# Effect of hydration status and variability of blood pressure and heart rate induced by hemodialysis on intradialytic changes of high sensitive troponin T

## Wpływ stopnia nawodnienia oraz zmienności ciśnienia tętniczego krwi i częstości rytmu serca w czasie hemodializy na śródddializacyjne zmiany stężeń wysokoczułej troponiny T

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## Abstract

**Introduction.** High sensitivity troponin T (TnT-hs) is biomarker of myocardial damage and ischemia. Despite its elevation troponin still preserve its usefulness as a marker of the cardiovascular risk and mortality in chronic kidney disease. Variations of hydration status between and during hemodialysis exert significant hemodynamic effects, which may negatively affect cardiovascular system and blood pressure and lead to myocardial damage.
The aim of the study was to access the effect of hydration status and variability of blood pressure and heart rate induced by hemodialysis on intradialytic changes of TnT-hs, in chronic hemodialysis patients.
**Material and methods.** In 50 chronic hemodialysis patients (35M, 15F, mean age 64 ± 12 years) blood pressure and heart rate were monitored noninvasively during HD session. Serum concentration of TnT-hs and hydration status were assessed before and after hemodialysis.
**Results.** TnT-hs concentration was above normal range in 98% patients before, and in all after hemodialysis. Median TnT-hs level was 82 ng/L before and 84 ng/L after hemodialysis, which comprised 586% and 600% of the upper limit of normal range. There was a small 2.4%, intradialytic increase of TnT-hs ($p = 0.004$). TnT-hs levels correlated positively with mean interdialytic weigh gain, before HD ($r = 0.43$, $p = 0.02$) and after HD ($r = 0.5$, $p = 0.003$). There was also a positive correlation between TnT-hs concentration and mean heart rate ($r = 0.37$, $p = 0.008$) and with mean systolic blood pressure during HD, before HD ($r = 0.3$, $p = 0.026$) and after HD ($r = 0.3$, $p = 0.031$).
**Conclusions.** Hemodialysis can be a risk factor of myocardial injury, especially in overhydrated patients.
**Key words:** hemodialysis, overhydration, troponin T, TnT-hs

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## Streszczenie

**Wstęp.** Wysokoczuła troponina T (TnT-hs) jest przydatnym klinicznie wskaźnikiem uszkodzenia komórek mięśnia sercowego. Stężenia TnT-hs u pacjentów z przewlekłą chorobą nerek są wyższe niż w populacji ogólnej, co wiąże się ze zwiększonym ryzykiem incydentów sercowo-naczyniowych oraz zgonu. Znaczne zmiany stopnia nawodnienia w czasie zabiegu hemodializy mogą niekorzystnie oddziaływać na układ sercowo-naczyniowy i ciśnienie tętnicze, co w efekcie może prowadzić do uszkodzenia kardiomiocytów.

Celem pracy była ocena wpływu stanu nawodnienia, zmian częstości rytmu serca (HR) i ciśnienia tętniczego (BP) w trakcie hemodializy (HD) na zmiany stężeń TnT-hs powodowane zabiegiem hemodializy u pacjentów długotrwale hemodializowanych.

**Materiał i metody.** U 50 pacjentów (35M, 15K, średnia wieku 64 ± 12 lat) z rozpoznaniem schyłkowej niewydolności nerek, długotrwale hemodializowanych, nieinwazyjnie monitorowano BP oraz HR podczas HD. Przed i po HD dokonano oceny stanu nawodnienia pacjenta oraz pobrano próbki krwi w celu oznaczenia stężenia TnT-hs.

**Wyniki.** Zwiększone stężenie w surowicy TnT-hs stwierdzono u 98% pacjentów przed zabiegiem HD oraz u 100% pacjentów po zabiegu. Mediana TnT-hs wynosiła 82ng/l przed HD i 84 ng/l po zabiegu, co wyniosło odpowiednio 586% oraz 600% wartości górnego zakresu referencyjnego. Stężenie TnT-hs podczas HD wzrastało nieznacznie o 2,4% (p = 0,04). Stężenie TnT-hs przed HD i po zabiegu korelowało ze średnim HR (r = 0,37; p = 0,008) oraz średnim skurczowym BP podczas zabiegu HD (przed HD r = 0,32; p = 0,026 i po HD r = 0,3; p = 0,031). Wykazano dodatnią korelację między przewodnieniem pomiędzy dializami a stężeniem TnT-hs przed HD (r = 0,43, p = 0,02) i po HD (r = 0,5, p = 0,003).

**Wnioski.** Zabieg hemodializy może zwiększać ryzyko uszkodzenia mięśnia sercowego, w szczególności w przypadku znacznego stopnia przewodnienia.


**Słowa kluczowe:** hemodializa, przewodnienie, troponina T, TnT-hs

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## Introduction

End-stage renal disease (ESRD) has been associated with a substantially reduced life expectancy [1]. The patients suffering from chronic kidney disease (CKD) have significantly higher cardiovascular and all-cause mortality compared to the general population. It is also known that the cardiovascular complications are the main cause of death in CKD population and the course of the cardiovascular disease (CVD) and its progression with age is significantly accelerated [2]. The pathogenesis of cardiovascular disease in CKD is multifactorial, including high prevalence of traditional risk factors such as hypertension, diabetes, atherogenic dyslipidemia and the factors specific to kidney disease, e.g., high concentration of uremic toxins, albuminuria, chronic inflammation, anemia and malnutrition, or calcium-phosphate disorders, arterial calcification, sodium and water overload, increased activity of the renin-angiotensin-aldosterone system and sympathetic tone [3].

Troponins are valuable prognostic biomarkers of CVD risk and mortality [4]. In the general population serum cardiac troponin levels are widely used to diagnose myocardial ischemia and damage. Cardiac troponin T (cTnT) and I are myocardial proteins that form a complex that plays a physiologic role in the regulation of myocardial contraction. The isoforms of human troponin are encoded by specific genes, hence these markers are considered to be unique to the heart. Troponin complex is located intracellularly, thus increased blood concentration of these markers indicates the cardiac injury. However serum troponin levels in the patients with renal failure are permanently elevated even in the absence of ischemia. Since there is no clear explanation of this phenomenon the diagnosis of heart disease or acute coronary syndrome remains challenging in this group. The previous studies have indicated that the reduced renal clearance is the most likely but not the sole mechanism for troponin elevation in CKD. Despite its constant elevation troponin still holds a potential as a marker of myocardial injury in CKD [5] and the troponins still preserve its usefulness as a marker of the cardiovascular risk and risk of short-term mortality [6].

Hemodialysis (HD) therapy is a life-sustaining procedure for the end-stage renal disease and is the most popular method of the renal replacement therapy. It involves toxin removal through molecule diffusion and fluid removal through ultrafiltration, however the specific schedule of this treatment and the variation of hydration status between and during

HD sessions exert significant hemodynamic effects, which may negatively affect cardiovascular system and blood pressure (BP). HD patients are characterized by a particularly high prevalence of coronary arteries atherosclerotic changes, left ventricular hypertrophy, arterial wall stiffness, reduced peripheral compliance, impaired microcirculation and ineffective vasoregulation, which may all predispose to reduced coronary reserve and cardiac ischemia. Additionally 20–30% of intermittent HD treatments are complicated by episodes of intradialytic hypotension (IDH). Hemodialysis procedure may also lead to myocardial stunning and hibernation [7]. All of these factors cumulate during hemodialysis that may lead to myocardial ischemia and injury, and thereby to cardiac troponin release.

High sensitivity troponin T (TnT-hs) is a biomarker that is widely measured to detect acute myocardial ischemia. Its assessment permits the detection of very low levels of TnT and may be particularly important in the patients with a short duration from symptom onset, but so far little has been known about the influence of a standard hemodialysis procedure on high sensitivity troponin T concentrations.

The aim of the study was to access the effects of hydration status, anemia, variations of blood pressure and heart rate induced by hemodialysis on intradialytic changes of high sensitivity troponin T, in chronic hemodialysis patients.

## Material and methods

The study group included 50 patients (35 men and 15 women, mean age 65 ± 12 years) with ESRD, treated by the intermittent hemodialysis using low-flux dialyzers with Helixone membrane (Fx-class Low Flux Dialysers, Fresenius Medical Care, Bad Homburg, Germany), 3 times per week, with short dialysis vintage (median 7 months, range 3–45 months). 72% of the patients were dialyzed through an arterio-venous fistula and 38% through a central venous catheter. The mean single hemodialysis session lasted 3 hours and 39 minutes with standard deviation (SD) 22 minutes. The causes of ESRD in study group were diabetic nephropathy 26% (n = 13), chronic glomerulonephritis 16% (n = 8), hypertensive nephropathy 10% (n = 5), polycystic kidney disease 10% (n = 5), nephrolithiasis 8% (n = 4), urosepsis 2% (n = 1) and unestablished etiology 28% (n = 14). Ischemic heart disease had been diagnosed before the onset of the study in 40% of patients and chronic heart failure in 24%. Thirty six percent of individuals in the study group were diabetic. Basic characteristics of the study group are shown in table I.

**Table I.** Clinical characteristics of the study group

| Subjects (n = 50) | |
|---|---|
| **Age (years)** | **65 ± 12** |
| Sex | Male 70% (n = 35)<br>Female 30% (n = 15) |
| Dialysis vintage (months) | Median 7<br>Min. 3, max. 45 |
| Time of each HD session | 3h 39 min. ± 22 min. |
| Vascular access through HD catheter | 25% (n = 14) |
| Vascular access through arterio-venous fistula | 75% (n = 36) |
| Ischemic Heart Disease | 40% (n = 20) |
| Diabetes Mellitus | 36% (n = 18) |
| Atrial Fibrillation | 14% (n = 7) |
| Chronic heart failure | 24% (n = 12) |
| Hemoglobin (HGB) (g/dL) | 10.7 ± 1.5 |
| HGB < 10 g/dL | 26% (n = 13) |
| HGB ≥ 10 g/dL | 74% (n = 37) |

All study procedures were performed during the second dialysis session of the week (mid-week dialysis). The chest pain or other symptoms suggesting acute coronary syndrome or exacerbation of chronic heart failure (CHF) as well as infections or other acute illnesses, were the exclusion criteria.

Blood sampling was performed at two timepoints: directly before the dialysis session (predialysis sample) and after the prescribed dialysis time was completed (postdialysis sample). The blood samples were collected for the measurement of the serum concentration of TnT-hs, NT-proBNP, urea, albumin and full blood count. For the additional calculations all postdialysis values of TnT-hs and NT-proBNP were adjusted for the changes in their concentration caused by hemoconcentration, caused by ultrafiltration, using formula [8]:

$$\textit{Adjusted TnT-hs formula} = \frac{\textit{current TnT-hs after HD}}{\textit{serum albumin after/before HD}}$$

The hydration status was assessed by bioimpedance spectroscopy (Body Composition Monitor, Fresenius Medical Care AG & Co, Bad Homburg, Germany), which involves placing 4 electrodes one on each extremity. The result taken for analysis was an arithmetic mean of three consecutive measurements. Overhydration grade was calculated using the following formula:

$$\textit{Grade of overhydration (\%)} = \frac{\textit{overhydration befor HD [kg]}}{\textit{dry weight [kg]}} \times 100\%$$

Additionally the information about the mean intradialytic weight gains and dry weight were collected from 2 months prior data acquisition and were used to calculate the percentage interdialytic weight gain.

Blood pressure and heart rate were monitored noninvasively, by BR-102 plus ABPM system (Schiller, Warsaw, Poland sp. z o.o.), during all hemodialysis procedure. The monitors cuff was placed on the non-dominant arm of the patient or, in case of patients dialyzed through an arterio-venous fistula, on the opposite arm. For the precise measurements cuff size was adjusted individually. The device recorded the readings of blood pressure and heart rate each 15 minutes, which resulted in up to 21 readings for a single hemodialysis session. Echocardiography was performed by one experienced echocardiographist on 36 patients of 50, within 2 hours after hemodialysis (Vivid q, GE Healthcare, Wauwatosa, USA).

The statistical calculations were performed with the Statistica 13.1 software (StatSoft Poland, Cracow, Poland). Shapiro-Wilk test was used to check the normality of data and non-parametric tests: Mann-Whitney U test for independent samples and Wilcoxon signed rank test for paired samples. Correlations were calculated using Spearman's formula.

## Results

High sensitivity serum cardiac troponin T concentration was above normal range in 98% patients before hemodialysis and in all patients after hemodialysis compared to the upper limit of reference range for the general population. Predialysis values of TnT-hs ranged from 14 to 255 ng/L and postdialysis from 16 to 234 ng/L. Median TnT-hs level accounted for 82 ng/L before and 84 ng/L after hemodialysis, which comprises 586% and 600% of the upper limit of normal range, respectively (Figure 1). The increase of TnT-hs induced by the hemodialysis procedure in whole study group was small — about 2.4%, but statistically significant ($p = 0.004$) (Figure 2). The high sensitivity troponin T levels correlated positively with overhydration status before a single hemodialysis procedure measured by body composition monitor both before ($r = 0.31$, $p = 0.03$) and after HD ($r = 0.28$, $p = 0.055$). TnT-hs correlated also with mean interdialytic weigh gain in two months before the study before HD ($r = 0.43$, $p = 0.02$) and after HD ($r = 0.5$, $p = 0.003$) (Figure 3). There was a positive correlation between TnT-hs concentration and mean heart rate before HD ($r = 0.37$, $p = 0.008$) and after HD ($r = 0.37$, $p = 0.0087$) (Figure 4), and with the mean systolic blood pressure during HD before HD ($r = 0.3$, $p = 0.026$) and after HD ($r = 0.3$, $p = 0.031$) (Figure 5). There was no statistically significant correlation between blood pressure and heart rate standard deviation with TnT-hs levels.

There was a negative correlation of TnT-hs before dialysis and hemoglobin ($r = –0.28$, $p = 0.047$). Patients with a hemoglobin level below 10 g/dL have significantly higher TnT-hs concentration compared to individuals with hemoglobin level above 10 g/dL, before HD: 107 vs. 73 ng/L ($p = 0.013$) and after HD 106.9 vs 79 ng/L ($p = 0.015$), respectively. TnT-hs concentrations did not change significantly during HD in anemic

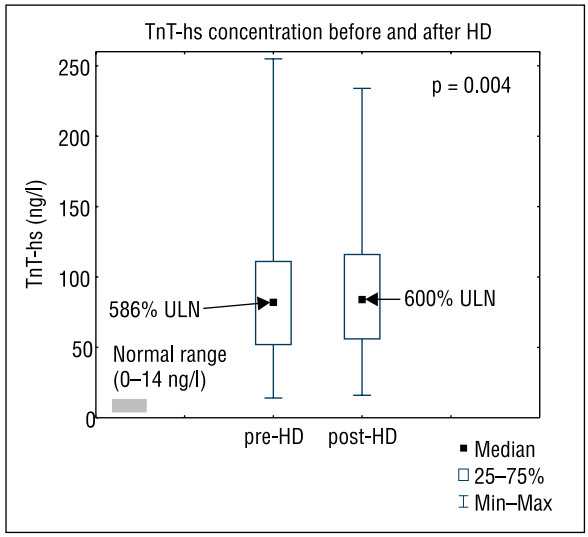


**Figure 1.** Serum concentrations of TnT-hs before and after hemodialysis

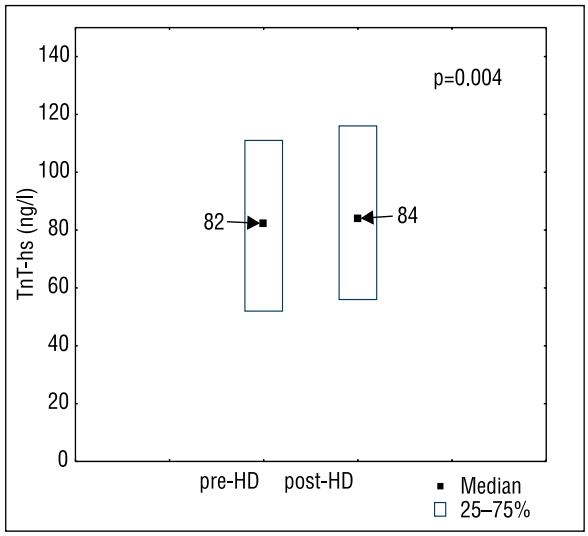


**Figure 2.** Intradialytic changes of TnT-hs serum concentration

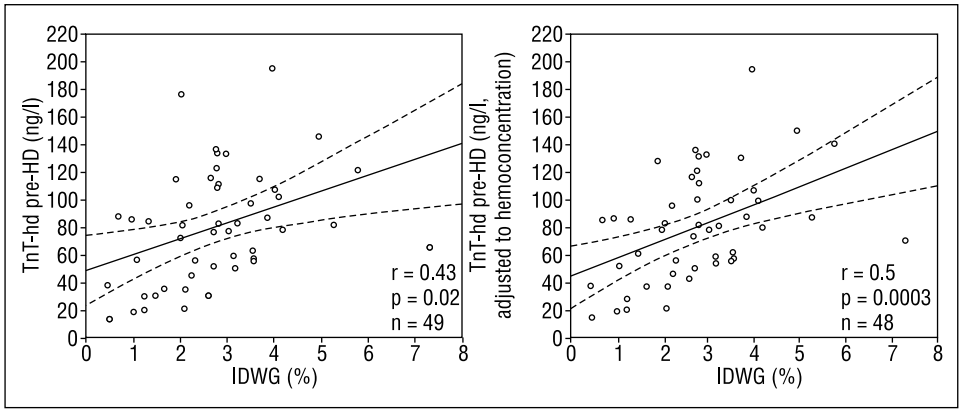


**Figure 3.** Correlation between interdialytic weigh gain and TnT-hs concentrations

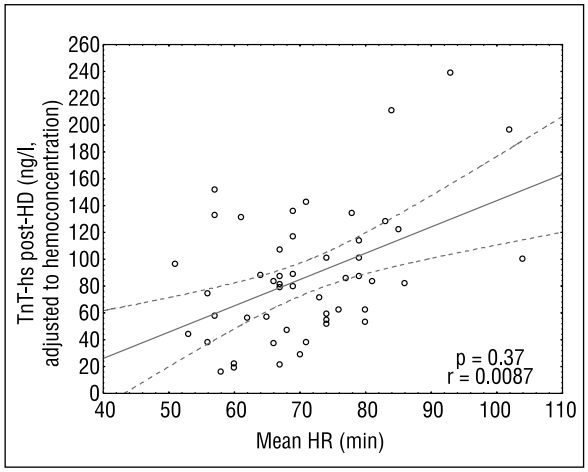


**Figure 4.Correlation** between heart rate during HD session and TnT-hs levels

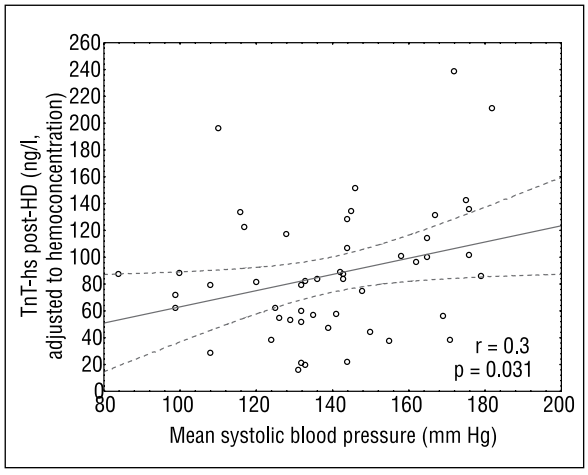


**Figure 5.** Correlation between mean SBP during HD session and TnT-hs levels

patients, moreover the increase of high sensitivity troponin T was revealed in those with hemoglobin level above 11 g/dL — from 70 to 75 ng/L (p = 0.014). In the subgroup of patients with diabetes the tendency to higher TnT-hs levels was noted, as shown in Figure 6. Predialysis, postdialysis levels and intradialytic changes of ThT-hs were similar in patients with and without ischemic heart disease and the same applied to chronic heart failure. High sensitivity troponin T concentrations correlated positively with left ventricle mass (r = 0.43; p = 0.01). Besides the intradialytic increase of TnT-hs in the patients with decreased left ventricle ejection fraction LVEF < 50% was 2.7 ng/L while in those with LVEF > 50% was much lower 0.8 ng/L (p = 0.02) (Figure 7).

## Discussion

Serum troponin assays are widely used in patients with ESRD undergoing hemodialysis despite the unspecific increase of their serum concentration. That was also seen in our patients since almost all of the study subjects had elevated levels of TnT-hs both pre- and post-dialysis. In one previous study of Mbagayasa et al, designed to evaluate a biological variation of cardiac troponin in stable HD patients, new-generation, serum high sensitivity troponin T was elevated in almost all patients, whereas troponin I was above normal range in only 30% of HD patients [9]. The mechanisms underlying troponin release in CKD include direct myocardial damage from circulating uremic endotoxins and an adverse metabolic milieu, subclinical epicardial or microvascular coronary artery disease (CAD) and heart failure, "demand" ischemia secondary to volume shifts and hemodynamic stressors during HD [10]. Multivessel CAD is often seen in angiographic studies of asymptomatic HD patients [11]. In contrast to what we have expected, cTnT-hs levels in our study group did not significantly differ in the individuals with or

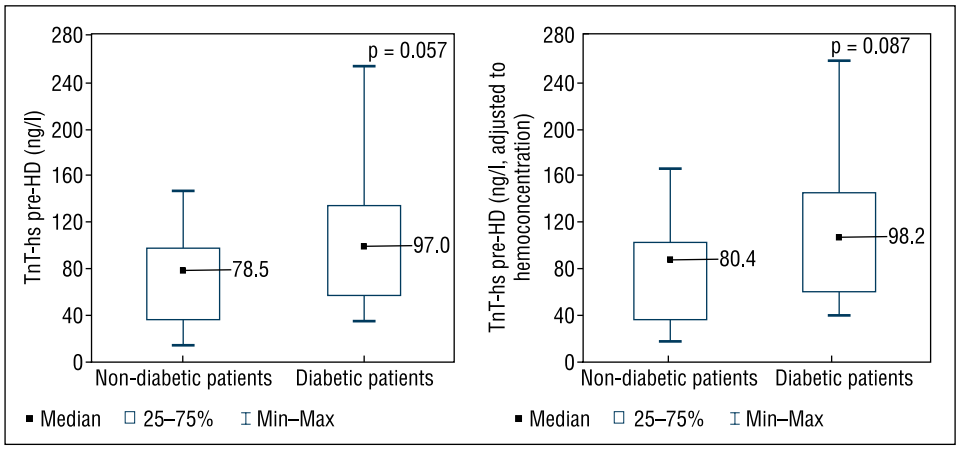


**Figure 6.** TnT-hs serum concentrations before and after HD in diabetic patients

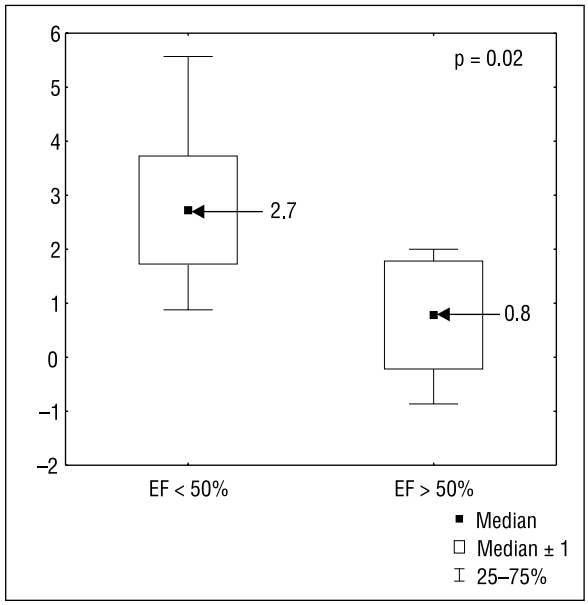


**Figure 7.** Intradialytic increase of TnT-hs in patients with decreased LVEF

without a cardiovascular disease history. The possible reason may be the underdiagnosis of CAD in our ESRD population. The concentration of cardiac high sensitivity troponin T correlated with left ventricle mass in our study that could be a consequence of a higher number of cardiomyocytes where this marker is stored and released from. In the patients with chronic kidney disease, the prevalence of left ventricular hypertrophy is strikingly increased that in particular applies to concentric hypertrophy. About 50% of the patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73 $m^2$ develops left-ventricular hypertrophy [12]. Factors such as reduced coronary reserve in chronic kidney disease and reduced cardiac capillary density in the thick cardiac muscle, could make large left ventricle muscle more susceptible to short episodes of ischemia and damage, as a consequences of hemodynamic changes during hemodialysis procedure, and more massive release of such cardiac biomarkers as troponins T.

The subgroup of hemodialyzed patients, in which we found a tendency to higher cardiac high sensitivity troponin T concentrations, were the patients with diabetes. In addition to high prevalence of coronary atherosclerosis, diabetic patients on hemodialysis have been shown to have a reduced coronary flow reserve even in the absence of coronary vessel lesions [13], what may predispose them to myocardial ischemia.

In our study we noted a small but a significant increase of the concentration of high sensitivity cardiac troponin T after a hemodialysis session. A diagnosis of myocardial infarction requires larger changes and the presence of symptoms and/or changes in ECG. However, even small increases might be associated with major adverse cardiac events in the further course of the disease, as shown in a post-surgery study [14].

Most previous studies of cardiac biomarkers in ESRD present conflicting results [15–19]. Postdialysis values increased, decreased or remained stable compared to predialysis concentrations. In most of the studies however older generation of troponin I and T assays were used, which levels become elevated only after 6 to 12 hours after the episode of ischemia. This is beyond the window of blood sampling in most of the currently available studies. TnT-hs assays seem to be more useful for that purpose as they detect smaller amounts of troponins and in shorter time after the event. Other factors could be also important, as a type of dialysis membrane used for the procedure. Sommerer et al. measured cTnT levels in 49 chronic hemodialyzed patients before and after HD session by a third generation assay [20]. Level of

cTnT increased significantly after a hemodialysis in which low-flux (LF) dialyzer was used, but remained unchanged when high-flux (HF) dialyzer was utilized. A main reason for the stable levels of cardiac markers in that study [20], or a reduction reported by others [8], is that the approximate 97% cutoff level of high flux dialyzers was i.e. 40 kDa, while for the low flux dialyzers cutoff was much lower, i.e. 6 kDa. The molecular weight of NT-proBNP is 8.5 kDa and troponin T 37 kDa and its fragments ranging in size from 8 to 25 kDa, so they can be easily removed during HF-HD procedure. The elevation of TnT during hemodialysis using low flux dialyzer, was in the authors' opinion partly due to hemoconcentration. In our observation, where the low flux membranes were used, the significant increase of TnT-hs was seen even after the correction for the effect of hemoconcentration, induced by withdrawal of fluid during dialysis. Similar results were obtained by Laveborn et al., who studied the change of cardiac biomarkers TnT-hs and NT-proBNP in 31 hemodialyzed patients after hemodialysis with high and low flux dialyzer. They noted, that during LF-HD the TnT-hs level increased from 95 to 101 ng/L ($p = 0.001$), whereas during HF-HD decreased from 84 to 70 ng/L ($p = 0.003$) [8]. The significant increase in TnT-hs during low-flux HD strongly indicates that the dialysis session may induce a potentially detrimental effect on the myocardium. The limited increase of TnT-hs after hemodialysis can reflect the myocardial damage but could also be a sign of a reduced myocardial blood flow or myocardial stunning during HD. The evidence of HD-induced myocardial ischemia came from electrocardiogram-based studies and isotopic perfusion imaging. Zuber et al. demonstrated silent ST-depression occurring during hemodialysis [21] and its rates varied between 15 to 40% in next studies [22–24]. Singh et al. observed the dialysis-induced myocardial perfusion defects in seven of ten patients, examined by single-photon emission computed tomography [25]. Another reason for the increase of the cardiac markers could be the exposure to coronary microemboli that are often present during HD because of the leakage of small air bubbles into the blood drains [26]. The capability of hemodialysis to induce subclinical myocardial ischemia could be related also to high ultrafiltration rate and hemodynamic instability. HD-induced myocardial stunning was identified in around 60% of 70 HD-patients studied with serial intradialytic echocardiography by Burton et al. [27]. In a multivariate analysis intradialytic reduction in BP and ultrafiltration volume were independent risk factors of heart injury. Selby and McIntyre also found that the ultrafiltration volumes were a risk factor for the development of myocardial stunning during dialysis [28]. In our analysis the fluid retained in the body between dialyses, that was reflected by the interdialytic weigh gain and overhydration status of patient before single HD procedure correlated positively with a predialysis cTnT-hs. What is interesting, we found that the patients with a decreased LVEF were particularly prone to cardiac damage during dialysis, because of higher elevation of TnT-hs during HD compared to those with LVEF > 50%. Such patients, besides general ill condition of the heart, are usually more overhydrated due to heart failure, what could be an additional risk factor of HD-induced cardiac stunning. Other candidate risk factor of chronic cardiac ischemia recognized in our study was a hemoglobin level below 10 g/dL, but the patients with hemoglobin values above 11 g/dL could be also predisposed to the acute myocardial ischemia during HD. TnT-hs in this group increased significantly by 5% during HD. It could be speculated that the hemoconcentration in such patients could predispose them to thrombosis and coronary arteries occlusion. It is generally recognized, that there has been no additional cardiovascular benefit from the correction of hemoglobin concentrations to above 12 g/dL.

The importance of the hemodynamic stability in the pathogenesis of HD-induced ischemic injury was illustrated in the studies that investigated the modification of dialysis technique to maintain adequate blood pressure [28]. Higher mean blood pressure and a reduction of intradialytic hypotension (IDH) episodes improved myocardial perfusion [29]. However in our study the levels of TnT-hs in the patients with IDH were similar to those in patients with optimal blood pressure control. Previous studies also showed that the local and global myocardial blood flow decreased during hemodialysis, independently from a concurrent level of systemic blood pressure [30]. We noticed a positive correlation of TnT-hs with systolic blood pressure and heart rate, suggesting that high blood pressure and fast heart rate might be also harmful. The correlation of TnT-hs with systolic blood pressure may be rather the result of a higher prevalence of left ventricle hypertrophy in patients with hypertension. Coronary blood flow takes place mostly during diastole, and the driving pressure gradient is the difference between mean diastolic pressure in the aortic root and mean right atrial pressure. Both the driving pressure gradient and the duration of diastole are the essential mechanical determinants of coronary blood flow [31]. That is why any factor that decreases the diastolic pressure-time integral will also decrease coronary blood flow, that

is, any decrease in diastolic aortic root pressure, any increase in right/left ventricular diastolic pressure, which may be caused be sudden changes of systemic blood pressure or any reduction in diastolic duration, which happens in acceleration of heart rate, will decrease coronary blood flow and can exacerbate ischemia during hemodialysis and thereby lead to troponin release.

In summary, the identification of clinical manifestations of cardiovascular disease, in particular ischemic heart disease, is challenging in patients with chronic kidney disease. Many patients with ESRD are asymptomatic or develop atypical manifestations despite a major acute ischemic event. Clinicians must be fully aware of this fact to avoid underdiagnoses of potentially life-threatening cardiovascular events. This is particularly relevant in hemodialyzed patients, who have notably worse prognoses. Chronically elevated troponins are frequent source of clinical uncertainty in this population. The knowledge about increased concentrations of cardiac high sensitivity troponin T and influencing factors, including hemodialysis procedure, is crucial for the identification which group of ESRD patients and in which clinical situation is at particular high risk of acute cardiovascular event.

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