LETTER TO THE EDITOR

FAILING HEART AND IMPORTANCE IN MYOCARDIAL TRACE ELEMENT: PRELIMINARY REPORT

B. KOZLOWSKA[1], B. SOCHANOWICZ[2], H. POLKOWSKA-MOTRENKO[2], M. KRUSZEWSKI[2,3], A. CICHA-MIKOŁAJCZYK[4], L. KRAJ[5,6], M. KUSMIERCZYK[7] and P. LESZEK[1]

[1]Department of Heart Failure and Transplantology, The National Institute of Cardiology, Warsaw, Poland; [2]Centre for Radiobiology and Biological Dosimetry, Institute of Nuclear Chemistry and Technology, Warsaw, Poland; [3]Department of Molecular Biology and Translational Research, Institute of Rural Medicine in Lublin, Poland; [4]Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion, National Institute of Cardiology, Warsaw, Poland; [5]Department of Hematology, Oncology and Internal Diseases, Warsaw Medical University, Warsaw, Poland; [6]Laboratory of Neurogenomics, Institute of Genetics and Animal Breeding, Polish Academy of Sciences, Jastrzebiec, Poland; [7]Department of Cardiac Surgery and Transplantology, National Institute of Cardiology Warsaw, Poland

Received October 17, 2019 – Accepted April 15, 2020

To the Editor,

Micronutrients and trace ions play a complex physiological and pathophysiological role in myocyte function. Therefore their proper levels are crucial to maintaining intracellular homeostasis, whereas dysregulation can cause significant pathological consequences.

Iron plays a crucial role in oxygen management (as a component of haemoglobin, myoglobin, oxidative enzymes and respiratory chain proteins). The maintenance of normal iron metabolism is particularly essential for cells characterized by fast metabolism and high energy demand, such as exercising skeletal myocytes and cardiomyocytes. Hence, in heart failure (HF), regardless of the presence of anemia, in iron-deficient patients, iron supplementation is recommended to improve functionality and quality of life. However, iron excess exerts harmful effects due to iron-induced oxidative damage, which can alter myocyte, but also endothelial and smooth muscle cell functions (1).

Zn (Zn) is a constituent of many enzymes important in cellular signaling pathways. Therefore, Zn deficiency induces changes in apoptotic, inflammatory, oxidative and nitric oxide pathways in cardiomyocytes, resulting in morphological and functional changes in cardiac tissue (2). However, also Zn excess can be harmful to myocytes. In HF, neurohormonal activation leads to increased Reactive oxygen species (ROS) and/or Reactive nitrogen species (RNS) production, which is related to increased Zn demand in cells (3). High levels of Zn promote dysregulation of Ca^{2+} turnover, which consequently leads to contractility impairment together with increase oxidative stress, mitochondrial dysfunction and cellular apoptosis (2). The role of selenium in cardiomyocytes is complex, and its deficiency promotes cell damage through activation of apoptosis and necrosis (4). In contrast, cobalt is found in living organisms only in cobalamin (vitamin B12) - necessary for the proper functioning of cells. However, excessive cobalt levels can cause

Key words: heart failure; myocardium; zinc; selenium; iron; cobalt

Corresponding Author:
Dr Bogna Kozłowska,
National Institute of Cardiology Warsaw,
Department of Heart Failure and Transplantology ,
Alpejska 42, 04-628 Warsaw, Poland
Tel.: +48 22 343 44 83 - Fax: +48 22 343 44 83
e-mail: bkozlowska@ikard.pl

0393-974X (2020)

apoptosis, necrosis and DNA oxidative damage (5).

In this study, zinc-Zn, iron-IR, selenium-Se and cobalt-Co concentration in the left ventricle (LV) of failing hearts (FH) were assessed and compared to LV from non-failing hearts (NFH).

MATERIALS AND METHODS

The FH samples (explanted hearts) were collected from 27 HF patients (21 males, 6 females, mean age 50±13 years) transplanted due to ischemic (n= 18) or non-ischemic (n=9) cardiomyopathy. The patients presented severe LV dysfunction with reduced ejection fraction (EF) (26±16%) and elevated NT-pro BNP levels (6076±5083 pg/ml), the available detailed clinical characteristics were presented previously (6). The control group consisted of 7 non-failing hearts (NFH) LV samples (mean age 30±10 years), who died from head trauma and were unsuitable for heart transplantation due to technical reasons. Subjects had LVEF within normal range (EF >60%)

Total myocardial ions concentration were assayed by Instrumental Neutron Activation Analysis (INAA). Frozen samples were lyophilized using Freezemobile XL (Virtis Company, New York, US), weighted and packed directly to HDPE snap-cap capsules (Faculteit Biologie, Vrije Universiteit, Amsterdam, Holland). Elemental standards were prepared by dropping appropriate amounts of the standard solution onto filter paper circles f = 7.7 mm (Schleicher & Schull, US) placed in high purity PE snap-cap capsules and left to dry. Since there are no certified human heart tissue reference materials of this type of matrix, the quality control was performed by analyzing certified reference material NIST 1577c Bovine Liver (National Institute of Standards and Technology - NIST, US). Samples and standards were irradiated at the neutron flux: 1014 cm-2 s-1 for 50 min in nuclear reactor MARIA (Świerk, Poland). After 3-week cooling, gamma-ray emission of the samples and standards was measured with the GENIE-2000 Canberra Gamma Spectrometry System. Data acquisition was accomplished using commercially available software GENIE 2000 (Canberra Industries, Inc. Meriden, US).

Statistical analysis

Test for normality of each analyzed parameter was performed by the Shapiro-Wilk test. Comparisons between groups (FH *vs* NFH) were performed with the ANOVA or Wilcoxon tests. Spearman's rank test was used to assess the correlation between the severity of HF based on the ejection fraction and NT-pro BNP and the concentration of individual ions.

RESULTS

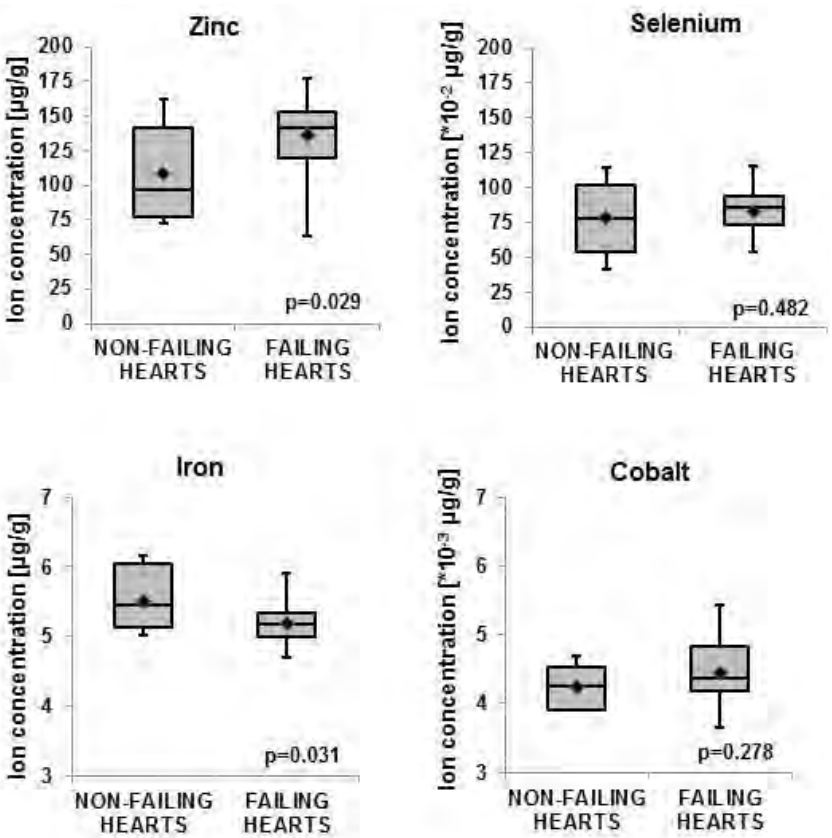
The analysis in FH LV revealed an increased Zn (136.17 μg/g±26.76 *vs* 108.6 μg/g±34.55; p=0.029) and reduced iron (186.34 μg/g±58.77 *vs* 267.89 μg/g ±129.1; p= 0.031) myocardial load as compared with NFH. No changes were found between FH/NFH in selenium and cobalt concentration (Fig. 1A). The observed changes were independent of etiology or gender (Fig. 1 B and C).

In correlation analysis, we attempted to correlate the severity of HF, based on EF and NT-pro BNP, with the level of ions. Although, important correlations were found only for selenium myocardial load, a positive correlation with EF (p=0.033, r=0.42) and negative correlation with NT pro-BNP (p=0.033, r=-0.49). Therefore, in the FH group the lower selenium concentration, corresponds with more severe left ventricle dysfunction (lower EF and higher NT-pro BNP).

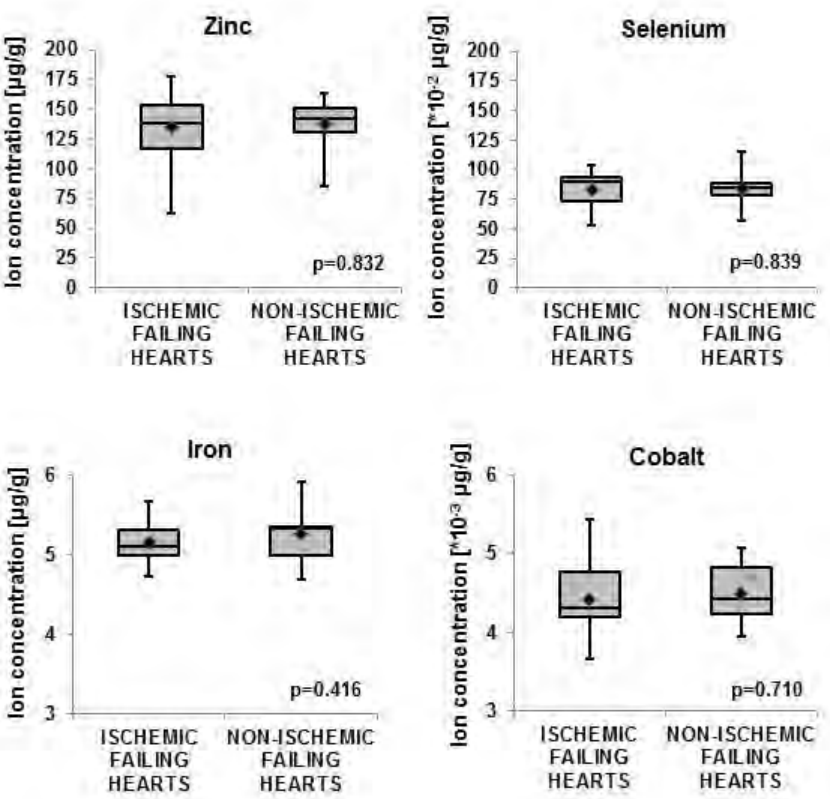
DISCUSSION

This study supports the observation that the iron load is reduced in advanced HF, as was published previously (6). Hence, the latest guidelines for HF treatment recommends iv iron supplementation in iron-deficient patients. With regard to Zn, we found in FH that its myocardial level is increased. Higher Zn levels may potentially affect myocyte functions. As been previously demonstrated, in isolated cardiomyocytes, pathological stress leads to a dramatic increase in cellular Zn load which, in turn, causes dysregulation of calcium transport, impairment in excitation-contraction coupling. Moreover, subsequent mitochondrial dysfunction causes elevated ROS/RNS production and, finally, stimulation of signaling pathways, leading to apoptosis (2). On the other hand, low Zn serum level was associated with impaired exercise capacity and high mortality (7). This discrepancy between myocardia/serum levels can be easily explained

A


Zinc
Ion concentration [µg/g]
200
175
150
125
100
75
50
25
0
p=0.029
NON-FAILING HEARTS
FAILING HEARTS
Selenium
Ion concentration [*10-2 µg/g]
p=0.482
NON-FAILING HEARTS
FAILING HEARTS
Iron
Ion concentration [µg/g]
7
6
5
4
3
p=0.031
NON-FAILING HEARTS
FAILING HEARTS
Cobalt
Ion concentration [*10-3 µg/g]
p=0.278
NON-FAILING HEARTS
FAILING HEARTS

B


Zinc
Ion concentration [µg/g]
200
175
150
125
100
75
50
25
0
p=0.832
ISCHEMIC FAILING HEARTS
NON-ISCHEMIC FAILING HEARTS
Selenium
Ion concentration [*10-2 µg/g]
p=0.839
ISCHEMIC FAILING HEARTS
NON-ISCHEMIC FAILING HEARTS
Iron
Ion concentration [µg/g]
6
5
4
3
p=0.416
ISCHEMIC FAILING HEARTS
NON-ISCHEMIC FAILING HEARTS
Cobalt
Ion concentration [*10-3 µg/g]
p=0.710
ISCHEMIC FAILING HEARTS
NON-ISCHEMIC FAILING HEARTS

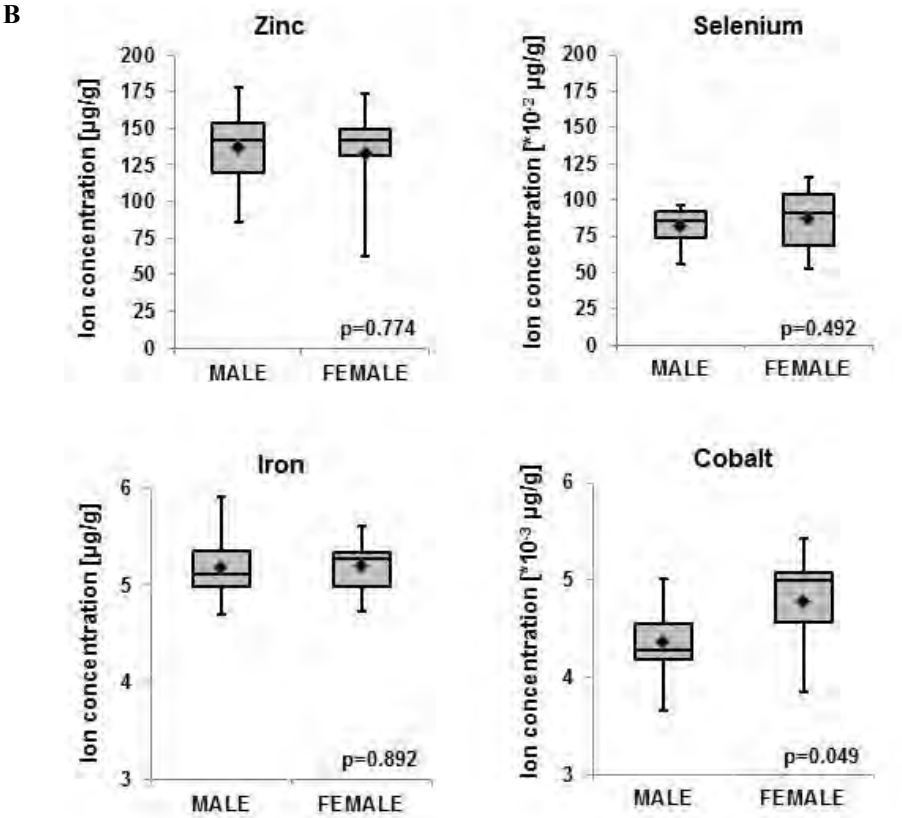


Fig. 1. ***A)*** *Ion (iron, zinc, cobalt, selenium) in non-failing (NFH) vs. failing (FH) myocardium The assessment of ions concentration between non-failing hearts (NFH) and failing hearts (FH) revealed increased zinc (136.17 µg/g±26.76 vs 108.6 µg/g±34.55; p=0.029), and reduced iron (186.34 µg/g±58.77 vs 267.89 µg/g ±129.1; p= 0.031) myocardial load in failing left ventricle. No changes were found changes between NFH/FH in selenium and cobalt concentration.* ***B)*** *Filing myocardium ions (iron, zinc, cobalt, selenium) concentration- comparison ischemic vs non-ischemic etiology. The assessment of ions concentration between ischemic and non-ischemic failing hearts revealed no significant difference.* ***C)*** *Filing myocardium ions (iron, zinc, cobalt, selenium) concentration comparison - male vs female. The assessment of ion concentration between male and female revealed no significant difference.*
Zinc, Selenium (row data), Iron, Cobalt (logarithmic data) ◆ *- Mean* ▭ *- Median*

by increased oxidative myocardial stress, which leads to upregulation in a Zn binding protein – metallothionein, and in turn increased Zn uptake (3). Thus, disrupted Zn homeostasis may be both the effect and also the cause of myocardial dysfunction. Our observation may seem important especially in Zn supplementation context.

There was no difference in selenium concentration between FH and NFH. However, only in HF patients, a correlation was demonstrated between the level of left ventricle dysfunction (EF and NT-proBNP – both different markers) and myocardial selenium load. To achieve a clear explanation, this finding needs further investigation. However, it is in line with publications showing that a selenium deficiency is associated with various manifestations of cardiomyopathy, such as cardiogenic shock, heart dysfunction, failure and arrhythmia. The condition was described for the first time in China and was named Keshan disease. All clinical symptoms were associated with histopathological findings including multifocal myocardial necrosis, often associated with infiltration of inflammatory cells. Selenium is a crucial component of selenoproteins, which maintain physiological muscle function (4).

It becomes apparent that proper balance of

micronutrients and trace ion homeostasis is essential for physiological functioning of cardiomyocytes. Therefore, further investigations, especially on Zn, selenium and other not fully explored trace ions are necessary to understand the crucial role of properly balanced micronutrition in HF.

The limitations of the present study are that the investigated patients presented with advanced HF. Also, a small population of 7 biopsies (NFH) from brain-injured donors was used as a reference for the analysis. Both groups did not receive the same treatment, also mean ages were different, therefore the results from the study should be interpreted cautiously. Unfortunately, serum levels of selected ions were not measured. Thus, it is impossible to compare myocardial ions load with their serum levels.

REFERENCES

1. Kobak KA, Radwańska M, Dzięgała M, et al. Structural and functional abnormalities in iron-depleted heart. Heart Fail Rev 2019; 24(2):269-77.
2. Turan B. A brief overview from the physiological and detrimental roles of zinc homeostasis via zinc transporters in the heart. Biol Trace Elem Res 2019; 188(1):160-76.
3. Rosenblum H, Wessler JD, Gupta A, Maurer MS, Bikdeli B. Zinc deficiency and heart failure: a systematic review of the current literature. J Card Fail 2020; 26(2):180-89.
4. Benstoem C, Goetzenich A, et al. Selenium and its supplementation in cardiovascular disease—what do we know? Nutrients 2015; 7(5):3094-118.
5. Packer M. Cobalt cardiomyopathy: a critical reappraisal in light of a recent resurgence. Circ Heart Fail 2016; 9(12).
6. Leszek P, Sochanowicz B, Szperl M, et al. Myocardial iron homeostasis in advanced chronic heart failure patients. Int J Cardiol 2012; 159(1):47-52.
7. Yoshihisa A, Abe S, Abe S, Kiko T et al. Association of serum zinc level with prognosis in patients with heart Failure. J Card Fail 2018;24(6):375-83.