic pain one year after cardiac surgery is also a significant problem. The following factors were found to be independent predictors of chronic thoracic pain: emergency surgery, re-sternotomy, severe pain (NRS ≥4) on the third postoperative day, female gender, remifentanil during cardiac surgery, age below 69 years, and a body mass index above 28 kg/$m^2$. These findings may inspire further research on the development, prevention and treatment of chronic pain.

Acute and chronic pain deserve the attention from all health professionals caring for patients before, during and (long) after cardiac surgery.

***Pain management in the ICU***

* A pain management program for treatment and prevention of pain at rest as well as procedural pain is warranted in ICU patients after cardiac surgery
* Reminders via a patient data management system to guide intervention based on pain scores may improve adherence to a pain management program and thereby refine pain management and reduce side effects.
* Recording explanations for deviating from the pain protocol may explain apparent non-compliance and may help to improve the protocol.
* An analgesia-based protocol combining the management of pain, anxiety and delirium may render the need for sedation superfluous once anxiety due to pain and delirium is treated adequately.

***Procedural pain***

* Every health care worker should realize that medical and nursing procedures may cause or increase pain.
* Assessment of pain during procedures is recommended by international guidelines.
* Prevention and treatment of procedural pain should be embedded in pain management programs in the ICU.
* Individualized treatment or prevention of procedural pain should include individual risk factors for adverse effects, previous reactions on treatment, signs of anxiety, and the individual drug's peak effect.
* Future studies comparing pharmacological strategies for procedural pain are necessary, as the ideal treatment for procedural pain is not fully established. Non-pharmacological strategies for relief of anxiety that may contribute to experiencing procedural pain may also be considered for research on procedural pain.

***Chronic pain***

* Chronic pain after cardiac surgery deserves more attention in the whole perioperative process involving awareness of the existence and possible development of chronic pain, and follow up and treatment of patients concerned.
* Patients should be informed of the risk of developing chronic pain before surgery.
* Nurses and doctors taking care of patients after cardiac surgery should be informed on pain and pain management after cardiac surgery.
* The "ideal" study to determine the significance of chronic pain after cardiac surgery should include a number of elements including preoperative, intraoperative (including all administered medication and anaesthetics), and early and late postoperative items.
* Research on remifentanil in relation to acute and chronic pain after cardiac surgery is warranted.
* Studies on chronic pain after cardiac surgery should consider earlier assessments than after one year, for example at 3 month intervals, which would permit both study of development of chronic pain and possibilities for intervention in the early postoperative phase.

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