

European Journal of Cardio-thoracic Surgery 40 (2011) 1309-1313

EUROPEAN IOURNAL OF CARDIO-THORACIC SURGERY

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Risk factors for chronic thoracic pain after cardiac surgery via sternotomy $\overset{\star}{\sim}$

Laura van Gulik^{a,*}, Linda I. Janssen^a, Sabine J.G.M. Ahlers^c, Peter Bruins^a, Antoine H.G. Driessen^b, Wim Jan van Boven^b, Eric P.A. van Dongen^a, Catheriine A.J. Knibbe^c

^a Department of Anesthesiology, Intensive Care and Pain Management, St. Antonius Hospital, Nieuwegein, The Netherlands Department of Cardiothoracic Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands ^c Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands

Received 17 January 2011; received in revised form 12 March 2011; accepted 21 March 2011; Available online 10 May 2011

Abstract

Objective: This study examines the influence of patient demographics and peri- and postoperative (<7 days) characteristics on the incidence of chronic thoracic pain 1 year after cardiac surgery. The impact of chronic thoracic pain on daily life is also documented. Methods: A prospective cohort study of 146 patients admitted to the intensive care unit after cardiac surgery via sternotomy was carried out. Pain scores (numeric rating scale 0-10) were recorded during the first 7 postoperative days. One year later, a questionnaire was used to evaluate the incidence in the 2 preceding weeks of chronic thoracic pain (numeric rating scale >0) associated with the primary surgery. Results: One year after surgery, 42 (35%) of the 120 responding patients reported chronic thoracic pain. Multivariate regression analysis of patient characteristics revealed that nonelective surgery, re-sternotomy, severe pain (numeric rating scale \geq 4) on the third postoperative day, and female gender were all independent predictors of chronic thoracic pain. In addition, the chronic sufferers reported more sleep disturbances and more frequent use of analgesics than their cohorts. Conclusions: We have identified a number of factors correlated with persistent thoracic pain following cardiac surgery with sternotomy. Awareness of these predictors may be useful for further research concerning both the prevention and treatment of chronic thoracic pain, thereby potentially ameliorating the postoperative quality of life of a significant proportion of patients. Meanwhile, chronic thoracic pain should be discussed preoperatively with patients at risk so that they are truly informed about possible consequences of the surgery. © 2011 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: ICU; Predictors; Chronic thoracic pain; Sternotomy; Women

1. Introduction

Chronic thoracic pain after cardiac surgery via sternotomy is a serious problem affecting 17-56% of patients [1-4]. Patients experiencing it report a significantly lower physical and mental health status compared with patients without chronic thoracic pain [5-7]. While the exact etiology of the pain is unknown, retrospective research suggests allergy to the osteosynthesis wire used for sternum closure [8], younger age [2,9], and the use of the internal mammary artery [10] to be risk factors. Few prospective studies, however, have investigated possible predictors of chronic thoracic pain after sternotomy and even fewer have evaluated the possible relationship between chronic and early postoperative pain [3]. This is of particular relevance as treatment is more

difficult once chronic thoracic pain has developed, leading to a considerably lower quality of health for these patients. The identification of good predictors of this negative outcome is therefore essential.

The present prospective study examined the influence of patient demographics and peri- and postoperative (<7 days) characteristics on the incidence of chronic thoracic pain 1 year after cardiac surgery. We concurrently recorded its negative impact on the daily lives of patients in terms of sleep disturbances and the use of analgesics.

2. Methods and materials

2.1. Patients

A prospective cohort study was performed of patients admitted to the St. Antonius Hospital Intensive Care Unit (ICU) after cardiac surgery via sternotomy during the period of 28 June 2006-18 August 2006. Patients were included if they were at least 18 years of age and were able to

 $^{^{*}}$ The study was performed at the 24-beds mixed ICU of the St. Antonius Hospital, Nieuwegein, The Netherlands.

^{*} Corresponding author. Address: Department of Anesthesiology, Intensive Care and Pain Management, St. Antonius Hospital, PO Box 3430, 3440 EM Nieuwegein, The Netherlands. Tel.: +31 88 3206725; fax: +31 88 3206749. E-mail address: lvangulik@hotmail.com (L. van Gulik).

Male/female	82/38
Age (years)	66.3 (27–86)
BMI (kg/m ²)	27.4 (±4.4)
Type of surgery	
CABG	54 (45%)
CABG and valve surgery	25 (21%)
Valve surgery	27 (22%)
Aortic surgery	14 (12%)
Diabetes	24 (20%)
EuroSCORE [21]	5 (0-12)

Table 1. Patient characteristics (N = 120)

Data are expressed as n (%), mean (\pm SD) or median (range).

communicate adequately after surgery, that is, if they were not neurologically damaged and able to communicate in either Dutch or English. Interventions included coronary artery bypass grafting (CABG), valve operations, combination of valve surgery and CABG and ascending aorta surgery (Table 1). The local hospital medical ethics committee approved both the protocol to systematically measure pain levels in the immediate postoperative period and the protocol to evaluate whether the same cohort of patients experienced chronic thoracic pain 10-12 months after surgery. The need for written informed consent was waived as the analysis of the data was fully anonymized.

2.2. Peri- and postoperative procedure and pain scores

In all patients, the anesthetic technique was standardized: midazolam or diazepam, fentanyl, and propofol were used for induction of anesthesia. Patients were paralyzed with pancuronium. Anesthesia was maintained with propofol, sevoflurane, nitrous oxygen, and either fentanyl or remifentanil, as preferred by the attending anesthesiologist. Pain scores were recorded both in the ICU and on the ward from day 0 until day 7 after surgery. Following local clinical

Table 2. Questionnaire on chro	nic thoracic pain 1	year after sternotomy.
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practice, pain levels were scored at least 3 times a day while in the ICU [11], and at least once a day while on the ward. Upon arrival in the ICU, patients received a continuous intravenous infusion of morphine (2 mg h^{-1}) in combination with acetaminophen (1 g orally or rectally 4 times a day), according to standard protocol [11]. Additional administration and tapering of morphine was executed by the attending intensivists and nurses based upon the reported pain scores. Pain was scored using the Numeric Rating Scale (NRS) in which '0' denotes no pain and '10' indicates the maximum pain imaginable. NRS \geq 4 was considered severe pain.

2.3. Pain scores 1 year after cardiac surgery

Ten to 12 months after cardiac surgery, all patients were contacted by telephone by one interviewer (LIJ) and asked about the presence of chronic thoracic pain and its possible impact on their daily lives by means of a questionnaire (Table 2). Chronic thoracic pain was defined as sternal and/or thoracic pain with an NRS > 0 in the 2 weeks preceding the interview that the patient identified as both post-surgical and different from possible earlier experiences with angina. Patients were asked to score their pain levels using the NRS for what they would consider the best (least pain) and worst (greatest pain) day in the 2 weeks prior. All questions referring to pain levels in the interview were based on the McGill Pain Questionnaire [12].

2.4. Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). Mann–Whitney *U*-test and the chi² test served to compare differences in non-parametric data and nominal data, respectively. In the univariate analysis, all possible variables were considered to compare patient groups with

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Question	Answer	
Have you experienced thoracic pain related to the surgery?	Yes/no	
What was the intensity of the pain on the best day? ^a	NRS 0–10	
What was the intensity of the pain on the worst day? ^b	NRS 0-10	
Where was the pain localized?	- Around the sternal wound	
	- Locally elsewhere on the thorax	
	- Diffuse pain in/on the thorax	
How would you characterize the pain?	- Aching	
	- Burning	
	- Other	
Have you experienced heart pain (the same as before the operation)?	Yes/no	
Have you used analgesics for the pain?	Yes/no	
Has the pain interrupted your sleep?	Yes/no	
Have you dreamed more often or differently since the operation?	Yes/no	
Has the pain limited your daily activities?	- Not at all	
	- A little	
	- A lot	
Did you resume your job?	- Yes, working full-time	
	- Yes, working part-time	
	- No, because of the pain	
	- No, different reason (retiremen	
Can you rate the quality of your health on a scale of $1-10$?	1-10	

The interview was based on the McGill Questionnaire [12] and concerned complaints experienced in the 2 weeks preceding the interview. ^a Day with the lowest pain scores in the 2 weeks before the interview.

 $^{\rm b}\,$ Day with the highest pain scores in the 2 weeks before the interview.

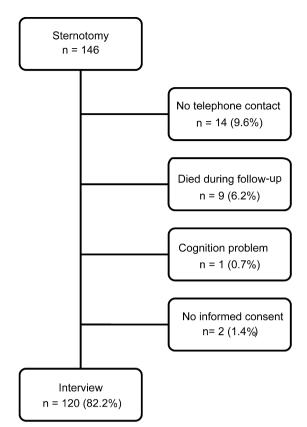


Fig. 1. Flow chart of study patients.

and without chronic thoracic pain. Multivariate logistic regression (MLR) analysis was then performed. Univariate predictors of outcome with a *p*-value <0.10 were selected for MLR analysis with stepwise backward elimination. The dependent variable was 'chronic thoracic pain' and possible predictors were used as independent variables. A sensitivity analysis was performed to preclude the influence of missing data (for 10 patients concerning pain scores on day 3) on the outcome of the MLR. The results are expressed as odds ratios and corresponding 95% confidence intervals (95% CIs). All

Table 3. Univariate	analysis of	predictors of	of chronic	thoracic pain.
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comparisons were two-tailed and a *p*-value <0.05 was considered statistically significant.

3. Results

Of a total of 146 patients, 120 were available and able to answer the questionnaire (Fig. 1). Patient characteristics for the responders are summarized in Table 1. One year after cardiac surgery, 42/120 patients (35%) reported thoracic pain (NRS > 0) in the preceding 2 weeks. On the worst day, 35 (29.2%) patients reported chest pain with an NRS \geq 4. Although most patients (91.7%) felt no pain (NRS = 0) on the best day, 7/10 patients with an NRS > 0 reported severe pain (NRS > 4).

Table 3 compares the peri- and postoperative characteristics of patients with and without chronic thoracic pain via univariate analysis. Based on this analysis, non-elective surgery, re-sternotomy during admittance, severe pain (NRS > 4) on postoperative day 3, and female gender were selected for multivariate logistic regression analysis with stepwise backward elimination. Multivariate analysis showed non-elective surgery, re-sternotomy during admittance, severe pain (NRS \geq 4) on postoperative day 3, and female gender to be independent predictors of chronic thoracic pain with corresponding odds ratios of 4.22, 3.38, 2.89, and 2.39, as shown in Table 4. The sensitivity analysis for the 10 missing pain scores on postoperative day 3 showed no difference in significance of the predictors of chronic pain resulting from the multivariate analysis.

The incidence of chronic pain was not different between the different types of surgery for the patients undergoing first-time surgery (104/120), that is, 19/50 (38%) for CABG, 8/22 (36%) for valve surgery, 6/19 (32%) for combined CABG and valve surgery, and 4/13 (31%) for aortic surgery (p < 0.95). Significantly more patients with chronic thoracic pain reported sleep disturbances due to the pain (15/42 (35.7%) vs 1/78 (1.3%), p < 0.001) and more frequent use of analgesics $(14/42 \ (33.3\%) \ vs \ 1/78 \ (1.3\%), \ p < 0.001)$ compared with those without chronic thoracic pain.

	No chronic pain (N = 78)	Chronic pain $(N = 42)$	Odds ratio [95% CI]	<i>p</i> -value
Patient characteristics				
Age	$\textbf{67.1} \pm \textbf{11.9}$	$\textbf{64.8} \pm \textbf{12.3}$	0.98 [0.95, 1.01]	0.22
Female gender	20 (25.6%)	18 (42.9%)	2.18 [0.98, 4.82]	0.05
EuroSCORE [21]	5 (0-12)	5 (0-11)	1.00 [0.87, 1.14]	0.94
Previous sternotomy	11 (14.1%)	5 (11.9%)	0.82 [0.27, 2.55]	0.74
Perioperative characteristics				
Non-elective surgery	6 (7.7%)	10 (23.8%)	3.75 [1.26,11.20]	0.01
Use of Internal mammary artery	38 (48.7%)	23 (54.8%)	1.27 [0.60,2.70]	0.53
Material closure of sternum:				
Steal	74 (94.9%)	39 (92.9%)	1	
Ethilon	4 (5.1%)	3 (7.1%)	0.72 [0.17, 3.06]	0.69
Co-analgesia with remifentanil	19 (24.4%)	13 (31.0%)	1.39 [0.61, 3.21]	0.44
Re-sternotomy during admittance	8 (10.3%)	10 (23.8%)	2.73 [0.99, 7.58]	0.05
Postoperative characteristics				
NRS \ge 4 on Day 1 (<i>N</i> = 114)	25 (32.1%)	14 (33.3%)	1.06 [0.47, 2.37]	0.90
NRS \geq 4 on Day 2 (N = 113)	25 (32.1%)	18 (42.9%)	1.80 [0.81, 4.00]	0.15
NRS \ge 4 on Day 3 (<i>N</i> = 110)	16 (20.5%)	15 (35.7%)	2.15 [0.93, 4.97]	0.07
Complicated healing of the sternum	5 (6.4%)	0	- · •	0.25

NRS: Numeric Rating Scale, Day: postoperative day. Values are reported as n (%), mean \pm SD or median (range).

1311

Table 4. Multivariate predictors of chronic thoracic pain 1 year after sternotomy.

	Odds ratio	[95% CI]	p-value
Non-elective surgery	4.22	[1.29, 13.84]	0.02
Re-sternotomy during admittance	3.38	[1.08, 10.54]	0.04
NRS \geq 4 on Day 3	2.89	[1.15, 7.23]	0.02
Female gender	2.39	[1.01, 5.65]	0.05

NRS: Numeric Rating Scale, Day: postoperative day.

Two-thirds of the 42 chronic pain sufferers localized their pain to the region of the sternotomy, whereas 28.6% felt it elsewhere in the thorax and 4.8% diffusely in a non-specified anatomical region in the thorax. Of these 42 patients, six (14.3%) stated that the pain had a minor or major influence on their daily lives. Six of them (14.3%) stopped working or worked only part-time because of the pain, six (14.3%) continued to work full time despite the pain, and 30 were retired. Angina was reported by 9/42 (21.4%) patients experiencing chronic pain and by 7/78 (9.0%) (p < 0.16) non-sufferers. There was no difference in patients without (n = 11, 14.1%) or with (n = 5, 11.9%) chronic pain who underwent a sternotomy previously.

4. Discussion

In this prospective study, we sought to identify risk factors for chronic thoracic pain after cardiac surgery via sternotomy as a first step toward early treatment and prevention hereof. To this end, we collected patient demographics, pain scores during the first 7 postoperative days, and various surgical variables. We then correlated these variables with the results of a follow-up telephone interview carried out 10-12 months after surgery. Chronic thoracic pain was reported by 35% of the 120 responding patients, with 29% of the 120 patients experiencing severe pain. With over 2 million procedures of open-heart surgery a year [13], chronic chest pain may be considered a serious complication with a high prevalence. Prevention of chronic thoracic pain is complicated by the fact that the pathophysiology and risk factors are not yet fully understood [14]. Kehlet explains the pathophysiology of chronic pain after surgery through reactive changes to nerves or to sensory transmitting systems in the spinal cord and brain that result in abnormal neural function with persistent postoperative pain.

The present study indicates that several peri- and postoperative patient characteristics correlate with the presence of chronic thoracic pain 1 year after cardiac surgery via sternotomy. In particular, non-elective surgery, resternotomy shortly after the original surgery, severe pain (NRS \geq 4) on day 3 after surgery, and female gender were strongly associated with chronic thoracic pain and can therefore be considered as risk factors for the condition.

Non-elective surgery was the strongest predictor for the development of chronic thoracic pain. To our knowledge, this has not been reported previously. In almost all studies on chronic thoracic pain after sternotomy, patients who underwent non-elective surgery were either excluded or analyzed separately. Our study, by contrast, included 16 (13%) patients who underwent non-elective surgery. Expanding upon the

explanation by Kehlet, it might be possible that in the case of emergency surgery, the central nervous system cannot adequately adapt to the new situation, resulting in a sensation of pain persisting beyond the usual healing period. This explanation is purely hypothetical, and further research into the relationship between emergency surgery and the development of chronic pain is warranted.

Non-scheduled emergency re-sternotomy during the hospitalization after the primary surgery was also a significant risk factor for chronic thoracic pain in our study. This may not have been fully appreciated in a previous study [2] due to a lower incidence of re-sternotomy; 3% (19 out of 625) of patients in that study versus 15% (18 out of 120) in the present report. Although the relatively high number of reoperations in the current study may render the group less representative, it is highly probable that only due to this high incidence, the association between re-sternotomy shortly after the primary surgery and chronic pain could be demonstrated. One explanation for the development of chronic thoracic pain in this group may be the repetitive tissue damage caused by the re-sternotomy. Although the repetition of a given operation has been recognized in general surgery as a risk factor for chronic pain [14], we observed no association between chronic thoracic pain and a previous medical history of sternotomy within our study group (16 patients or 13%).

Two retrospective studies [2,5] proposed that pain in the early postoperative phase, as indicated by a higher opioid consumption, was a risk factor for chronic thoracic pain but did not report pain scores. Two further studies found an association between higher pain scores on day 4 [3] or on day 5 [15] after surgery with persistent chest pain. We therefore prospectively recorded pain scores from patients in the ICU as soon as possible after surgery. Pain experienced on day 3 but not days 1 or 2 - after surgery correlated with the incidence of chronic thoracic pain. These findings are in line with the results of Jensen and Ho, who reported that satisfactory analgesia from epidural medication during surgery and during the first days after intervention could not prevent patients from developing chronic thoracic pain [16,17]. Pain endured during the first 2 postoperative days may thus not be the trigger for the development of chronic pain. By day 3, however, tapering of analgesics in combination with increased strain on the fresh wound through mobilization could lead to a continued stimulation of the sensory transmitting systems, resulting in the persistence of pain.

The impact of sex-based differences in physiological responses to noxious stimuli is an active area of research, as epidemiologic studies demonstrate that women are substantially more likely to suffer clinical pain than men. Women have been reported to experience more pain in the early postoperative phase after cardiac surgery and to experience more chronic pain after major thoracotomy [18,19]. In our present study, we found that a greater proportion of women than men suffered persistent chest pain after cardiac surgery via sternotomy (43% vs 26%, respectively). Other studies have not found this correlation [2,5,7], but the populations in those cases included at most 25% of women, as opposed to 32% in the present report, and may thus not have had the statistical power to detect the effect. Although sex

differences in biological and psychosocial mechanisms in reaction to painful stimuli and differences in response to treatment have been reported previously [20], the underlying causes of this gender bias remain unclear.

While the data sets of pain levels in the first postoperative week of both the ICU and ward were available as a result of a previous study [11], the telephone interviews were performed specifically for this study. Patients were asked to describe their symptoms for the 2 preceding weeks retrospectively. This approach thus provides a single point estimate of the incidence of chronic pain and is subject to failures of memory. It would be of interest to determine whether the same results would be obtained if patients were asked to maintain a diary and register pain scores prospectively during 2 weeks. While this approach could be incorporated in future studies, one advantage of the telephone interview is its high response rate, which is not subject to compliance issues (87.6% of the patients who were alive could be evaluated by this method). Another issue in the design of our study is the number of pain measurements in the first postoperative week. In the ICU, pain was scored three times a day but only once a day while on the ward. In light of our results showing that pain levels on postoperative day 3 are associated with chronic pain, it seems important to reconsider this low number of pain measurements per day on the ward. Lastly, the reader might wonder how to translate the numbers on chronic pain to his own specific group of patients, as the current studied group is quite heterogeneous. However, we presented the patients group in total, as the incidence of chronic pain was not significantly different between patients undergoing different kinds of surgery and with or without a sternotomy in their history.

In conclusion, our study shows that non-elective surgery, re-sternotomy shortly after the original surgery, severe pain on the third postoperative day, and female gender are independent predictors for the development of chronic thoracic pain. Awareness of these predictors may be useful for further studies, as the current knowledge regarding the etiology, prevention, and treatment of chronic thoracic pain is still too limited. Further research is mandatory, as the postoperative quality of life of a significant proportion of patients may potentially be ameliorated. Meanwhile, chronic thoracic pain should be discussed preoperatively with patients at risk, so that they are truly informed about possible consequences of their upcoming surgery.

Acknowledgments

We sincerely thank Ms Madeleine E. Lemieux, from the Department of Pediatric Oncology, Dana-Farber Cancer

Institute, Children's Hospital Boston and Harvard Medical School, Boston, USA, for the linguistic revision of our article.

References

- Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic poststernotomy pain after cardiac surgery—a prospective study. Acta Anaesthesiol Scand 2001;45:940–4.
- [2] Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic post-sternotomy pain. Acta Anaesthesiol Scand 2001;45:935–9.
- [3] Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006;105:794–800.
- [4] Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). Pain 2001;92:11–7.
- [5] Taillefer MC, Carrier M, Belisle S, Levesque S, Lanctot H, Boisvert AM, Choiniere M. Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. J Thorac Cardiovasc Surg 2006;131:1274–80.
- [6] Bruce J, Drury N, Poobalan AS, Jeffrey RR, Smith WC, Chambers WA. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. Pain 2003;104:265–73.
- [7] Gjeilo KH, Klepstad P, Wahba A, Lydersen S, Stenseth R. Chronic pain after cardiac surgery: a prospective study. Acta Anaesthesiol Scand 2010;54:70–8.
- [8] Fine PG, Karwande SV. Sternal wire-induced persistent chest pain: a possible hypersensitivity reaction. Ann Thorac Surg 1990;49:135–6.
- [9] Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chiolero R, von Segesser LK. Pain location, distribution, and intensity after cardiac surgery. Chest 2000;118:391–6.
- [10] Cohen AJ, Moore P, Jones C, Miner TJ, Carter WR, Zurcher RP, Lupkas R, Edwards FH. Effect of internal mammary harvest on postoperative pain and pulmonary function. Ann Thorac Surg 1993;56:1107-9.
- [11] van Gulik L, Ahlers SJ, Brkic Z, Belitser SV, van Boven WJ, van Dongen EP, Knibbe CA, Bruins P. Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. Eur J Anaesthesiol 2010;27:900-5.
- [12] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
- [13] Pezzella AT. Global aspects of cardiothoracic surgery with focus on developing countries. Asian Cardiovasc Thorac Ann 2010;18:299–310.
- [14] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.
- [15] King KM, Parry M, Southern D, Faris P, Tsuyuki RT. Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. Heart 2008;94:493–7.
- [16] Jensen MK, Andersen C. Can chronic poststernotomy pain after cardiac valve replacement be reduced using thoracic epidural analgesia. Acta Anaesthesiol Scand 2004;48:871–4.
- [17] Ho SC, Royse CF, Royse AG, Penberthy A, McRae R. Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. Anesth Analg 2002;95:820–3. table of contents.
- [18] Ochroch EA, Gottschalk A, Troxel AB, Farrar JT. Women suffer more short and long-term pain than men after major thoracotomy. Clin J Pain 2006;22:491-8.
- [19] Puntillo K, Weiss SJ. Pain: its mediators and associated morbidity in critically ill cardiovascular surgical patients. Nurs Res 1994;43:31–6.
- [20] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley 3rd JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447–85.
- [21] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.