The Effect of Anesthetic Technique on Cardiac Troponin-T and Systemic Inflammatory Response after Major Abdominal Cancer Surgery

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Abstract

Objectives: this study aims at assessment of acute inflammatory response; measured by high sensitivity C-reactive protein (hs-CRP), and myocardial injury; measured by serum cardiac troponin-T (Tn-T) in patients undergoing elective major abdominal cancer surgery with general anaesthesia or combined general and lumbar epidural anesthesia.

Methods: The study included 60 ischemic patients undergoing elective major abdominal cancer surgery with risk factor(s) like(history of myocardial infraction, diabetes, hypertension, obesity or heavy smoking)randomly assigned into 2 groups; 30 patients each to receive general anesthesia (G1) or combined general and epidural anesthesia (G2). Pain severity, time to first request of rescue analgesic, analgesic consumption, hemodynamics and side effects were recorded in first 72 hrs postoperative. Serum Tn-T and hs-CRP, ECG were assessed peroperatively and 1,2,3 days postoperativly also 12-lead ECGs were recorded before and 1,2,3 days after surgery.

Results: The mean VAS scores were significantly reduced in G2 allover time in comparison to G1 (p<0.05) except at 32hrs postoperatively. Mean time to first request for rescue analgesic was significantly prolonged in G2 compared to G1 (p=0.001). Mean morphine consumption was significantly reduced in G2 (p<0.001). Mean serum level of CPR increased in both groups. Mean level of serum troponin-T was significantly increased only in G1 compared to baseline value (p<0.05) with no significant difference between G1 and G2. There were 5 patients (16.6%) in G1 and 2 patients (6.6%) in G2 showed serum troponin-T level > 0.03ng/ml. Regarding ECGs changes there were 2 patients (6.6%) in G1 and one patient (3.3%) in G2 showed new ischemic changes postoperatively in the form of depressed ST segment >1mm.

Conclusion: The use of LEA with general anesthesia in high risk patients with ischemic heart disease undergoing major non-cardiac surgery is associated with less perioperative acute inflammatory response, less post-operative pain and can reduce the perioperative myocardial damage.

Introduction

Despite major advances in peri-operative management techniques, Myocardial Infarction (MI) remain the most common cause of postoperative morbidity and mortality in patient undergoing non-cardiac surgery [1]. Patients experiencing MI in the peri-operative period have a hospital mortality of 15%-25% [2-5]. The high mortality rate could be due to difficulty in detecting peri-operative MI because typical Electrocardiographic (ECG) changes and classical clinical symptoms are often absent [6]. As a growing number of elderly patients at risk of cardiac diseases are undergoing surgery, management of such complication will remain a significant clinical and economical challenge in the future.

The diagnosis of MI traditionally relies on rise and fall of cardiac enzymes such as Creatinine Kinase (CK), creatine kinase muscle and brain isoenzyme (CK-MB), Troponin I and T. With evidence of ischemia [clinical symptoms such as chest pain, supportive electrocardiographic changes] [3]. Troponin is more sensitive and specific, and correlate more closely with the amount of cardiac damage that occurs than CK-MB and is the favoured cardiac enzyme for testing. Troponin T has been found to have a higher positive and negative predictive values, sensitivity and specificity than either troponin I or CK-MB [7]. A rise in troponin T is not normally associated with musculoskeletal trauma [7,8]. Troponin levels begin to rise 4-6 h after the onset of symptoms, similar to CK-MB. Peak values occur 18-24 h after the onset of symptoms. Serum troponin persists for 7-14 days due to its slow release and degradation which allows for increased detection time window of cardiac events [9].

However, cardiac ischemia can be difficult to recognize in the post-operative period because of their silent nature and electrocardiograph changes may be hard to detect, often being non-q wave in origin. However, given there is no current consensus about what defines an infraction in the post-operative setting, perhaps all that can be deduced is that an elevation in troponin, for example, might indicate myocardial injury and provide prognostic information [3].

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute phase reactant protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some type of bacteria) in order to activate the complement system via C1Q complex to facilitate their destruction by the phagocytes [10].

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CRP is synthesized by the liver in response to factors released by adipocytes [11,12]. It is a member of the pentraxin family of proteins [11]. C-reactive protein was the first Pattern Recognition Receptor (PRR) to be identified [13].

The power of preoperative hs-CRP levels in predicting cardiac events in patients undergoing noncardiac surgery was stated in few reports with conflicting results [14]. The effect of using Lumbar Epidural Anesthesia (LEA) combined with general anesthesia on the acute inflammatory response as well as myocardial injury after major abodomino-pelvic surgery in cancer patients has not been studied before.

The primary end point of this study was to assess the influence of lumbar epidural anesthesia on postoperative inflammatory response and myocardial damage after abdominal cancer surgery.

Methods

After obtaining approval from hospital ethics committee and written informed consent from the patient, we enrolled 60 ischemic patients (identified from the patients history and from the ECG) scheduled for elective major abdominal cancer surgery with one or more of the following risk factors (previous history of MI, diabetes, hypertension, obesity (BMI >25 kg/m²) and/or heavy smoking).

Patients with polymyositis, serum creatinine over 200 mmol/L, platelet count <150×109 L, international normalized ratio >1.1, active neurological disease, cutaneous disorder at the epidural insertion site, and patients with infections or previous laparoscopic procedures in the last 2 weeks were excluded from the study.

All patients were evaluated preoperatively for the assessment of the operative risk by a cardiologist according to Lee index [15]. ECG was recorded and analyzed for the preoperative ischemic changes. Patients pre-operatively were instructed in how to evaluate their own pain using the VAS ranging from 0 to 10 (with 0=no pain and 10=the worst pain imaginable) [16]. Five mg oral diazepam was received night before surgery.

On arrival in the operative room, IV line was inserted and before an infusion of lactated ringers solution was started a venous sample was taken for serum troponin and hs-CRP, then using an on line research randomizer (http://www.randomizer.org), patients were randomly allocated into 2 groups; group 1 (G1) who received standard general anesthesia and group 2 (G2) who received standard general anesthesia and epidural anesthesia.

Anesthesia technique

Before induction of anesthesia an epidural catheter was placed at the L2-L3 intervertebral space under local anaesthesia with the use of a loss of resistance technique and that was followed by injection of 10 ml (100 mg) lidocaine 1%, 10 ml (25 mg) bupivacaine 0.25% and 5 mg morphine. General anesthetia was induced by fentanyl 1.5 µg/kg, propofol 2-3 mg/kg and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cisatracurium 0.5 mg/kg. Anesthesia was maintained by isoflurane 1-1.5 MAC, fentanyl 0.5 µg/kg and cisatracurium 0.03 mg/kg given when indicated. Patients were mechanically ventilated to maintain $ETCO_2$ between 33-36 mmHg.

Outcome definitions

Hypotension was defined as 15% decrease in systolic blood pressure from base-line. It was treated with IV boluses of ephedrine 0.1 mg/

kg and normal saline 5 ml/kg and the same doses were repeated if required. Bradycardia was defined as heart rate less than 40 bpm or as inappropriate slow heart rate despite hypovolemia. It was treated with atropine 1 mg IV. Hypoxia was defined as an oxygen saturation value <90%. At the end of the operation muscle relaxation was reversed by neostigmine 50µg/kg and atropine 10 µg/kg. Patients were extubated and transferred to Post Anesthesia Care Unit (PACU). Post operative analgesia comprised Patient-Controlled Analgesia (PCA) with an initial morphine bolus of 0.1 mg\kg once pain was expressed by the patient or if VAS score ≥ 3, followed by 1 mg boluses with a lockout period of 5 min.

Perioperative monitoring

All patients were monitored for 72 hours post-operatively in the

Variables	G1	G2	P-value
Age (years)	52.4 ± 10.8	54.2 ± 13.4	NS
Weight (kg)	77.4 ± 31.2	72.5 ± 9.7	NS
Height (cm)	162.5 ± 6.9	164.07 ± 1.47	NS
Male gender	16 (53%)	17 (57%)	NS
Type of surgery			
Open colectomy	11 (36.7%)	7 (23.3%)	NS
Open cystectomy	9 (30%)	12 (40%)	NS
Abdominoperineal resection	10 (33.3%)	11 (36.7%)	NS
Site of ischemia			
Lateral	5 (16.7%)	4 (13.3%)	NS
Inferior	15 (50%)	16 (53.3%)	NS
Anterior	6 (20%)	7 (23.3%)	NS
Mixed	4 (13.3%)	3 (10%)	NS
Risk factors			
1-Previous history of MI	1 (3.3%)	2 (6.6%)	NS
2-Heavy smoker	7 (23.3%)	6 (20%)	NS
3-DM	9 (30%)	8 (26.6%)	NS
4-Hypertension	12 (40%)	14 (46.6%)	NS
5-Obesity	5 (16.6%)	4 (13.3%)	NS
Lee index, Risk of MPCE % (95% CI)			
2, 2.4 (1.3–3.5)	22 (73%)	21 (70%)	NS
≥ 3, 5.4 (2.8–7.9)	8 (27%)	9 (30%)	NS
Duration of surgery (hours)	3.15 ± 0.87	3.30 ± 1.04	NS

Data are expressed as mean ± SD or number (%). CI, confidence interval; NS, Non significant; MPCE, major perioperative cardiac events

Table 1: Demographic data, clinical characteristics and duration of surgery.

VAS	G1	G2	P value
T0	4.06 ± 1.76	2.13 ± 0.43	<0.0001
4h Postoperative	2.53 ± 0.50	2.10 ± 0.30	<0.0001
8h Postoperative	2.43 ± 0.50	2.03 ± 0.18	<0.0001
12h Postoperative	3.01 ± 0.99	2.00 ± 0.00	<0.0001
16h Postoperative	2.96 ± 0.88	2.03 ± 0.41	<0.0001
20h postoperative	2.80 ± ± .88	2.03 ± 0.31	<0.0001
24h postoperative	2.90 ± 0.99	2.00 ± 0.26	<0.0001
32h postoperative	2.60 ± 0.72	2.46 ± 0.73	NS
40h postoperative	2.66 ± 0.92	2.20 ± 0.40	0.014
48h postoperative	3.03 ± 0.88	2.20 ± 0.48	<0.0001
60h postoperative	3.46 ± 0.89	2.30 ± 0.53	<0.0001
72h postoperative	3.03 ± 0.66	2.36 ± 0.49	<0.0001

Data are expressed as mean ± SD.To, immediate postoperative, NS, Non significant; h, hours

Table 2: VAS score postoperative at rest.

Variables	G1	G2	P^2value
CRP0	5.06 ± 1.81	5.02 ± 1.85	NS
CRP1	38.64 ± 13.64 P^1<0.0001	26.85 ± 12.60 P^1<0.0001	0.001
CRP2	31.62 ± 10.13 P^1<0.0001	29.84 ± 11.52 P^1<0.0001	NS
CRP3	33.68 ± 12.7 P^1<0.0001	28.80 ± 10.39 P^1<0.0001	NS

Data are expressed as mean ± SD.
P1, significant compared to baseline value; P2, significant between 2 groups; CRP0, CRP preopertive; CRP1, CRP at first day postoperative; CRP2, CRP at 2nd day postoperative; CRP3, CRP at 3rd day postoperative; NS, Non significant

Table 3: C-reactive protein mg/L.

Variables	G1	G2	P^2value
Serum troponin 0	0.017 ± 0.005	0.018 ± 0.005	0.278
Serum troponin 1	0.031 ± 0.04 P^1 0.04	0.019 ± 0.012 P^1 0.712	0.131
Serum troponin 2	0.03 ± 0.038 P^1 0.05	0.018 ± 0.010 P^1 0.951	0.110
Serum troponin 3	0.03 ± 0.039 P^1 0.047	0.019 ± 0.012 P^1 0.581	0.135

Data are expressed as mean ± SD.
P1, significant compared to baseline value; P2, significant between 2 groups; Troponin0, Troponin preopertive; Troponin 1, Troponin at first day postoperative; Troponin 2, Troponin at 2nd day postoperative; Troponin 3, Troponin at 3rd day postoperative

Table 4: Serum troponin T level ng/ml.

Variables	G1	G2	P-value
Nausea	10 (33.3%)	6 (20%)	0.042
Vomiting	8 (26.6%)	3 (10%)	0.007
Itching	2 (6.6%)	3 (10%)	NS

Data are expressed as number (%). NS; Non significant

Table 5: Side effects.

postoperative care unit: standard monitoring (Non Invasive Blood Pressure (NIBP), oxygen saturation (SO$_2$ %) and ECG), Central Venous Pressure (CVP) was inserted intraoperatively and measured intra- and postoperatively. VAS and post operative consumption of analgesic in the form of PCA morphine was recorded. Twelve-lead ECGs were recorded once a day for 3 days postoperatively. ECGs were assessed by a cardiologist, who was unaware of cTnT values or clinical symptoms and outcome. ECGs were assessed for new persistent Q waves >0.04 second and new ST segment depression or elevation (>0.1 mV at 0.08 second after the J point) in at least 2 contiguous leads of the same vascular territory. Transmural infarction was defined as new Q waves.

Laboratory measurements

Serum Tn-T and hs-CRP were assessed from venous samples obtained preoperatively and daily for 3 days postoperatively. Troponin T was measured in plasma using the electrochemiluminescence immuno assay "ECLIA" on Roche Elecsys 1010 immunoassay analyzer, with a reference value of <0.03 ng/ml [17]. Hs-CPR was detected immunoenzymometric assay include high affinity and specificity antibodies (enzyme and immobilized) with different and distinct epitope recognition in excess and native antigen with a reference value in the range of 0.068-8.2 mg/L [18].

Statistical Analysis

Analysis was performed using the SPSS soft ware version 17 (Chicago- USA). Data were expressed as mean ± SD or number (frequencies). Continous data were analyzed using independent sample T-test. Categorical data were compared using Cho-Square test with Fisher-Exact test. A P value <0.05 was considered statistically significant.

Results

There were no significant differences among groups in demographic data and clinical characteristics; type of surgery, site of ischemia, risk factors, Lee index for estimated preoperative risk and duration of surgery (Table 1). Also, there were no significant differences among groups in hemodynamic parameters measured during the intra and postoperative period; non invasive blood pressure, pulse rate, SO$_2$%, respiratory rate and CVP.

The mean VAS scores were significantly reduced in G2 at all time points studied in comparison to G1 except at 32 hours postoperative (Table 2). The mean time to first request for rescue analgesic requirement was significantly prolonged in G2 (16.13 ± 2.38 hours) in comparison to G1 (0.19 ± 0.07 hours), P=0.001. Total morphine consumption IV in the PACU in the 72 hours postoperativly was significantly reduced in G2 (13.75 ± 2.23 mg) compared to G1 (31.83 ± 7.75 mg), (p<0.001).

Serum level of hs-CRP showed a significant increase in both groups compared to baseline value at 1, 2, 3 days postopertive, with a significantly higher CRP level in G1 compared to G2 in day 1 postopertive (P=0.001) (Table 3).

However, serum level of troponin T was significantly increased in days 1, 3 postopertive in G1 but not in G2 compared to baseline value. However, there was no significant difference between G1 and G2 in troponin level all over the study period (Table 4). Five patients in G1 (16.6%) and 2 patients in G2 (6.6%) showed serum troponin T level >0.03 ng/ml. Regarding ECGs changes, 2 patients (6.6%) in G1 (with peak serum troponin level of 0.15 ng/ml and 0.18 ng/ml) and one patient (3.3%) in G2 (with peak serum troponin level of 0.10 ng/ml) showed new ischemic changes postoperatively in the form of depressed ST segment >1 mm. Nausea and vomiting but not itching were significantly less in G2 compared to G1 (Table 5).

Discussion

The present study found that combined general and epidural anesthesia was associated with less myocardial damage in the perioperative period, which was not the case using general anesthesia alone, also the use of LEA with general anesthesia was associated with less pain perception in all post operative time as assessed by VAS and increase in mean time to first request for rescue analgesic compared to general anesthesia alone. Levy et al. suggested that an increased troponin measurment after surgery is an independent predictor of mortality, particularly within the first year [19]. He also suggested that the burden of mortality is higher within the first year after surgery for patients with a postoperative troponin rise.

MI is the most common major peri-operative vascular complication [20]. It is associated with poor prognosis. However, asymtomatic perioperative MI is as strongly associated as symptomatic MI with 30 day mortality. Therefore, routine monitoring of cardiac biomarkers after surgery is essential. The highest risk for death after perioperative MI is in the first 48 hours; regardless of whether the patient experiences ischemic symptoms. This highlights the need to quickly diagnose and intensely monitor and implement treatments for perioperative MI, just as with nonoperative MI [21-23]. Recent studies suggest that a troponin or CK-MB measurment after surgery may independently

perdict a patient's intermediate (≤ 12 months) or long-term (more than 12 months) risk of death or a major cardiovascular event [24,25]. So some investigators have advocated monitoring perioperative troponin levels in patients undergoing noncardiac surgery to identify patients at risk [25,26]. Most patients with perioperative ischemia remain asymptomatic, and serum markers of myocardial ischemia, such as CK-MB and cardiac troponins, usually do not increase [27,28]. perioperative pain is a potent trigger for the stress response, activates the autonomic system [29]. and is thought to be an indirect cause of adverse effect on various organ systems, also it can activate sympathetic efferent nerves and increase heart rate, inotropy, and blood pressure, although activation of the sympathetic nervous system can increase indices of myocardial oxygen demand and result in ischemia [30-36]. The perioperative stress is associated with hypercogulability and the release of proinflammatory cytokines into the circulation caused by excessive activity of the neuroendocrine systems, particularly due to insufficient pain control in the postoperative period [37]. Vasospasm caused by this stress response impairs the coronary blood flow and consequently increased contractility of the myocardium disturbs the balance between the supply and the need for oxygen that may lead to outcomes ranging from myocardial ischemia to severe cardiac injury [27,38,39]. Tachycardia-induced increase in shear force on an atherosclerotic plaque, together with stress-induced hypercoagulation, may induce plaque rupture with subsequent myocardial hypoperfusion or ischaemia [26,27,38,39]. Both LEA and analgesia were found to reduce pulmonary and cardiac complications, and improve myocardial oxgenation and tissue reperfusion [40]. This has been attibuted to several related mechanisms among which is the LEA-induced analgesia that suppresses the hormonal and autonomous response to surgery by inhibiting afferent stimuli and modulating the neurohormonal pathways to produce anti- ischemic actions and decrease the severity of myocardial ischemia [39,41-43]. Cardiac morbidity was shown to be lower among patients undergoing major vascular surgery after the adminstration of general anesthesia combined with postoperative epidural analgesia compared to the adminstration of general anesthesia alone and postoperative systemic opioid analgesia [44]. A meta analysis revealed a significant reduction in venous thromboembolism in patients undergoing surgery for hip fracture under regional anesthesia compared with general anesthesia, but resulted in only a marginally better effect on early mortality [45].

In a study involving 60 patients with risk of Coronry Artery Disease (CAD) scheduled to undergo lower extremity surgery, patients were divided into three groups, one was given general anesthesia followed by intravenous patient-controlled analgesia, the second group was given lumber epidural anesthesia followed by lumbar epidural analgesia and the third group was given general anesthesia combined with intra and postoperative thoracic epidural analgesia. They found that plasma cardiac troponin I concentrations were within normal limits (<0.1 mg/L) in all the 3 groups and they concluded that opioids and local anesthetics also contributed to the positive effects of TEA and lumbar epidural anesthesia plus analgesia. For high-risk cardiac patients, epidural anesthesia followed by epidural postoperative analgesia should be preffered [46]. In the study of dogan et al. 40 patients were divided into two groups, regional anesthesia group and general anesthesia group, during elective cesarian delivery [47]. Serum troponin T, creatinine kinase-MB, and myoglobin levels were measured preoperatively (baseline) and at 1, 5, and 24 hours postoperatively. In all 40 cases, troponin T levels were in the normal range at all time points studied. In both groups, mean serum creatinine kinase-MB and myoglobin levels at one and 5 hours postoperatively were significantly

higher than baseline (p<0.05). These high CK-MB and myoglobin levels were returned to normal ranges at the end of the study. In a study of peyton et al. they found that there was no evidence that perioperative epidural analgesia significantly influences major morbidity or mortality after major abdominal surgery [48].Priestly et al. found no difference in troponin levels between General Anesthesia (GA) alone and GA plus High Thoracic Epidural Anesthesia (HTEA) groups, Loick et al. found significantly reduced troponin T levels in their HTEA group [49,50].

In this study, inflammatory response to surgery measured by hs-CRP significantly increased in both groups from the first postoperative day with persistent elevation till the third day. This inflammatory response was less with LEA compared to general anesthesia in the first post operative day. It is considered that hs-CRP is a general marker for inflammation. Recently, it was found that high hs-CRP levels were significantly associated with an increased risk of perioperative MI [51]. Ridker and colleagues, however, suggested, that extremely high hs-CRP levels (>10 mg/L) may be useful for predicting cardiovascular disease and thrombotic events [52]. Use of hs-CRP may add to risk estimation in a limited subset of individuals who are at intermediate predicted risk according to the Framingham risk score (which is a tool designed for adults aged 20 and older who do not have heart disease or diabetes). Low levels in high risk population don't reduce the risk and high levels in low risk groups don't increase the risk [45,53].Rashidinejad et al. in their study found a strong positive corrlation between serum hs-CRP and troponin. They also concluded that this positive correlation could be a useful biomarker for predicting extended myocardial involvement in patients with acute myocardial infarction [54].

Since many variables can elevate CRP, this is not a very specific prognostic indicator. Cancer is one of the situations that can raise serum hs-CRP and its level has been linked to the disease extent and possibility of recurrence [55]. This can explain the high baseline hs-CRP level in the studied patient groups.

Conclusion

The LEA combined with general anesthesia in high risk patients with ischemic heart disease undergoing major abdominal cancer surgery provided better pain relief, and a lower CRP in the first 3-days postoperatively than general anesthesia alone. Ischemic cardiac events related to serum troponin T and ECG were similar in both groups. Our findings suggest that LEA with general anesthesia is associated with less perioperative acute inflammatory response and can reduce the perioperative myocardial damage.

References

1. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, et al. (1990) Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 323: 1781-1788.

2. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, et al. (1993) The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 118: 504-510.

3. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW (1998) Myocardial infarction after noncardiac surgery. Anesthesiology 88: 572-578.

4. Kumar R, McKinney WP, Raj G, Heudebert GR, Heller HJ, et al. (2001) Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med 16: 507-518.

5. Shah KB, Kleinman BS, Rao TL, Jacobs HK, Mestan K, et al. (1990) Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. Anesth Analg 70: 240-247.

6. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, et al. (2005)

Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 173: 779-788.

7. Higham H, Sear JW, Sear YM, Kemp M, Hooper RJ, et al. (2004) Peri-operative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes--a study in high-risk surgical patients. Anaesthesia 59: 318-323.

8. Neill F, Sear JW, French G, Lam H, Kemp M, et al. (2000) Increases in serum concentrations of cardiac proteins and the prediction of early postoperative cardiovascular complications in noncardiac surgery patients. Anaesthesia 55: 641-647.

9. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (2007) Universal definition of myocardial infarction. J Am Coll Cardiol 50: 2173-2195.

10. Thompson D, Pepys MB, Wood SP (1999) The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 7: 169-177.

11. Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. J Clin Invest 111: 1805-1812.

12. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S (2005) Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 288: H2031-H2041.

13. Mantovani A, Garlanda C, Doni A, Bottazzi B (2008) Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 28: 1-13.

14. Martins OM, Fonseca VF, Borges I, Martins V, Portal VL, et al. (2011) C-Reactive protein predicts acute myocardial infarction during high-risk noncardiac and vascular surgery. Clinics (Sao Paulo) 66: 773-776.

15. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, et al. (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100: 1043-1049.

16. Watanabe S, Koyama K (1989) Visual analogue pain scale with convenient digitizer. Anesthesiology 71: 481.

17. Dawson-Bowling S, Chettiar K, Cottam H, Worth R, Forder J, et al. (2008) Troponin T as a predictive marker of morbidity in patients with fractured neck of femur. Injury 39: 775-780.

18. Ridker PM, Glynn RJ, Hennekens CH (1998) C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 97: 2007-2011.

19. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, et al. (2011) Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 114: 796-806.

20. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, et al. (2008) Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 371: 1839-1847.

21. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, et al. (1996) Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 57: 37-44.

22. Cohen MC, Aretz TH (1999) Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 8: 133-139.

23. Ellis SG, Hertzer NR, Young JR, Brener S (1996) Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 77: 1126-1128.

24. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, et al. (2003) Association of cardiac troponin, CK-MB, and myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 42: 1547-1554.

25. Oscarsson A, Eintrei C, Anskär S, Engdahl O, Fagerström L, et al. (2004) Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol Scand 48: 1071-1079.

26. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, et al. (2002) Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 106: 2366-2371.

27. Suttner S, Lang K, Piper SN, Schultz H, Röhm KD, et al. (2005) Continuous intra and postoperative thoracic epidural analgesia attenuates brain natriuretic peptide release after major abdominal surgery. Anesth Analg 101: 896-903.

28. McCann RL, Clements FM (1989) Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. J Vasc Surg 9: 583-587.

29. Kehlet H (1989) Surgical stress: the role of pain and analgesia. Br J Anaesth 63: 189-195.

30. Anand KJ, Hickey PR (1992) Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326: 1-9.

31. Mangano DT, Siliciano D, Hollenberg M, Leung JM, Browner WS, et al. (1992) Postoperative myocardial ischemia. Therapeutic trials using intensive analgesia following surgery. The Study of Perioperative Ischemia (SPI) Research Group. Ansthesiology 76: 342-353.

32. Beattie WS, Buckley DN, Forrest JB (1993) Epidural morphine reduces the risk of postoperative myocardial ischaemia in patients with cardiac risk factors. Can J Anaesth 40: 532-541.

33. Wasylak TJ, Abbott FV, English MJ, Jeans ME (1990) Reduction of postoperative morbidity following patient-controlled morphine. Can J Anaesth 37: 726-731.

34. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, et al. (1991) Perioperative myocardial ischemia in patients undergoing noncardiac surgery--I: Incidence and severity during the 4 day perioperative period. The Study of Perioperative Ischemia (SPI) Research Group. J Am Coll Cardiol 17: 843-850.

35. Hollenberg M, Mangano DT, Browner WS, London MJ, Tubau JF, et al. (1992) Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 268: 205-209.

36. Leung JM, O'Kelly BF, Mangano DT (1990) Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 73: 802-814.

37. Meissner A, Rolf N, Van Aken H (1997) Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. Anesth Analg 85: 517-528.

38. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, et al. (1990) Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 323: 1781-1788.

39. Rodseth RN, Padayachee L, Biccard BM (2008) A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. Anaesthesia 63: 1226-1233.

40. Schuster M, Gottschalk A, Freitag M, Standl T (2004) Cost drivers in patient-controlled epidural analgesia for postoperative pain management after major surgery. Anesth Analg 98: 708-713, table of contents.

41. Berendes E, Schmidt C, Van Aken H, Hartlage MG, Rothenburger M, et al. (2004) A-type and B-type natriuretic peptides in cardiac surgical procedures. Anesth Analg 98: 11-19, table of contents.

42. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, et al. (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347: 161-167.

43. Loick HM, Schmidt C, Van Aken H, Junker R, Erren M, et al. (1999) High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. Anesth Analg 88: 701-709.

44. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T (1987) Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66: 729-736.

45. Lloyd-Jones DM, Liu K, Tian L, Greenland P (2006) Narrative review: Assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med 145: 35-42.

46. Canan A, Celalettin D, Ednan B, Haci AA, Ali FE, et al. (2010) Effects of three different methods of anesthesia on the release of brain natriuretic peptid in patients with cardiac risk undergoing lower extremity surgery Turk J Med Sci 40: 405-414.

47. Rafi D, Alparslan B, Ayten B, Sedar E, Belkis T (2008) Frequency of electrocardiographic changes indicating myocardial ischemia during elective cesarean delivery with regional and general anesthesia: detection based on

continuous holter monitoring and serum markers of ischemia. J Clin Anesth 20: 347-351.

48. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, et al. (2003) Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. Anesth Analg 96: 548-548, table of contents.

49. Priestley MC, Cope L, Halliwell R, Gibson P, Chard RB, et al. (2002) Thoracic epidural anesthesia for cardiac surgery: the effects on tracheal intubation time and length of hospital stay. Anesth Analg 94: 275-282, table of contents.

50. Loick HM, Schmidt C, Van Aken H, Junker R, Erren M, et al. (1999) High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. Anesth Analg 88: 701-709.

51. Waurick R, Van Aken H (2005) Update in thoracic epidural anaesthesia. Best Pract Res Clin Anaesthesiol 19: 201-213.

52. Ridker PM, Cook N (2004) Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation 109: 1955-1959.

53. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M (2009) C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med 151: 483-495.

54. Rashidinejad H, Hosseini SM, Moazenzadeh M, Azimzadeh BS, Mirzaeipour F, et al. (2012) Relationship between serum level of high-sensitive C-reactive protein and extension of myocardial involvement in patients with acute myocardial infarction. Rom J Intern Med 50: 211-215.

55. Woo Y, Hyung WJ, Obama K, Kim HI, Pak KH, et al. (2012) Elevated high-sensitivity C-reactive protein, a marker of advanced stage gastric cancer and postgastrectomy disease recurrence. J Surg Oncol 105: 405-409.