# Dynamics of the troponin I levels in the first days after heart transplantation (HTX) in the own material – a pilot study

## Dynamika zmian stężeń troponiny I w pierwszych dobach po przeszczepieniu serca (HTX) w materiale własnym – pilot study

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## Abstract

**Background:** Troponin is a valuable and highly used marker for the assessment of the myocardial damage. Elevated troponin levels are the result of myocardial injury irrespective of etiology.
**Aim:** Evaluation of dynamics of troponin I changes in the first days (since "0" to 3rd day) after heart transplantation (HTX).
**Material and methods:** Retrospective analysis of 42 patients aged 21 to 62 years, average age 47.4 ±12.4. Study group consisted of the patients which hearts were harvested by two surgeons according to the identical protection scheme using CELSIOR cardioplegic solution. In all patients troponin I levels in the following days after HTX were measured.
Dynamics of troponin I changes was assessed, using the one-step immunoenzymatic test (normal values to 0.1 ng/ml) in all of the patients in the first days after HTX. The highest daily value was taken into the analysis.
**Results:** Average troponin I levels in the subsequent days after HTX were as follows: 21.7 ±22.1; 21.3 ±22.5; 17.6 ±20.3; 13.2 ±15.3 ng/ml. Based on ANOWA (Kruskal-Wallisa) test statistically significant troponin I levels decrease in the consecutive days after HTX ($p$ = 0.0002) was noted. The biggest decrease was observed between days "0" and "3" and between days "1" and "3" (respectively: 54.1 and 53.7%); the smallest decreased appeared between days "0" and "1" after HTX (0.7%).
**Conclusion:** Immediately after HTX significantly elevated troponin I levels can be observed that could be connected with perioperative myocardial injury caused by the heart harvesting and transplantation.
**Key words:** heart transplantation, troponin, donor's heart.

## Streszczenie

**Wstęp:** Troponina I jest wiarygodnym i powszechnie stosowanym markerem uszkodzenia mięśnia serca. Zwiększenie stężenia troponiny jest wynikiem uszkodzenia mięśnia serca o różnej etiologii.
**Cel:** Ocena dynamiki zmian stężeń troponiny I w pierwszych dobach (od 0. do 3. doby włącznie) po przeszczepieniu serca (ang. *heart transplantation* – HTX).
**Materiał i metody:** Analizą retrospektywną objęto 42 chorych w wieku od 21 do 62 lat, średnio 47,4 ±12,4. Badaną grupę stanowili pacjenci, których serca pobierało dwóch chirurgów wg identycznego schematu protekcji z zastosowaniem kardiopleginy CELCIOR i u których zmierzono stężenia troponiny I w kolejnych dobach po HTX.
Oceniono dynamikę zmian stężenia troponiny I oznaczanej metodą jednostopniowego testu immunoenzymatycznego (norma od 0,1 ng/ml) w identyczny sposób u wszystkich chorych, w pierwszych dobach po HTX. W przypadku więcej niż jednego poziomu oznaczanego w ciągu doby do analizy brano najwyższą wartość uzyskaną w danej dobie.
**Wyniki:** Średnie stężenie troponiny I w kolejnych dobach po HTX wyniosło kolejno: 21,7 ±22,1; 21,3 ±22,5; 17,6 ±20,3; 13,2 ±15,3 ng/ml. Na podstawie testu ANOVA (Kruskal-Wallisa) stwierdzono istotne statystycznie zmniejszenie stężenia tropiny I w kolejnych dobach po HTX ($p$ 0,0002). Największy spadek zanotowano pomiędzy dobą 0. i 3. oraz pomiędzy dobą 1. i 3. (odpowiednio: 54,1 i 53,7%), a najmniejszy spadek pomiędzy 0. i 1. dobą po HTX (0,7%).
**Wnioski:** Bezpośrednio po transplantacji serca obserwuje się znacznie zwiększone stężenia troponiny I, zmniejszające się istotnie w kolejnych dobach, co może świadczyć o obecnym urazie okołooperacyjnym związanym z pobraniem i przeszczepieniem serca.
**Słowa kluczowe:** przeszczep serca, troponina, serce dawcy.

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## Background

Despite intensive development of the new surgical and pharmacological options of the end-stage cardiac failure treatment, heart transplantation (HTX) still remains a necessary and successful method. Even facing the lack of control studies, HTX seems to significantly increase survival, exercise capacity, return to work, and quality of life in comparison to conventional treatment. According to European Society of Cardiology (ESC) Guidelines, HTX has the first class of recommendation with level of evidence C [1].

Half-life time in adult cardiac recipients gradually increases since the first successful HTX operations. Recently about 50% of the patients survive more than 10 years. However early mortality about 10-20% appears still high, especially when compared with classical cardiac surgery procedures. The most frequent direct cause of death between "0" and 3rd days post HTX is graft failure that makes more than 40% of all-cause mortality in that period. In front of chronic heart donors lack, more and more often "marginal donors" have to be accepted for transplantation. Older donor age, impaired donor cardiac function or longer ischemic time may potentially increase risk of early graft failure [2].

Analysis of the damage markers in the transplanted heart early after heart transplantation seems valuable.

Troponin is built in between of actin filaments and is bounded with tropomiozin C. It is functionally connected with contraction of skeletal muscles (and, what is more important, heart muscle). Its structure has been described as the complex of three proteins.

From among three troponin subunits (C, I, T), very sensitive and recognized marker of the heart damage is troponin I that connected with actin and stabilized troponin–tropomiozin complex. Increased troponin level points not only for myocardial infarction (as described in the guidelines for the diagnosis of myocardial infarction) but also allows for evaluation of myocardial injury expanse irrespectively of its etiology [3].

Troponin seems to be a valuable marker for the assessment of the extension and dynamics of the potential damage of the transplanted heart.

The aim of the study was evaluation of troponin I levels dynamics in the first days after HTX ("0" to 3rd day).

## Material and methods

### *Material*

Retrospective analysis contained 42 patients (4 female, 38 male) in the age 21 to 62 years, average 47.4 ±12.4 years. Study group consisted of the patients which hearts were harvested by two surgeons (two of the authors) according to the same protection scheme with the use of CELSIOR cardioplegic solution. Troponin I levels in the first and the following days after HTX were measured.

### *Methods*

Dynamics of changes in the troponin I levels was evaluated. Troponin I level was measured in all of the patients using the method of one-stage immunoenzymatic test (normal up to 0.1 ng/ml). The highest value obtained during the same day was taken into the statistical analysis.

### Myocardial protection

CELSIOR is the cardioplegic solution and it was always used for the donor heart protection. The main components of the solution are the following: Mannitol, Lactobionic acid, Glutamic acid, Histidine, Calcium chloride, Potassium chloride (15 mmol), Magnesium chloride. The solution is slightly alkaline (pH = 7.3), slightly hypertonic (242-368 mOsmol/l) with low viscosity (1.15 cSt), and has a high buffering capacity (acidic approximately 11 mmol, alkaline approximately 7 mmol).

During harvesting the donor heart was arrested with 2 litres of CELSIOR cardioplegic solution given directly into aortic bulb. Simultaneously the heart was cooled by the cold physiological solution with crashed ice, given directly into the donor pericardium. After excision of the heart, the third litre of cardioplegic solution CELCIOR was given into aortic bulb. During transport the heart was placed in the same cardioplegic solution in temperature of 10 degrees Celsius. The fourth litre of CELCIOR was infused directly after unpacking the heart and directly before the implantation.

### Statistical techniques

Statistical analysis was performed using STATISTICA 8.0 software. First, type of the variables distribution was assessed with basic statistical packages. Because all the analysed parameters had the distribution distant from the normal one, non-parametric tests were used. Non-parametric ANOVA Kruskal Walis variation analysis was utilized. Results were described as arithmetic averages with statistical deviation. $P < 0.05$ was considered as statistically significant.

## Results

The average troponin I level in the consecutive days after HTX was as follows: starting from 21.7 ±22.1 ng/ml in "0" day to 13.2 ±15.3 ng/ml in 3rd day (Table I, Fig. 1).

Based on ANOVA test (Kruskal-Wallis) the statistically significant decrease of troponin I levels was described in the following days after HTX ($p = 0.0002$). The biggest decrease was noted between "0" and "3" days (54.1%), the smallest one appeared between "0" and "1" days after HTX (0.7%) (Table II).

## Discussion

The process of cardiomyocyte lesion during ischemia is complex. Deficiency of substrates and oxygen impairs ATP turn over. Activation of glycolysis leads (through anaerobic processes) to intracellular acidosis. In the next step the following processes can be observed: ionic disturbances, inflammation, phospholipases activation and increase in synthesis of thromboxan A2 or PAF (platelet activating factor). The consequences of these processes are cardiomyocytes lesion, their necrosis and manifestation of necrotic markers.

**Table I.** Average troponin I levels in the consecutive days after HTX (trop0 – troponin I "0" day; trop1 – troponin I 1st day, trop2 – troponin I 2nd day, trop3 – troponin I 3rd day after HTX)

| | Average value (ng/ml) | Standard deviation (± SD) |
|---|---|---|
| Trop0 | 21.7 | 22.1 |
| Trop1 | 21.3 | 22.5 |
| Trop2 | 17.6 | 20.3 |
| Trop3 | 13.2 | 15.3 |

**Table II.** Analysis of the percentage decrease of troponin I levels in the following days after HTX (trop0 – troponin I "0" day; trop1 – troponin I 1st day, trop2 – troponin I 2nd day, trop3 – troponin I 3rd day after HTX)

| | Percentage of change |
|---|---|
| Trop0 – Trop1 | –0.7 |
| Trop1 – Trop2 | –30.9 |
| Trop2 – Trop3 | –33.0 |
| Trop0 – Trop2 | –31.5 |
| Trop1 – Trop3 | –53.7 |
| Trop0 – Trop3 | –54.1 |

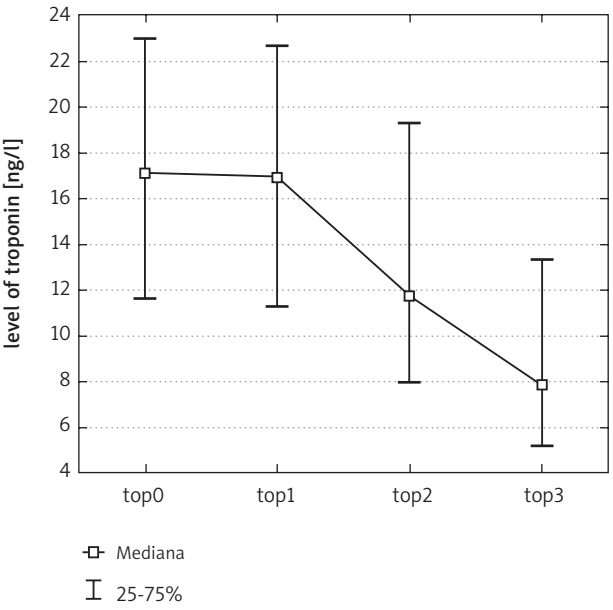


**Fig. 1.** Analysis of troponin level decrease in the following days after HTX
*(trop0 – troponin I "0" day; trop1 – troponin I 1st day, trop2 – troponin I 2nd day, trop3 – troponin I 3rd day after HTX)*
*ANOVA Kruskal-Wallis test; p = 0.0002*

The ideal marker of ischemia should have the following features:
- fast release from the cell in the amount proportional to the extent of injury,
- occurrence only in the definite tissues (e.g. cardiomyocytes),
- high concentration [4].

There are at least several ischemic myocardial injury markers (creatine phosphokinase and its isoenzymes, apartate aminotransferase, lactatet dehydrogenaze, mioglobin, troponin). However, it is the troponin, that seems to be an ideal and the most objective ischemia markers recommended by National Academy of Clinical Biochemistry (NACB) and the latest guidelines of ESC [4-6].

Our data shows the very high levels of troponin I in the first days after HTX. Statistical analysis show the highest troponin level directly after HTX, which significantly decrease in the following 3 days.

There is only limited data concerning troponin levels analysis after HTX. Zimmerman *et al*. in 1993 described the group of 19 patients after HTX, which troponin T levels up to 90 days after HTX were studied.

In contradistinction to our results showing the highest troponin I levels in "0" day after HTX gradually decreasing to 3rd day, the authors observed consistently increasing troponin T levels with maximum value on 7th day. Moreover, they noted elevated troponin T levels through the following weeks au to the 3rd month after HTX. Troponin values are impossible to compare because of different types of troponin (I and T) used [7]. Similarly to Zimmermann *et al*., Halwachs *et al.* during examining 15 patients after HTX observed the highest levels of troponin T between 3rd and 14th day after HTX. Additionally, the authors observed statistically significant influence of pulmonary hypertension in the transplanted patient, but not total ischemic time on troponin levels [8].

Labarrere *et al*. demonstrated the significant influence troponin released after heart transplantation on long-term operation results. In the group of 110 patients after HTX they observed elevated troponin I levels in the half of the patients in the 12-month follow-up. In comparison with the control population (undetectable troponin levels) these patients had significantly higher risk of vasculopathy and late graft failure [9].

Elevated troponin levels was also connected with acute cardiac rejection of the transplanted heart. Siaplaouras *et al*. demonstrated that troponin I is not a sensitive but a specific marker of acute rejection in children [10].

The literature as well as the own experience emphasize the important role of the troponin levels after HTX monitoring. Prolongation of control period for troponin levels up to at least 12 months seems useful. It can allow more complex and proper analysis of the long-term transplanted heart function.

Study limitation:
- retrospective analysis based on archive data,
- limited study group,
- impossibility of explicit comparison with the literature due to analysis of different troponin types (I or T),
- replacement of troponin I (used before) by highly sensitive troponin T (in 2010) in the authors` centre, that complicates further analysis.

The study was conducted with the approval of Local Bioethical Committee (KBET/224/B/2010).

## Conclusion

Immediately after heart transplantation significantly elevated troponin I levels can be observed, with subsequent significant decrease that could demonstrate perioperative injury connected with harvesting and heart transplantation. To the 3rd day (examined period) after HTX significantly elevated troponin I levels could be still noted.

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