DOI: 10.5114/kitp.2014.45679

Does the postoperative troponin I blood concentration measured in the perioperative period influence hemodynamic function of a transplanted heart?

Karol Wierzbicki[1], Maciej Bochenek[1], Anna Kędziora[1], Krzysztof Sojecki[1], Dorota Ciołczyk-Wierzbicka[2], Piotr Węgrzyn[1], Rafał Drwiła[1], Bogusław Kapelak[1], Irena Milaniak[1], Jerzy Sadowski[1]

[1]Department of Cardiovascular Surgery and Transplantology, Jagiellonian University, Medical College, John Paul II Hospital, Krakow, Poland
[2]Chair of Medical Biochemistry, Jagiellonian University, Medical College, Krakow, Poland

Kardiochirurgia i Torakochirurgia Polska 2014; 11 (3): 289-293

Abstract

Introduction: Plasma troponin I (TnI) concentration is a well-established and widely-used marker of myocardial damage.
Aim: To determine the correlation between TnI concentration measured within the first 4 days following heart transplantation (HTX) and clinical course, with consideration of hemodynamic performance.
Material and methods: The retrospective study included 54 patients (12-62 years) who underwent HTX. TnI levels were assessed over the first 4 post-operative days. Hemodynamic parameters were assessed daily at Swan-Ganz catheterization and echocardiography. The number of required inotropic drugs was also analyzed.
Results: There is a strong and positive correlation between the mean TnI levels and the mean number of required inotropic drugs (r = 0.51, p = 0.00), and also mean central venous pressure (CVP) (r = 0.33, p = 0.015). A weak trend towards a positive correlation between the mean values of pulmonary capillary wedge pressure (PCWP) and the mean plasma TnI levels was observed. There was no correlation between mean TnI levels and mean values of ejection fraction (EF) and cardiac output (CO). Detailed analysis showed a statistically significant correlation between TnI levels on days 3 and 4 after HTX and PCWP on the preceding days (r = 0.32, p = 0.04; r = 0.46, p = 0.006 respectively). Furthermore, a strong, inverse correlation between TnI levels on day 3 and CO on day 4 following HTX was observed (r = –0.44, p = 0.03).
Conclusions: Plasma TnI could be a useful marker for assessing the hemodynamic function after HTX.
Key words: heart transplantation, troponin I, hemodynamic parameters.

Streszczenie

Wstęp: Stężenie osoczowe troponiny I (TnI) jest uznanym i powszechnie stosowanym wskaźnikiem uszkodzenia mięśnia sercowego.
Cel pracy: Określenie zależności pomiędzy osoczowymi stężeniami TnI a przebiegiem klinicznym z uwzględnieniem funkcji hemodynamicznej alograftu w pierwszych 4 dobach po przeszczepie serca (HTX).
Materiał i metody: Badaniem retrospektywnym objęto 54 pacjentów (12–62 lat), u których wykonano HTX. Stężenia osoczowe TnI oznaczano w 4 kolejnych dobach po przeszczepie. Parametry hemodynamiczne mierzone były codziennie przy użyciu cewnika Swana-Ganza oraz echokardiografii. Liczba wymaganych w okresie pooperacyjnym leków presyjnych również podlegała ocenie.
Wyniki: Wykazano silną dodatnią korelację pomiędzy średnim osoczowym stężeniem TnI a średnim zapotrzebowaniem na liczbę leków presyjnych (r = 0,51, p = 0,00). Pozytywną korelację zaobserwowano również dla uśrednionych wartości ośrodkowego ciśnienia żylnego (CVP) (r = 0,33, p = 0,015). Wykazano słabą tendencję w kierunku dodatniej korelacji pomiędzy średnią wartością ciśnienia zaklinowania w tętnicy płucnej (PCWP) a średnim osoczowym stężeniem TnI (r = 0,23, p = 0,09). Nie znaleziono istotnej korelacji pomiędzy średnim osoczowym stężeniem TnI a uśrednionymi wartościami frakcji wyrzutowej (EF) i rzutu serca (CO). Szczegółowa analiza wykazała istotną, dodatnią korelację pomiędzy osoczowymi stężeniami TnI w 2. i 3. dobie po HTX a wartościami PCWP mierzonymi w dobach poprzedzających (odpowiednio r = 0,32, p = 0,04; r = 0,46, p = 0,006). Ponadto zaobserwowano silną, ujemną korelację pomiędzy osoczowym stężeniem TnI w 2. dobie a CO w 3. dobie po HTX (r = –0,44, p = 0,03).
Wnioski: Stężenie osoczowe TnI może być użytecznym wskaźnikiem służącym do oceny funkcji hemodynamicznej przeszczepionego serca.
Słowa kluczowe: przeszczep serca, troponina I, parametry hemodynamiczne.

Address for correspondence: Karol Wierzbicki, Department of Cardiovascular Surgery and Transplantology, Jagiellonian University, Medical College, John Paul II Hospital, Prądnicka 80, 31-202 Krakow, Poland, e-mail: lolekwierzbicki@onet.pl

Introduction

Heart transplantation (HTX) is the ultimate and accepted treatment option in patients with end-stage heart failure (if other treatments fail). In the newest ESC (European Society of Cardiology) guidelines it remains the gold-standard treatment with acceptable, long-term survival. The recent ISHLT (International Society for Heart and Lung Transplantation) registry shows a half-life time (the time for which 50% of patients survived) of more than 10 years.

According to the ESC guidelines, HTX significantly improves survival, physical capacity, and quality of life [1, 2].

Nevertheless, the donor shortage, which limits heart transplants, is difficult to eliminate. The number of heart transplants performed each year has not increased and there has been a reduction observed worldwide in recent years. The ISHLT Registry shows that in Europe the number of heart transplants has decreased by over 40% over the last two decades [2].

Undoubtedly, this fact affects the condition of recipients, as it prolongs the waiting time. Facing reality we have to admit that nowadays, qualification for HTX is reserved almost exclusively for urgent patients [3, 4]. Criteria for qualifying patients for HTX on the high-urgency (HU) list are presented on the official POLTRANSPLANT website [3].

As we conclude from our clinical experience, patients who are qualified for HTX urgently, suffer from a more eventful postoperative course compared to non-urgent patients. Similar outcomes were observed by Haneya *et al*., whose research showed markedly increased prevalence of comorbid conditions and rate of secondary organ impairment in patients waiting for HTX on the high-urgency list [5]. Additionally to the circumstances described above, the necessity to accept marginal donors makes the postoperative course even more difficult.

Considering the current situation, searching for potential markers which will be potent to demonstrate the injury of the allograft is crucial to reduce the risk of postoperative complications.

In our study we decided to conduct an analysis of troponin I (TnI) as such biomarker. As we concluded from our previous studies and according to other research performed worldwide, significantly elevated troponin I levels can be observed immediately after heart transplantation. That could demonstrate perioperative injury connected with harvesting and implanting the heart. However, reports on the relationship between troponin levels and the postoperative course over the first days following HTX are few [6-11].

Aim of the study

The purpose of the present study was to assess the relationship between troponin I levels measured over the first few days after HTX and the hemodynamic function of the transplanted heart.

Material and methods

The retrospective analysis included 54 patients (5 females, 49 males) aged 12-62 years (median age: 52, IQR = 15).

The inclusion criteria in this study were as follows: 1. Availability of troponin I levels measured over the first days after HTX (from day 1 to day 4). Troponin I levels were measured using the one step immunoenzymatic assay (SIEMENS, Germany, normal range below 0.1 ng/ml). 2. Donor hearts procured using the same standard techniques and the same cardioplegic solution (CELSIOR) in a volume of 4 liters (heart procurement and graft protection were described in our pilot study) [6].

All patients operated on in the Department of Cardiovascular Surgery and Transplantology, Institute of Cardiology, Jagiellonian University College of Medicine at John Paul II Hospital in Krakow and meeting the inclusion criteria were included in the analysis (changes in the methodology and type of measured troponin were the most important factors limiting the size of the study group).

Function of the transplanted heart was evaluated daily with assessment of:

- echocardiographic parameters – measurements were performed using GE Vivid I and GE Vivid 7; left ventricle ejection fraction (LVEF) was assessed using semi-quantitative measurement verified with the biplane Simpson's method,
- hemodynamic parameters – pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) – were evaluated invasively at the ICU using a Swan-Ganz catheter; measurements of cardiac output (CO) were performed using the bolus thermodilution procedure; the mean value estimated from 3 successive measurements was considered as the final result of the test,
- inotropic support – need for routinely used inotropic drugs (adrenaline, dobutamine, norepinephrine and the phosphodiesterase type 5 inhibitor milrinone) – was assessed, based on quantitative evaluation of the number of administered drugs.

In case of more than one measurement per day, the highest value of TnI, CVP, PCWP and the lowest value of CO and EF were introduced into the analysis. Mean values of above-listed parameters measured over 4 days were analyzed for correlations using statistical methods. If no correlation was found, further detailed analysis of the data was performed.

Statistical analysis

Analyses were performed using STATISTICA v. 10 software (StatSoft, Inc.). Continuous variables were assessed for normal distribution using the Shapiro-Wilk test. Data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. To assess the relationship between non-normally distributed variables, Spearman's rank correlation coefficient test (Spearman's rho) was calculated. A p-value of ≤ 0.05 was considered statistically significant.

Results

Over the first consecutive days after HTX, troponin I levels were elevated, reaching a maximum median value

Tab. I. Median troponin I levels measured over first consecutive days following HTX

	Median	qr
Troponin I	16.9	9.9
Troponin II	17.08	11.2
Troponin III	11.6	13
Troponin IV	7.61	8.1

of 17.08 ng/ml on day 2 (Troponin II) (Table I). A strong positive correlation was established for the mean plasma TnI levels and the mean number of required inotropic drugs at a statistically significant level (r = 0.51, p = 0.00) (Fig. 1). There was also a positive correlation between mean plasma TnI levels and mean CVP (r = 0.33, p = 0.015) (Fig. 2). A weak trend towards a positive correlation between mean values of PCWP and the mean plasma TnI levels on the borderline of statistical significance was observed (r = 0.23, p = 0.09) (Fig. 3). However, a detailed analysis showed a significant positive relationship between TnI levels on day 3 and PCWP on day 2 (r = 0.32, p = 0.043), as well as between TnI levels on day 4 and PCWP on day 3 following HTX (r = 0.46, p = 0.006). Despite the fact that there was no relationship between mean plasma TnI concentrations and the mean values of EF and CO, we found a strong, statistically significant, inverse correlation between TnI levels on day 3 and CO on day 4 (r = –0.44, p = 0.03).

Discussion

Cardiac troponins are the most specific and sensitive laboratory markers of myocardial cell injury. Since the heart transplantation procedure is associated with many factors that can cause damage to the myocardium, plasma troponin concentrations are usually markedly elevated during the postoperative period [6, 9, 11]. Although troponin levels

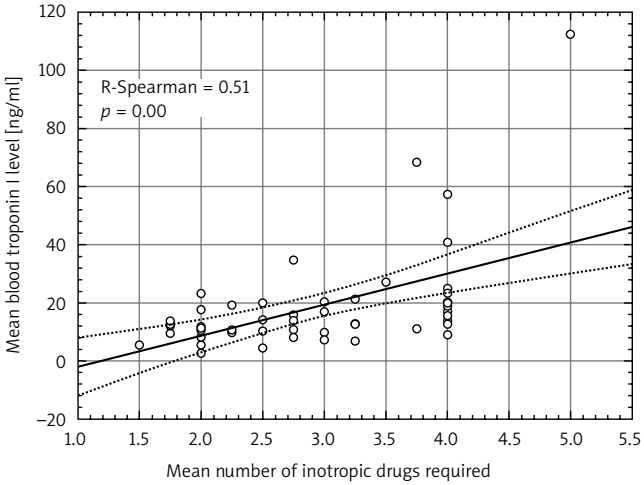

Fig. 1. Correlation between mean plasma troponin I concentration and mean number of required inotropic drugs measured over 4 days after heart transplantation (R-Spearman – Spearman rank correlation coefficient)

are usually assessed following HTX, their role and significance are not fully determined yet.

There is some evidence confirming usefulness of their evaluation as a tool for prognosticating outcomes of transplanted patients. Our previous analyses established a significant relationship between troponin levels and clinical course early after HTX [6, 7]. Some papers underline the relation between troponin level and the risk of allograft rejection or ischemic damage of myocardium in the early postoperative period [12, 13]. Other studies have revealed the important role of troponins in predicting long-term survival. Erbel *et al*. found a major impact of troponin release in 6 weeks after HTX on 1 year survival [14]. In 2000 Labarrere *et al*. published follow-up results of 110 graft recipients. They found significantly higher incidence of coronary artery disease (vasculopathy) and graft failure at 5 years following HTX among patients with persistently elevated

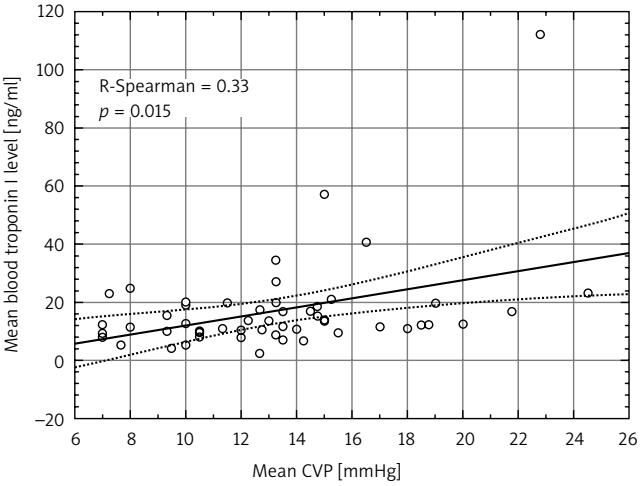

Fig. 2. Correlation between mean plasma troponin I concentration and mean value of central venous pressure measured over 4 days after heart transplantation (R-Spearman – Spearman rank correlation coefficient)

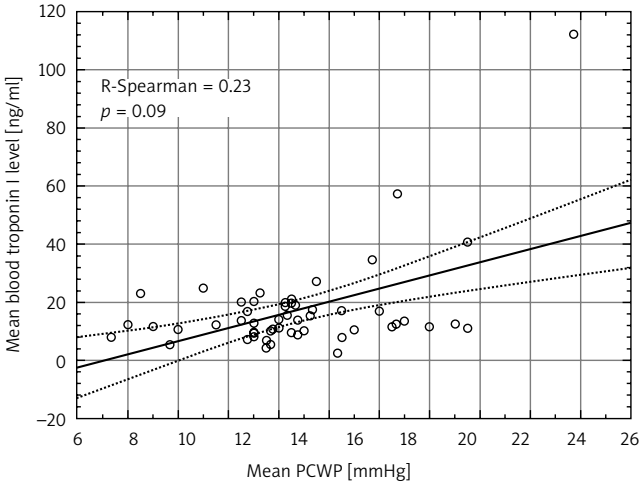

Fig. 3. Interdependence between mean plasma troponin I concentration and mean value of pulmonary capillary wedge pressure measured over 4 days after HTX – statistical trend (R-Spearman – Spearman rank correlation coefficient)

troponin I levels during one year after HTX compared with those with undetectable troponins over the first month following HTX [10].

In this study we decided to analyze the correlation between mean plasma troponin I levels measured in the first 4 postoperative days and hemodynamic function of transplanted heart. We analyzed EF, CO, CVP, and PCWP, as these parameters are routinely used to recognize left and right ventricle dysfunction and to diagnose primary graft failure (PGF), which is the main cause of early mortality in transplanted patients. According to the 2013 ISHLT annual report, PGF accounts for 36% of deaths within 30 days after HTX [8, 15]. Thus, knowledge of risk factors and symptoms is crucial for immediate diagnosis and treatment of this condition.

Although there is no universally accepted clinical definition of PGF, it can be described as severe systolic dysfunction of the graft and severe hemodynamic compromise without any obvious anatomic or immunologic cause leading to low output syndrome (LOS), which requires high-dose inotropic or mechanical support. The diagnosis is performed based on commonly assessed hemodynamic parameters [8].

Echocardiographic measurements of the RVEF and LVEF were defined in Siniawski's research as the most useful in distinguishing between PGF and other, less fatal, aberrations [16]. Similar results were concluded from the research by D'Alessandro *et al*., who determined LVEF < 55% as a predictive factor for primary graft failure (PGF) [17].

In our study we did not find any substantial influence of mean plasma troponin I levels measured in the first 4 days after HTX on LVEF or on CO. It is probably because of the fact that in patients with failing systolic function of the heart, more powerful inotropic support was applied. However, a statistically significant correlation between TnI level measured on day 3 and CO measured on day 4 was observed. Taking into account the small size of the study group, this fact should encourage further investigation of the relationship between the two variables, as this result suggests that elevation of TnI level may overtake exacerbation of LV systolic function.

In the analysis of hemodynamic function of the transplanted heart we also included CVP and PCWP, as these parameters are routinely measured in order to describe right (CVP) and left (PCWP) ventricle dysfunction. In previously mentioned research by Siniawski, CVP and PCWP were also assessed in order to recognize PGF, although interdependence with troponin levels was not established [16].

Our research revealed a positive correlation between mean plasma troponin I levels and mean CVP. We could also observe a statistical trend towards higher values of mean PCWP in patients with elevated mean plasma TnI concentration ($r = 0.23$, $p = 0.09$). In view of the fact that detailed analysis revealed two cases of a statistically significant correlation between PCWP and TnI (see the results), the trend is becoming more relevant and deserves scrutiny.

Standard treatment of PGF comprises routine use of moderate- to high-dose inotropic agents and, in more severe cases, mechanical circulatory support (IABP, ECMO) [18]. The intensity of inotropic support is usually combined with a higher incidence rate of PGF [8].

Our study analyzed the correlation between average troponin I levels and requirement for inotropic support and a statistically significant influence was found – more inotropic drugs need to be introduced in patients with higher troponin I levels.

In summary, our research demonstrates troponin as a significant and valuable parameter which could influence the postoperative course. Troponin I measurements performed on a daily basis might be useful in anticipating and monitoring the potential failure of a transplanted heart.

According to our best knowledge, there are no papers investigating similar correlations. The present study, which should be considered as preliminary, reveals statistically proven effects of troponin I levels measured over the first days after HTX on the hemodynamic function of the transplanted heart. Nevertheless, the small size of the study group does not allow any definite conclusions, and another study should be conducted to finally confirm our results.

The limitations of the study were the retrospective analysis of the data, small sample size, and statistical analysis based on non-parametric tests.

Conclusions

Marked elevation of plasma troponin I levels observed early after heart transplantation influence the hemodynamic function of the transplanted heart. Mean troponin I levels measured over the first 4 days after HTX positively correlated with: 1) mean central venous pressure ($p = 0.015$), 2) mean pulmonary capillary wedge pressure (statistical trend) ($p = 0.09$), 3) mean requirement for inotropic drugs ($p = 0.00$) in the analogical period.

Detailed analysis also revealed correlations between: 1) TnI level on day 3 with CO on day 4 ($p = 0.03$) and 2) PCWP on day 2 with TnI on day 3 and PCWP on day 3 with TnI on day 4 ($p = 0.00$).

Troponin I levels should be considered as an easily assessed marker of graft dysfunction. However, it requires further confirmation. We recommend troponin I evaluation on a daily basis during the first days following HTX.

Acknowledgements

The current study obtained approval from the Bioethics Committee KBET/224/B/2010 and is a part of the K/ZDS/002427 project.

Disclosure

The authors report no conflict of interest.

References

1. Task Force Members. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-1847.

2. www.ishlt.org
3. www.poltransplant.org.pl
4. Smits JM. Actual situation in Eurotransplant regarding high urgent heart transplantation. Eur J Cardiothorac Surg 2012; 42: 609-611.
5. Haneya A, Haake N, Diez C, Puehler T, Cremer J, Schmid C, Hirt SW. Impact of the Eurotransplant high-urgency heart allocation system on the outcome of transplant candidates in Germany. Thorac Cardiovasc Surg 2011; 59: 93-97.
6. Wierzbicki K, Sobczyk D, Milaniak I, Bochenek M, Piątek J, Drwiła R, Kapelak B, Krupa F, Przybyłowski P, Ciołczyk-Wierzbicka D, Sadowski J. Dynamics of the troponin I levels in the first days after heart transplantation in the own material – a pilot study. Kardiochir Torakochir Pol 2011; 8: 379-382.
7. Wierzbicki K, Bochenek M, Sobczyk D, Milaniak I, Kapelak B, Ciołczyk-Wierzbicka D, Drwiła R, Przybyłowski P, Bartuś K, Sadowski J. Ocena wpływu zwiększonych stężeń troponiny I mierzonej w okresie okołooperacyjnym na przebieg kliniczny u chorych po transplantacji serca w materiale własnym. Kardiochir Torakochir Pol 2012; 3: 357-360.
8. Amarelli C, De Santo LS, Marra C, Maiello C, Bancone C, Della Corte A, Nappi G, Romano G. Early graft failure after heart transplant: risk factors and implications for improved donor-recipient matching. Interact Cardiovasc Thorac Surg 2012; 15: 57-62.
9. Wierzbicki K, Sobczyk D, Milaniak I, Bochenek M, Kapelak B, Drwiła R, Wróbel K, Bartuś K, Ciołczyk-Wierzbicka D, Przybyłowski P, Sadowski J. Influence of the selected factors connected with heart donor on the troponin I levels in the perioperative period after heart transplantation in own material. Kardiochir Torakochir Pol 2011; 4: 516-520.
10. Labarrere CA, Nelson DR, Cox CJ, Pitts D, Kirlin P, Halbrook H. Cardiac-specific troponin I levels and risk of coronary artery disease and graft failure following heart transplantation. JAMA 2000; 284: 457-464.
11. Zimmermann R, Baki S, Dengler TJ, Ring GH, Remppis A, Lange R, Hagl S, Kübler W, Katus HA. Troponin T release after heart transplantation. Br Heart J 1993; 69: 395-398.
12. Wierzbicki K, Sobczyk D, Milaniak I, Bochenek M, Ciołczyk-Wierzbicka D, Frasik W, Rudnicka-Sosin L, Kapelak B, Drwiła R, Bartuś K, Przybyłowski P, Sadowski J. Ocena zależności pomiędzy stężeniami troponiny I mierzonymi we wczesnym okresie po transplantacji serca a obrazem histopatologicznym przeszczepionego serca. Kardiochir Torakochir Pol 2012; 9: 226-230.
13. Battes L, Caliskan K, Rizopoulos D, Constantinescu A, Akkerhuis M, Manintveld O, Kardys I. Use of NT-proBNP, CRP or Troponin T For Non-Invasive Detection of Allograft Rejection in Heart Transplant Recipients. Circulation 2012; 126: A15229.
14. Erbel C, Taskin R, Doesch A, Dengler TJ, Wangler S, Akhavanpoor M, Ruhparwar A, Giannitsis E, Katus HA, Gleissner CA. High-sensitive Troponin T measurements early after heart transplantation predict short- and long-term survival. Transpl Int 2013; 26: 267-272.
15. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Yusen RD, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report – 2013; focus theme: age. J Heart Lung Transplant 2013; 32: 951-964.
16. Siniawski H, Dandel M, Lehmkuhl HB, Hiemann N, Kemper D, Knosalla C, Stein J, Weng Y, Hetzer R. Clinical, haemodynamic and echocardiographic features of early cardiac graft dysfunction. Kardiol Pol 2012; 70: 1010-1016.
17. D'Alessandro C, Golmard JL, Barreda E, Laali M, Makris R, Luyt CE, Leprince P, Pavie A. Predictive risk factors for primary graft failure requiring temporary extra-corporeal membrane oxygenation support after cardiac transplantation in adults. Eur J Cardiothorac Surg 2011; 40: 962-970.
18. Iyer A, Kumarasinghe G, Hicks M, Watson A, Gao L, Doyle A, Keogh A, Kotlyar E, Hayward C, Dhital K, Granger E, Jansz P, Pye R, Spratt P, Macdonald PS. Primary graft failure after heart transplantation. J Transplant 2011; 2011: 175768.