



Perioperative Cardiac Troponin I Levels in Patients Undergoing Total Hip and Total Knee Arthroplasty: A Single Center Study

Mir Mohammad Taghi Mortazavi¹, Jafar Ganjpour Sales², Masoud Nouri-Vaskeh^{3,4,*}, Masoud Parish^{1,**} and Salar Abdolhosseynzadeh⁵

¹Department of Anesthesiology and Critical Care, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

²Department of Orthopedics Surgery, Shohada Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

³Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁵Tabriz University of Medical Sciences, Tabriz, Iran

*Corresponding author: Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Postal Code: 5166614756, Tabriz, Iran. Email: mnvaskeh@tbzmed.ac.ir

**Corresponding author: Department of Anesthesiology and Critical Care, Faculty of Medicine, Tabriz University of Medical Sciences, Postal Code: 5166614756, Tabriz, Iran. Email: masoudparish@yahoo.com

Received 2018 September 12; Revised 2018 October 20; Accepted 2018 November 10.

Abstract

Background: Cardiac injury is one of the significant perioperative complications in major orthopedic surgeries and its early diagnosis is useful in the reduction of postoperative comorbidity. The cardiac troponin is a sensitive and specific biomarker for detecting this damage.

Objectives: The aim of this study was to evaluate the levels of perioperative cardiac troponin I (cTnI) before and after arthroplasty in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA). The effects of related variables and probable major cardiac complications were evaluated in this study.

Methods: For one year, in a prospective, cross-sectional study, the serum levels of cTnI before and 48 hours after arthroplasty were evaluated in 52 patients. Possible contributing factors including age, gender, body mass index (BMI), daily activity, history of hospitalization due to cardiovascular diseases, underlying illness, and medications were recorded. The Chi-square test, Pearson correlation, and Spearman test were used to examine the relationship between variables.

Results: The mean cTnI increased significantly after arthroplasty ($P < 0.001$). There was no significant relationship between age ($P = 0.708$), gender ($P = 0.225$), BMI ($P = 0.195$), daily activity (0.441), underlying illness ($P = 0.244$), and cTnI levels after arthroplasty. Linear regression showed BMI was significantly correlated with troponin changes ($P = 0.006$). Five patients had heart palpitations and one had chest pain, but none of the patients had any findings in favor of cardiac injury.

Conclusions: cTnI levels after THA and TKA increased significantly, but this elevation was in the normal range. In addition, none of them had a new cardiac complication after arthroplasty.

Keywords: Troponin I, Replacement Arthroplasty, Postoperative Complication, Orthopedics

1. Background

As our population age increases, the need for arthroplasty surgery increases physiological stress (1-3). In addition, arthroplasty in the elderly is more likely to lead to increased morbidity due to multiple factors (4, 5). Despite good surgical outcomes, major perioperative complications may occur. There are reports of more incidences of cardiac complications in these patients (6). The incidence of perioperative acute myocardial infarction (MI) was reported between 0.25% in total hip arthroplasty (THA) and 0.18% in total knee arthroplasty (TKA) (7). Moreover, in recent studies, the incidence of perioperative myocardial in-

jury in non-cardiac surgery was 16% and the majority of them (82%) had not any ischemic symptom. Typical chest pain was shown in only 6% of the patients (8).

Perioperative cardiac complications represent a major concern after orthopedic surgery. One of the diagnostic methods is the evaluation of cardiac troponin I (cTnI) serum level, which is used as a marker for tissue damage in the MI (9). In clinical practice, increasing serum levels of cTnI is a criterion used for the detection of cardiac injury (10). Nevertheless, this is also affected by non-cardiac diseases and non-ischemic heart diseases (11). The troponin biomarker is one of the proteins controlling the reaction

between actin and myosin by calcium (12). This protein has cytosolic and structural deposits, but most of the reserves are of a construction type. The initial release of troponin in cardiac injuries is thought to be cytotoxic (13). With the proliferation of ischemia, the destruction of actin and myosin filaments occurs, leading to the release of troponin (14). Conditions such as septic shock can reduce ventricular performance. It can increase the cTnI levels without causing necrosis by presenting the permeability of the myocyte membrane and ventricular dysfunction (15).

Regarding the predictive role of cTnI in perioperative cardiac damage and due to inadequate data about the effect of related variables, this study was designed to measure the level of cTnI before and after arthroplasty for one year in patients undergoing THA and TKA at an orthopedic center. We also examined the related factors affecting cTnI levels and major cardiac complications associated with cTnI changes.

2. Methods

After receiving an approval from the Local Research Ethics Committee (number IR.TBZMED.REC.1396.484) and obtaining informed consent for inclusion from all subjects before they participated in the study, all patients older than 40 years of age who were undergoing TKA and THA at an orthopedic center between September 2016 and August 2017 were enrolled. They included 52 patients, comprising 20 unilateral total knee and 32 total hip arthroplasty cases. The exclusion criteria were the patients with end-stage renal disease, acute MI, recent MI, atrial fibrillation, hypertrophic cardiomyopathy, tachycardia, rhabdomyolysis, and strenuous exercise that might change the cTnI levels. After confirming the indication of arthroplasty (16, 17), a medical history including underlying illnesses, drug history, history of hospitalization due to cardiovascular disease, daily activity, and history of previous surgery were recorded. Several weeks before scheduled arthroplasty, the patients had a preoperative anesthetic evaluation. General anesthesia was used in all patients with midazolam (Aburaihan, Iran) 0.03 mg/kg and fentanyl (Rottexmedica, Germany) 1 - 2 μ g/kg. For induction, propofol (Fresenius Kabi, Austria) 2 mg/kg and atracurium besylate (Aburaihan, Iran) 0.5 mg/kg were taken and the intubation was performed. During the surgery, given the hemodynamic conditions, the patients had an intravenous infusion at 0.05 - 0.2 mcg/kg/min remifentanyl (Hameln, Germany). Isoflurane (AbbVie Ltd., UK) 0.6 - 0.8% and nitrous oxide plus oxygen gas (50%:50%) were utilized along with remifentanyl for maintenance of anesthesia. For analgesia after arthroplasty, oral acetaminophen (Arya, Iran) and intravenous morphine sulfate (Darou Pakhsh, Iran) were pre-

scribed as needed. During the arthroplasty, patients underwent non-invasive blood pressure (NIBP) and cardiac monitoring. Therapeutic measures were taken if the changes in blood pressure were more than 30% of the basic level. In the patients under TKA, the duration of the closure of the tourniquet and possible hemodynamic changes were recorded. cTnI values of higher than 1.3 ng/mL were considered positive and the assay sensitivity was 0.030 ng/mL. Before and after arthroplasty, electrocardiogram (ECG) was performed and changes were evaluated by a cardiologist. The cTnI level was evaluated at the beginning of the entry to the post-anesthesia care unit, as well as at one and six hours after arthroplasty. Patients with elevated levels of cTnI were assessed continuously; the cases with increased levels, ECG changes, or angina symptoms presented further action taken by the cardiologist. Patients with evidence of MI were transferred to the cardiac care unit (CCU) for additional workup. In the postoperative period, more evaluation would be done in case of signs and symptoms of deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). To compare troponin changes before and after arthroplasty, troponin levels were compared before and 48 hours after arthroplasty.

Data were analyzed using IBM SPSS version 23. The Kolmogorov-Smirnov test and histograms were used to check the normality of data distribution. In order to investigate the relationship between variables, Chi-square, Pearson Correlation, and Spearman tests were used. The Independent Sample *t*-test and Paired Sample *t*-test were used to compare the mean of the data. Multi-variable Linear Regression analysis was used to modulate confounding variables. In this study, the $P < 0.05$ was considered significant.

3. Results

The demographic and preoperative clinical findings are summarized in Table 1. The mean cTnI level before arthroplasty was 0.14 ± 0.05 ng/mL: 0.15 ± 0.05 ng/mL in THA and 0.12 ± 0.04 ng/mL in TKA patients. There was no significant difference in the mean preoperative cTnI level between the two groups ($P = 0.270$). The mean cTnI level after arthroplasty was 0.3 ± 0.17 ng/mL with a range of 0.1 - 0.8; this value was 0.33 ± 0.19 ng/mL in THA and 0.25 ± 0.11 ng/mL in TKA patients. The Paired Sample *t*-test showed that the mean cTnI level significantly increased 48 hours after arthroplasty compared to the preoperative level ($P < 0.001$). In addition, Independent Samples *t*-test showed that there was no significant difference in the cTnI level between the two groups after arthroplasty ($P = 0.073$). There were no out-of-range changes in the hemodynamic status. Before arthroplasty, ECG was normal in 48 cases and in two cases, there was tall T; one case of Q wave in lid 3 and one

case of poor R progression without any changes were observed after arthroplasty. Six patients were admitted to the intensive care unit (ICU) after arthroplasty. Other patients did not need to be admitted to the ICU or CCU. Six patients had a cardiac complication after arthroplasty comprising five cases of heart palpitation and one case of chest pain; none of them had any changes in ECG and echocardiography or excessive increase in cTnI levels. Moreover, none of the patients had signs and symptoms of DVT or PTE. There was no significant correlation between age and cTnI levels after arthroplasty ($P = 0.474$). The mean cTnI level after arthroplasty was 0.3 ± 0.15 ng/mL in males and 0.3 ± 0.18 ng/mL in females; the between-gender difference was not significant ($P = 0.900$). In addition, the correlation between BMI and cTnI changes after arthroplasty was not significant ($P = 0.195$). In the evaluation of the correlation of daily activity with cTnI levels, in patients with a sedentary lifestyle, the mean postoperative cTnI level was 0.24 ± 0.34 ng/mL and in patients with an active life, it was 0.29 ± 0.14 ng/mL ($P = 0.44$). The mean postoperative cTnI level in patients with a history of hospitalization due to cardiovascular diseases was 0.2 ± 0.09 ng/mL and in patients without the history, it was 0.31 ± 0.17 ng/mL ($P = 0.553$). The linear regression test showed the BMI is the only variable that could affect cTnI levels after arthroplasty (Table 2).

4. Discussion

Due to postoperative analgesia and hypnotic drugs, MI may be clinically silent. The underlying diseases such as diabetes mellitus can trigger the asymptomatic MI. Some previous studies reported the different sensitivities for ECG with the highest sensitivity of 73% for MI detection (18, 19). In addition, the enzyme levels evaluation is a noninvasive, safe, and sensitive method for the detection of cardiac complications.

According to the results of this study, the mean cTnI level significantly increased 48 hours after arthroplasty compared to the preoperative level; however, in all of the patients, the values did not exceed the normal range. Based on the diagnostic criteria for MI (20), the results of the present study suggested that none of the THA and TKA patients had a new perioperative cardiac complication.

The cTnI levels elevation after non-cardiac surgery was reported by Urban et al. (21). Inconsistent with the present study findings, despite that the mean cTnI levels after non-cardiac surgery increased, none of them had MI.

In a study of cTnI levels in patients undergoing orthopedic surgery with risk factors for coronary artery diseases, only five patients had an increasing cTnI levels and 11 patients had creatine kinase-MB elevation among 85 patients

Table 1. Preoperative Demographic and Clinical Data

All THA,TKA Procedure (N = 52)	Values ^a
Age (y)	63.9 \pm 10.8 (min = 40, max = 79)
40 - 49	7 (21.9)
50 - 59	5 (9.6)
60 - 69	22 (42.3)
70 - 79	18 (34.6)
Gender (M/F)	20/32 (38.5/61.5)
Weight (kg)	78.4 \pm 9.8 (min = 58, max = 95)
BMI (kg/m²)	29.84 \pm 4.17 (min = 22.38, max = 38.78)
Type of surgery	
THA	32 (61.5)
TKA	20 (38.5)
Medical history	
DM	12 (23.1)
HTN	26 (50)
IHD	6 (11.5)
COPD	3 (5.8)
Medication	
Metformin	6 (11.5)
Insulin	4 (7.7)
ARB	22 (42.3)
Hypolipidemic agents	7 (13.4)
Surgery history	19 (36.5)
Active/sedentary lifestyle	43/9 (82.7/17.37)

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary diseases; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; THA, total hip arthroplasty; TKA, total knee arthroplasty.

^aValues are expressed as mean \pm SD or number (percentages) unless otherwise indicated.

(22). In contrast, in our study, we found the cTnI levels in the normal range in all of the 52 patients.

One of the previous well-designed studies in patients with hip surgery was performed by Ausset et al. (23) showing that 12.5% of patients had elevated cTnI levels during admission. In addition, 45% of patients with elevated cTnI during follow-up suffered from a major cardiac event. In contrast, in our study, none of the patients had a cardiac event but troponin levels significantly increased after arthroplasty although they were in the normal range. Our study is limited in the long-term outcome because we did not follow up patients after discharge from the hospital.

In another study, the incidence of cTnI elevation in older patients was 52.9% and after one year, 32.4% sustained a cardiac complication (24).

Table 2. Factors Affecting Troponin Changes After Arthroplasty

Variables	Beta Coefficient	P Value
Age	-0.625	0.708
Gender	0.302	0.225
BMI	0.678	0.006
Disease history	0.308	0.244
Medication	0.475	0.125
Admission history	-0.478	0.208
Surgical type	-0.43	0.102
Active life style	0.095	0.697
Preoperative troponin	0.723	0.723

Abbreviation: BMI, body mass index.

In a similar observation by Chong et al. (25) on the troponin levels and cardiac outcome in orthopedic surgeries, the incidence of troponin elevation pre and postoperatively was 15.5% and 37.4%, respectively, the majority of which was asymptomatic. The first day after surgery was the common day for postoperative troponin elevation. However, 5.7% had symptoms of myocardial ischemia. In terms of postoperative ECG change, the correlation between ECG change and troponin elevation was poor. The average age of patients in that study was about two decades higher than that in our study, and only half of the patients had major orthopedic surgery. Similarly, there was no relationship between demographic factors and troponin levels. These findings are similar to those of previous studies. As Ausset et al. (23) reported, there was no meaningful relationship between increased troponin levels, the age, and the incidence of postoperative cardiac complications in patients undergoing hip surgery.

A recent single-center study (26) of the cardiac event in patients undergoing THA, TKA, and posterior spinal fusion showed that 20.6% of patients at risk of postoperative cardiac ischemia had elevated cTnI levels; 8.7% of patients had a myocardial injury and 1.2% of these patients (10/805) had a postoperative MI. Although this study just evaluated the patients at risk of postoperative myocardial ischemia, the significant troponin elevation confirms our findings of the postoperative elevation of cardiac troponin. In addition to the differences in inclusion criteria, the challenging differences between these two studies have the opposite effect of risk factors on troponin levels. Therefore, in our study, among the demographic factors, only the relationship between BMI and troponin was significant, but in this study, age had a significant relationship with troponin.

This increase in troponin levels can be due to other features requiring further investigation. As previous studies

have shown, there are several reasons for increasing troponin without necrosis, including tachycardia and bradycardia (27), atrial fibrillation (28), septicemia (29), hypertrophic cardiomyopathy (30), coronary vasospasm (31), stroke and subarachnoid hemorrhage (32), rhabdomyolysis (33), renal failure (34), aortic dissection (35), infiltrative diseases such as amyloidosis (36), drug poisoning such as Adriamycin (37), and hypovolemia (33). According to the present study, all increases in cTnI levels after arthroplasty are not necessarily attributed to myocardial injury. As six patients studied had symptoms of heart disease, further investigation showed that they had no cardiac problems. Therefore, arthroplasty can be added to the factors listed above as a troponin enhancer.

However, this study has some limitations. Follow-up of the patients was not long enough. Moreover, increased troponin without clinical findings needs to be studied more physiopathologically. The assay used in some studies was highly sensitive to cTnI, but the assay used in this study is a routine assay in our hospitals across the country; thus, the results can be more practical. Although our data were collected at a single center, the study setting was an academic and referral hospital. It is suggested conducting the analysis of the cTnI according to the patient's condition and by considering other effective factors.

4.1. Conclusion

The findings of this study showed that troponin levels increased significantly after THA and TKA, but all of them were in the normal range. The postoperative increase of cTnI in the normal range was not associated with clinical sign and symptoms. No ECG changes were observed in any of the patients after surgery, and none of them developed a cardiac injury. Only was BMI associated with troponin changes after surgery.

Footnotes

Authors' Contribution: Study concept and design: Mir Mohammad Taghi Mortazavi, Jafar Ganjpour Sales and Salar Abdolhosseynzadeh; acquisition of data: Mir Mohammad Taghi Mortazavi, Jafar Ganjpour Sales, Masoud Nouri-Vaskeh, Masoud Parish, and Salar Abdolhosseynzadeh; analysis and interpretation of data: Mir Mohammad Taghi Mortazavi, Jafar Ganjpour Sales, Masoud Nouri-Vaskeh, and Masoud Parish; drafting of the manuscript: Masoud Nouri-Vaskeh, Masoud Parish, and Mir Mohammad Taghi Mortazavi; critical revision of the manuscript for important intellectual content: Mir Mohammad Taghi Mortazavi, Jafar Ganjpour Sales, Masoud Nouri-Vaskeh, Masoud Parish, and Salar Abdolhosseynzadeh; statistical anal-

ysis: Masoud Nouri-Vaskeh and Masoud Parish; administrative, technical, and material support: Jafar Ganjpour Sales, Mir Mohammad Taghi Mortazavi, and Salar Abdolhosseynzadeh; study supervision: Mir Mohammad Taghi Mortazavi.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Considerations: Ethical approval code: IR.TBZMED.REC.1396.484.

Funding/Support: No funding was received for this study.

References

- Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among medicare beneficiaries, 1991-2010. *JAMA*. 2012;308(12):1227-36. doi: 10.1001/2012.jama.1153. [PubMed: 23011713]. [PubMed Central: PMC4169369].
- Rahimzadeh P, Imani F, Sayarifard A, Sayarifard S, Faiz SH. Ultrasound-guided fascia iliaca compartment block in orthopedic fractures: Bupivacaine 0.2% or 0.3%? *Med J Islam Repub Iran*. 2016;30:433. [PubMed: 28210598]. [PubMed Central: PMC5307510].
- Guimaraes-Pereira L, Valdoleiros I, Reis P, Abelha F. Evaluating persistent postoperative pain in one tertiary hospital: Incidence, quality of life, associated factors, and treatment. *Anesth Pain Med*. 2016;6(2):e36461. doi: 10.5812/aapm.36461. [PubMed: 27252908]. [PubMed Central: PMC4886451].
- Rahimzadeh P, Imani F, Faiz SHR, Entezary SR, Zamanabadi MN, Alebouyeh MR. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. *Clin Interv Aging*. 2018;13:73-9. doi: 10.2147/CIA.S147757. [PubMed: 29379278]. [PubMed Central: PMC5757490].
- Lee KH, Kim JY, Kim JW, Park JS, Lee KW, Jeon SY. Influence of ketamine on early postoperative cognitive function after orthopedic surgery in elderly patients. *Anesth Pain Med*. 2015;5(5):e28844. doi: 10.5812/aapm.28844. [PubMed: 26587403]. [PubMed Central: PMC4644306].
- Viola J, Gomez MM, Restrepo C, Maltenfort MG, Parvizi J. Preoperative anemia increases postoperative complications and mortality following total joint arthroplasty. *J Arthroplasty*. 2015;30(5):846-8. doi: 10.1016/j.arth.2014.12.026. [PubMed: 25669131].
- Menendez ME, Memtsoudis SG, Oppeter M, Boettner F, Gonzalez Della Valle A. A nationwide analysis of risk factors for in-hospital myocardial infarction after total joint arthroplasty. *Int Orthop*. 2015;39(4):777-86. doi: 10.1007/s00264-014-2502-z. [PubMed: 25172363].
- Puelacher C, Lurati Buse G, Seeberger D, Szagary L, Marbot S, Lampart A, et al. Perioperative myocardial injury after noncardiac surgery: Incidence, mortality, and characterization. *Circulation*. 2018;137(12):1221-32. doi: 10.1161/CIRCULATIONAHA.117.030114. [PubMed: 29203498].
- Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: A cohort study. *Lancet*. 2015;386(10012):2481-8. doi: 10.1016/S0140-6736(15)00391-8. [PubMed: 26454362]. [PubMed Central: PMC4765710].
- Masson S, Latini R, Mureddu GF, Agabiti N, Miceli M, Cesaroni G, et al. High-sensitivity cardiac troponin T for detection of subtle abnormalities of cardiac phenotype in a general population of elderly individuals. *J Intern Med*. 2013;273(3):306-17. doi: 10.1111/joim.12023. [PubMed: 23216903].
- Oberweis BS, Nukala S, Rosenberg A, Guo Y, Stuchin S, Radford MJ, et al. Thrombotic and bleeding complications after orthopedic surgery. *Am Heart J*. 2013;165(3):427-33. doi: 10.1016/j.ahj.2012.11.005. [PubMed: 23453114]. [PubMed Central: PMC3595114].
- Shanmugam NR, Muthukumar S, Tanak AS, Prasad S. Multiplexed electrochemical detection of three cardiac biomarkers cTnI, cTnT and BNP using nanostructured ZnO-sensing platform. *Future Cardiol*. 2018;14(2):131-41. doi: 10.2217/fca-2017-0074. [PubMed: 29388803].
- Lindert S, Cheng Y, Kekenes-Huskey P, Regnier M, McCammon JA. Effects of HCM cTnI mutation R145G on troponin structure and modulation by PKA phosphorylation elucidated by molecular dynamics simulations. *Biophys J*. 2015;108(2):395-407. doi: 10.1016/j.bpj.2014.11.3461. [PubMed: 25606687]. [PubMed Central: PMC4302190].
- Apple FS, Collinson PO; Ifcc Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem*. 2012;58(1):54-61. doi: 10.1373/clinchem.2011.165795. [PubMed: 21965555].
- Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J*. 2011;32(4):404-11. doi: 10.1093/eurheartj/ehq456. [PubMed: 21169615].
- Chang CB, Yoo JH, Koh JJ, Kang YG, Seong SC, Kim TK. Key factors in determining surgical timing of total knee arthroplasty in osteoarthritic patients: age, radiographic severity, and symptomatic severity. *J Orthop Traumatol*. 2010;11(1):21-7. doi: 10.1007/s10195-010-0086-y. [PubMed: 20169392]. [PubMed Central: PMC2837816].
- Dreinhofer KE, Dieppe P, Sturmer T, Grober-Gratz D, Floren M, Gunther KP, et al. Indications for total hip replacement: Comparison of assessments of orthopaedic surgeons and referring physicians. *Ann Rheum Dis*. 2006;65(10):1346-50. doi: 10.1136/ard.2005.047811. [PubMed: 16439438]. [PubMed Central: PMC1798326].
- Gibler WB, Young GP, Hedges JR, Lewis LM, Smith MS, Carleton SC, et al. Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: Serial CK-MB sampling in the emergency department. The Emergency Medicine Cardiac Research Group. *Ann Emerg Med*. 1992;21(5):504-12. [PubMed: 1570904].
- Gibler WB, Lewis LM, Erb RE, Makens PK, Kaplan BC, Vaughn RH, et al. Early detection of acute myocardial infarction in patients presenting with chest pain and nondiagnostic ECGs: Serial CK-MB sampling in the emergency department. *Ann Emerg Med*. 1990;19(12):1359-66. [PubMed: 2240745].
- O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet*. 2016;388(10046):761-75. doi: 10.1016/S0140-6736(16)30506-2. [PubMed: 27431356].
- Urban MK, Jules-Elysee K, Loughlin C, Kelsey W, Flynn E. The one year incidence of postoperative myocardial infarction in an orthopedic population. *HSS J*. 2008;4(1):76-80. doi: 10.1007/s11420-007-9070-3. [PubMed: 18751868]. [PubMed Central: PMC2504276].
- Jules-Elysee K, Urban MK, Urquhart B, Milman S. Troponin I as a diagnostic marker of a perioperative myocardial infarction in the orthopedic population. *J Clin Anesth*. 2001;13(8):556-60. [PubMed: 11755323].
- Ausset S, Auroy Y, Lambert E, Vest P, Plotton C, Rigal S, et al. Cardiac troponin I release after hip surgery correlates with poor long-term cardiac outcome. *Eur J Anaesthesiol*. 2008;25(2):158-64. doi: 10.1017/S0265021507001202. [PubMed: 17666156].
- Chong CP, Lam QT, Ryan JE, Sinnappu RN, Lim WK. Incidence of postoperative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. *Age Ageing*. 2009;38(2):168-74. doi: 10.1093/ageing/afn231. [PubMed: 19008306].
- Chong CP, van Gaal WJ, Profitis K, Ryan JE, Savage J, Lim WK. Electrocardiograph changes, troponin levels and cardiac complications after orthopaedic surgery. *Ann Acad Med Singapore*. 2013;42(1):24-32. [PubMed: 23417588].
- Urban MK, Wolfe SW, Sanghavi NM, Fields K, Magid SK. The incidence of perioperative cardiac events after orthopedic surgery: A single institutional experience of cases performed over one year. *HSS J*.

- 2017;**13**(3):248–54. doi: [10.1007/s11420-017-9561-9](https://doi.org/10.1007/s11420-017-9561-9). [PubMed: [28983217](https://pubmed.ncbi.nlm.nih.gov/28983217/)]. [PubMed Central: [PMC5617821](https://pubmed.ncbi.nlm.nih.gov/PMC5617821/)].
27. Jeremias A, Gibson CM. Narrative review: Alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med*. 2005;**142**(9):786–91. [PubMed: [15867411](https://pubmed.ncbi.nlm.nih.gov/15867411/)].
 28. White HD. Pathobiology of troponin elevations: Do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol*. 2011;**57**(24):2406–8. doi: [10.1016/j.jacc.2011.01.029](https://doi.org/10.1016/j.jacc.2011.01.029). [PubMed: [21658560](https://pubmed.ncbi.nlm.nih.gov/21658560/)].
 29. Landesberg G, Jaffe AS, Gilon D, Levin PD, Goodman S, Abu-Baih A, et al. Troponin elevation in severe sepsis and septic shock: The role of left ventricular diastolic dysfunction and right ventricular dilatation*. *Crit Care Med*. 2014;**42**(4):790–800. doi: [10.1097/CCM.000000000000107](https://doi.org/10.1097/CCM.000000000000107). [PubMed: [24365861](https://pubmed.ncbi.nlm.nih.gov/24365861/)].
 30. Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. *Vasc Health Risk Manag*. 2011;**7**:597–603. doi: [10.2147/VHRM.S24509](https://doi.org/10.2147/VHRM.S24509). [PubMed: [22102783](https://pubmed.ncbi.nlm.nih.gov/22102783/)]. [PubMed Central: [PMC3212425](https://pubmed.ncbi.nlm.nih.gov/PMC3212425/)].
 31. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (coronary artery spasm in patients with acute coronary syndrome) study. *J Am Coll Cardiol*. 2008;**52**(7):523–7. doi: [10.1016/j.jacc.2008.04.050](https://doi.org/10.1016/j.jacc.2008.04.050). [PubMed: [18687244](https://pubmed.ncbi.nlm.nih.gov/18687244/)].
 32. Scheitz JF, Mochmann HC, Witzendichler B, Fiebach JB, Audebert HJ, Nolte CH. Takotsubo cardiomyopathy following ischemic stroke: A cause of troponin elevation. *J Neurol*. 2012;**259**(1):188–90. doi: [10.1007/s00415-011-6139-1](https://doi.org/10.1007/s00415-011-6139-1). [PubMed: [21681632](https://pubmed.ncbi.nlm.nih.gov/21681632/)].
 33. Lim W, Whitlock R, Khera V, Devereaux PJ, Tkaczyk A, Heels-Ansdell D, et al. Etiology of troponin elevation in critically ill patients. *J Crit Care*. 2010;**25**(2):322–8. doi: [10.1016/j.jcrc.2009.07.002](https://doi.org/10.1016/j.jcrc.2009.07.002). [PubMed: [19781898](https://pubmed.ncbi.nlm.nih.gov/19781898/)].
 34. Patil H, Vaidya O, Bogart D. A review of causes and systemic approach to cardiac troponin elevation. *Clin Cardiol*. 2011;**34**(12):723–8. doi: [10.1002/clc.20983](https://doi.org/10.1002/clc.20983). [PubMed: [22120679](https://pubmed.ncbi.nlm.nih.gov/22120679/)].
 35. Lee MJ, Park YS, Ahn S, Sohn CH, Seo DW, Lee JH, et al. [Clinical features of acute aortic dissection patients initially diagnosed with ST-segment elevation myocardial infarction]. *J Korea Soci Emergency Med*. 2016;**27**(1):30–5. Korean.
 36. Meigher S, Thode HC, Peacock WF, Bock JL, Gruberg L, Singer AJ. Causes of elevated cardiac troponins in the emergency department and their associated mortality. *Acad Emerg Med*. 2016;**23**(11):1267–73. doi: [10.1111/acem.13033](https://doi.org/10.1111/acem.13033). [PubMed: [27320126](https://pubmed.ncbi.nlm.nih.gov/27320126/)].
 37. Eggers KM, Lind L, Ahlstrom H, Bjerner T, Ebeling Barbier C, Larsson A, et al. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J*. 2008;**29**(18):2252–8. doi: [10.1093/eurheartj/ehn327](https://doi.org/10.1093/eurheartj/ehn327). [PubMed: [18606612](https://pubmed.ncbi.nlm.nih.gov/18606612/)].