

The possible molybdenum involvement on right ventricular performance in LVAD patients – initial study

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Abstract:

Background: The left ventricular device (LVAD) implantation has evolved as a standard of care for heart failure (HF) patients. Optimal management is paramount, including additional strategies to achieve durable results. The study aimed to compare the right ventricular characteristics after LVAD implantation with trace element serum accumulation and to estimate the potential impact of specific trace elements on right ventricular performance.

Method: There were 25 male patients in median (Q1 – Q3) age of 56 (51 – 62) years treated with left ventricular assist device implantation (HM3, Abbott Corp. USA) due to end-stage heart failure.

Results: Patients presented with NYHA status I (12 (48%) patients) and II (13 (52%) patients) on the control follow-up check-ups, the median (Q1 – Q3) time of 421 (296 - 1277) days. The right ventricular diameter dilatation was observed in 7 (28%) patients and regression in 8 (32%) more patients. Among trace elements analysis, the significant differences related to molybdenum concentration between patients characterized by RV dilatation (1.76 (1.73 – 2.00) vs no-RV deterioration 2.61 (2.19 – 2.95) ug/l) was noted ($p=0.030$). While comparing the patients characterized by RV diameter regression (3.23 (2.92 – 3.61) ug/l vs control group (2.00 (1.73 – 2.19) ug/l), the significant difference related to molybdenum concentration was noticed ($p=0.018$).

Conclusions: The low serum molybdenum concentration can be linked to adverse right ventricular performance after LVAD implantation, contrary to higher molybdenum values related to right ventricular regression.

Keywords: LVAD 1; MCS 2; heart failure 3; trace elements 4; molybdenum 5.

1. Introduction

Heart failure is one of the current epidemiological problems that, in the end-stage disease, can be successfully treated by left ventricular assist device (LVAD) implantation [1]. Currently, novel drugs are under investigation to improve patients' clinical status [2]. As donation shortage borders organ transplantation, implantable LVAD devices have evolved as a standard of care for heart failure patients. Fully magnetic levitation is an almost exclusively implanted type of LVAD and is regarded as destination therapy in a high prevalence of clinical situations [3]. The satisfactory long-term results of mechanical support [4] depend on accurate patient referrals based on right ventricular characteristics [5]. Late right heart failure (RHF) is associated with decreased survival and right ventricular (RV) dysfunction dependent on various preoperative factors [6]. The right ventricle's complex anatomy and load-dependent physiology subsidize the struggle to predict and prevent post-LVAD right ventricular (RV) dysfunction. The progressive RV deterioration in durable LVAD recipients was reported to induce prothrombotic activation [7].

In the Remission from Stage D Heart Failure (RESTAGE-HF) multicenter study [8], LVAD therapy accompanied by medical support reported the intriguing phenomenon of myocardial structural and function recovery. Post-LVAD implantation, possible heart function improvement, and reverse structural remodeling were reported in relation to molecular indices [9]. The person-related genetic characteristics resulting in proteomic profiles convince distinct processes that, at least in theory, could be modified by co-factors.

Trace elements are considered co-factors of various enzymes involved in cardiovascular pathology [10,11,12]. They represent the possible marker of inflammatory activation [13] that their body concentration can be modified, and either insufficiency or excessive accumulation may result in a pathological process spurt [14]. The inflammatory background of cardiovascular pathology has been well presented [15,16]. The dependence of atherosclerosis location in the coronary bed on trace elements body gathering was presented in our previous reports [17,18].

One of the essential trace elements for metabolic homeostasis maintained in human organisms is Molybdenum (Mo) [19]. Molybdenum is regarded as a vital trace element involved in various homeostatic functions, including xanthine oxidase reductase (XOR), and is a key mediator in generating oxidative stress [20]. Another molybdenum-containing enzyme with a notable role in the oxidation processes is aldehyde oxidases (AOs) next to sulfite oxidase (SOX) [21,22]. Previous studies reported a mean serum Mo concentration of 0.58 ± 0.34 $\mu\text{g/l}$ among

healthy participants [23]. In the context of cardiovascular diseases, molybdenum may influence oxidative stress through its role as a cofactor for xanthine oxidase, which catalyzes the synthesis of uric acid, during which free oxygen radicals are produced. These free radicals can contribute to cell and tissue damage, one of the mechanisms leading to cardiovascular diseases [24].

The study aimed to compare the right ventricular characteristics after LVAD implantation with trace element serum accumulation and to estimate the potential impact of specific trace elements on right ventricular performance.

2. Materials and Methods

2.a. Patients

There were 25 male patients in median (Q1 – Q3) age of 56 (51 – 62) years treated with left ventricular assist device – Heartmate 3 (HM3) implantation (Abbott Corp., Illinois, USA) due to end-stage heart failure. There were 15 (60%) patients with non-ischemic and 10 (40%) with ischemic cardiomyopathy diagnosis.

All patients included in the analysis were white caucasian males with no dietary restrictions or additional supplementations.

On the control follow-up check-ups, the median (Q1 – Q3) time of 421 (296 - 1277) days, the echocardiographic results were compared with clinical status, and laboratory tests and trace elements serum evaluation.

2.b. Methods

The clinical evaluation was based on the New York Heart Association (NYHA) scale, a 6-minute walking test (6MWT) followed by transthoracic echocardiography performed by experienced echocardiographers and supported routine y laboratory tests, including N-terminal propeptide brain natriuretic peptide (NT-pro-BNP) serum concentrations.

2.b.1. Blood sample preparation

Serum samples were immediately frozen after collection in sealed polypropylene (PP) tubes until further processing. The samples were brought at room temperature and then mineralized using a high-pressure, closed microwave digestion system (Ethos One, Milestone,

Italy). Subsequently, 1 mL of the sample was transferred to quartz vessels containing 2 mL of 65% HNO₃ (Suprapur, Merck) and 0.5 mL of 30% H₂O₂ (Traceselect, Sigma Aldrich), and placed in a PP falcon tube. The digestion process was carried out in three stages: (1) a 15-minute ramp time to 200°C with a power of 1200 W, (2) a 45-minute hold time at 200°C and 1200 W, and (3) a 30-minute cooling period. The resulting solutions were quantitatively transferred to volumetric flasks and diluted to 40 mL with demineralized water (Direct-Q-3 UV, Merck, Darmstadt, Germany). Certified reference materials (CRMs) were used to assess the accuracy and establish the traceability of the measurement results: Trace Elements Serum L-2 (Seronorm, Billingstad, Norway) and ClinChek Serum Control Level II (Germany). Procedural blank solutions and certified reference materials were prepared in the same manner as the test samples.

2.b.2. Microchemical analytical procedure:

Inductively coupled plasma mass spectrometry ICP-MS Agilent 7700x system (Agilent, Santa Clara, CA, USA) was used to determine the concentration of the elements in the digested serum samples. The instrumental parameters were automatically optimized using the Tuning Solution (Agilent). The operating conditions for the ICP-MS were as follows: RF power was 1550 W; the plasma gas flow rate was 16 L min⁻¹; the nebulizer gas flow rate was 0.95 L min⁻¹, and the auxiliary gas flow rate was 0.90 L min⁻¹. The octopole reaction system (QRS) with helium was used to eliminate spectral interferences, with a helium flow rate of 3.5 mL/min. A 10 µg L⁻¹ solution of ⁸⁹Y and ¹⁰³Rh was used as an internal standard to eliminate non-spectral interferences. An external calibration curve was prepared by preparing 5 standard solutions in the concentration ranges and 5–500.0 µg L⁻¹ for Ca, Mg, K, Fe µg L⁻¹, and 0.05–50 µg L⁻¹ for other elements. Calibration solutions were prepared by diluting a 10 mg L⁻¹ multielement stock solution in 5% HNO₃ (Multi-Element Calibration Standard 3, PerkinElmer, Waltham, MA, USA).

2.b.3. Microchemical analytical performance:

The analytical method parameters were estimated based on repeated measurements of blank solutions, calibration standards, and CRMs. The linearity of the calibration curve was calculated as the correlation coefficient (R), with values of 0.9996 for all analytes. The LOD values ranged from 0.003 µg L⁻¹ for Mo to 5 µg L⁻¹ for Ca, K. The limit of detection (LOD) was calculated according to $LOD = 3.3 S/b$, where S is the standard deviation of the results

obtained for the blank samples and b is the sensitivity ($n = 5$). Precision values, calculated as coefficient of variation (CV) (%), ranged from 1.2% to 3.6% for all elements. The trueness of the analytical method was assessed by analyzing the certified reference materials (CRM) Seronorm™ Trace Elements Serum L-2 and ClinChek Serum Control Level II, which were subjected to the preparation steps according to the above-described procedure. Trueness, expressed as recovery values (%), ranged from 95% to 104%. The Student's t -test results indicated no significant differences between the measured concentrations (mean $\pm$ SD) and the certified concentrations (mean $\pm$ standard uncertainty). In order to perform molybdenum triplicate analyses for reference materials, Seronorm L-2 (non-certified Mo value 0.9 $\mu\text{g/L}$) and ClinChek Serum Control Level I (certified Mo content $1.64 \pm 0.64 \mu\text{g/L}$) showed values (mean $\pm$ SD) of 0.95 ± 0.08 and $1.61 \pm 0.12 \mu\text{g/g}$, respectively.

2.c. Statistical analysis:

Since data did not follow a normal distribution, continuous variables were reported as medians and interquartile ranges (Q1-Q3). Categorical data were presented as numbers and percentages. The Mann-Whitney test was used to compare interval parameters between groups. Categorical data were compared using a chi-square test of independence. The ANOVA (parametric) and Mann-Whitney (non-parametric variables) tests for repeated measurement tests were applied to compare preoperative and postoperative data. Statistical analysis was performed using JASP statistical software (JASP Team; 2023. Version 0.18.1). $P < 0.05$ were considered statistically significant.

2.d. Bioethics Committee

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Poznan University of Medical Sciences, Poznan, Poland (protocol code 695/20 on November 4th, January 2020) for studies involving humans. The written informed consent was obtained from the individuals enrolled in the study.

3. Results

Patients underwent outpatient clinic evaluation as a part of routine check-up protocol. They were presented with NYHA status I (12 (48%) patients) and II (13 (52%) patients). The pump

function was uneventful, maintaining a median (Q1 - Q3) blood output of 4.4 (4.2 – 4.6) liter/minute by generating a speed of 5200 (5075 – 5300) RPM.

The right ventricular dimensions were compared with preoperative characteristics on control transthoracic echocardiography. The right ventricular diameter dilatation was observed in 7 (28%) patients and regression in 8 (32%) more patients. Patients were divided into subgroups accordingly, as presented in Table 1.

Table 1. Demographical and clinical characteristics of analyzed groups.

Parameters	Group 1 RV dilatation n=8	Group 2 no RV dilatation n=17	P Group 1 vs 2	Group 3 RV regression n=7	Group 4 no RV regression n=18	P Group 3 vs 4
Demographical						
1. Age (years) (median (Q1 – Q3))	54 (39 - 61)	59 (54 - 62)	0.472	58 (53 - 62)	58 (52 – 62)	0.911
2. BMI (kg/m2) (median (Q1 – Q3))	28.7 (26.4 – 29.6)	27.8 (26.5 – 28.1)	0.381	27.8 (25.2 – 29.7)	28.4 (26.7 – 28.7)	0.872
Clinical:						
1. present status						
NYHA class I (n (%))	1 (13)	10 (59)	0.042*	4 (57)	9 (50)	0.108
NYHA class II (n (%))	7 (87)	7 (41)	0.042*	3 (43)	9 (50)	0.108
2. primary diagnosis						
DCM (n (%))	4 (50)	11 (65)	0.782	5 (71)	11 (61)	0.796
ICM (n (%))	4 (50)	6 (35)	0.782	3 (43)	7 (39)	0.796
3. Co-morbidities:						
Arterial hypertension (n (%))	2 (25)	5 (29)	0.642	2 (29)	5 (28)	0.784
Diabetes mellitus (n (%))	2 (25)	5 (29)	0.642	2 (29)	5 (28)	0.784
Preoperative PH (n (%))	3 (38)	12 (71)	0.025*	5 (71)	10 (56)	1.000
Arterial fibrillation (n (%))	2 (25)	8 (47)	0.167	3 (43)	7 (39)	0.796
6MWT (m) (median (Q1 – Q3))	370 (360 - 398)	398 (365 - 460)	0.520	454 (389 - 518)	370 (360 - 405)	0.245

Abbreviations: BMI – body mass index, DCM – dilated cardiomyopathy, NYHA -New York Heart Association, ICM – ischemic cardiomyopathy, m -meters, n – number, PH -pulmonary hypertension defined in right catheterization as pulmonary vascular resistance above 2 Wood Units, RV – right ventricular Q- quartiles, 6MWT – 6-minute walking test.

Patients' clinical status was evaluated by a 6-minute walking test (6MWT), resulting in 370 (360 – 398) m in Group 1 vs 398 (365 – 460) m in Group 2 (p=0.520). A non-significant difference (p=0.245) between Groups 3 and 4 was observed in 6MWT (454 (389 - 518) m vs 370 (360 - 405) m). The 6MWT distances achieved in group 1 (RV dilatation) were significantly shorter than in group 3 (RV regression) (370 (360 - 398)m vs 454 (389 - 518)m, p=0.021).

The results from transthoracic echocardiographic examination on check-up were compared to preoperative values as presented in Table 2.

Table 2. Preoperative and postoperative echocardiographic results in analyzed groups.

Parameters	Group 1 RV dilatation n=8	Group 2 no RV dilatation n=17	P Group 1 vs 2	Group 3 RV regression n=7	Group 4 no RV regression n=18	P Group 3 vs 4
Preoperative						
LVDD (mm) (median (Q1 – Q3))	67 (59.8 – 70.2)	68 (63 – 75)	0.426	68 (66- 73)	65 (60 – 71)	0.383
RVDD (mm) (median (Q1 – Q3))	28 (25 - 32)	37 (33 – 39)	0.004*	35 (34 – 37)	31 (26 – 37)	0.232
LAD (mm) (median (Q1 – Q3))	46 (43 – 48)	46 (43 – 54)	0.585	46 (44 – 51)	46 (43 – 49)	0.873
IVs (mm) (median (Q1 – Q3))	10 (9 – 11)	10 (9 - 11)	0.970	10 (9 – 11)	10 (9 – 11)	0.654
TAPSE (mm) (median (Q1 – Q3))	15 (13 – 15)	15 (14 – 15)	0.536	15 (15 – 17)	14 (13 – 15)	0.068
LVEF (%) (median (Q1 – Q3))	20 (15 - 22)	15 (13 – 18)	0.181	13 (10 – 15)	15 (15 – 23)	0.086

Postoperative:						
LVDD (mm) (median (Q1 – Q3))	71 (62 – 81)	62 (57 – 70)	0.111	64 (58 – 71)	62 (60 – 75)	1.000
RVDD (mm) (median (Q1 – Q3))	34 (33 – 38)	33 (31 – 37)	0.307	32 (30 – 33)	34 (33 – 40)	0.015*
LAD (mm) (median (Q1 – Q3))	54 (51 – 55)	50 (46 – 52)	0.146	50 (47 – 52)	52 (49 – 55)	0.283
IVs (mm) (median (Q1 – Q3))	10 (10 – 11)	10 (10 – 11)	0.560	10 (10 – 11)	10 (10 – 11)	0.932
TAPSE (mm) (median (Q1 – Q3))	15 (13 – 15)	15 (14 – 17)	0.409	17 (15 – 20)	14 (13 – 15)	0.020*
LVEF (%) (median (Q1 – Q3))	20 (15 – 23)	20 (15 – 21)	1.000	20 (18 – 22)	20 (15 – 20)	0.667

Abbreviations: LAD – left atrium diameter, LVEF – left ventricular ejection fraction, LVDD – left ventricular diastolic diameter, RV –right ventricular, RVID – right ventricular left ventricular diastolic diameter, mm – millimeters, n – numbers, TAPSE -tricuspid, annular plane systolic excursion, Q – quartiles.

The serum samples from routine check-ups in outpatient clinical were obtained, and chemical analysis was performed, as presented in Table 3.

Table 3. Trace elements analysis in presented groups [$\mu\text{g L}^{-1}$].

Trace elements concentrations:	Group 1 RV dilatation n=8	Group 2 no RV dilatation n=17	P Group 1 vs 2	Group 3 RV regression n=7	Group 4 no RV regression n=18	P Group 3 vs 4
Li (median (Q1-Q3))	1.01 (0.45 – 2.14)	1.49 (0.15 – 14.72)	0.870	0.29 (0.15 – 23.27)	1.49 (0.45 – 2.21)	0.852
Mg (median (Q1-Q3))	20479 (18307 – 20862)	21661 (20787 – 22393)	0.202	20959 (20787 – 24090)	20862 (18307 – 21748)	0.482
Al (median (Q1-Q3))	5.41 (3.44 – 9.04)	40.7 (18.7 – 52.44)	0.073	24.7 (18.7 – 143.6)	9.04 (3.4 – 40.7)	0.282
K (median (Q1-Q3))	161974 (150891 – 166745)	162887 (155631 – 168629)	0.876	166118 (164503 – 168629)	156461 (150891 – 166745)	0.373
Ca (median (Q1-Q3))	71283 (70084 – 77957)	72159 (69967 – 73574)	1.000	72159 (71788 – 72561)	71284 (69276 – 77957)	0.864
Ti (median (Q1-Q3))	55.1 (52.3 – 67.2)	50.6 (44.5 – 65.0)	0.530	50.6 (47.9 – 76.3)	55.1 (48.1 – 67.2)	1.000
V (median (Q1-Q3))	0.12 (0.01 – 0.45)	0.21 (0.01 – 1.52)	0.866	0.42 (0.21 – 1.52)	0.12 (0.01 – 0.45)	0.701
Mn (median (Q1-Q3))	1.36 (0.45 – 5.08)	0.21 (0.04 – 1.67)	0.414	1.27 (0.64 – 1.67)	0.45 (0.07 – 5.08)	0.852
Co (median (Q1-Q3))	0.67 (0.50 – 0.93)	0.77 (0.61 – 1.21)	0.432	0.70 (0.61 – 0.74)	0.91 (0.51 – 1.43)	0.727
Cu (median (Q1-Q3))	927 (906 – 1017)	1245 (1133 – 1492)	0.149	1133 (963 – 1189)	1133 (927 – 1414)	0.727
Zn (median (Q1-Q3))	473 (463 – 532)	507 (450 – 657)	0.876	6.23 (515 – 663)	492 (463 – 532)	0.600
Se (median (Q1-Q3))	58.8 (54.2 – 60.2)	55.4 (47.7 – 60.6)	0.639	62.2 (60.6 – 63.7)	54.2 (47.0 – 58.8)	0.100
Rb (median (Q1-Q3))	108 (101 – 114)	89 (78 – 92)	0.106	90 (90 – 92)	101 (80 – 114)	0.864
Mo (median (Q1-Q3))	1.76 (1.73 – 2.00)	2.61 (2.19 – 2.95)	0.030*	3.23 (2.92 – 3.61)	2.00 (1.73 – 2.19)	0.018*
Fe (median (Q1-Q3))	1355 (1000 – 3841)	1689 (551 – 2798)	0.202	913 (712 – 1338)	1000 (361 – 1887)	1.000

Abbreviations: Al – aluminum, Ca – calcium, Co- cobalt, Cu – copper, Fe-iron, Mg-magnesium, Mn – manganese, Mo – molybdenum, n – number, Li – lithium, K-potassium, Rb – rubidium, RV – right ventricular, Se – selenium, T – titanium, V-vanadium, Q- quartile, Zn – zinc.

The significant differences related to molybdenum concentration between group 1 vs. 2 (1.76 (1.73 – 2.00) ug/l vs. 2.61 (2.19 – 2.95) ug/l, p=0.030) and group 3 vs. 4 (3.23 (2.92 – 3.61) ug/l vs. 2.00 (1.73 – 2.19) ug/l, p=0.018) were noted as presented in Figures 1 and 2, respectively.

Figure 1.

Molybdenum concentration [$\mu\text{g L}^{-1}$] in group 1 (right ventricular (RV) postoperative dilatation) vs. group 2 (no RV dilatation in the postoperative course).

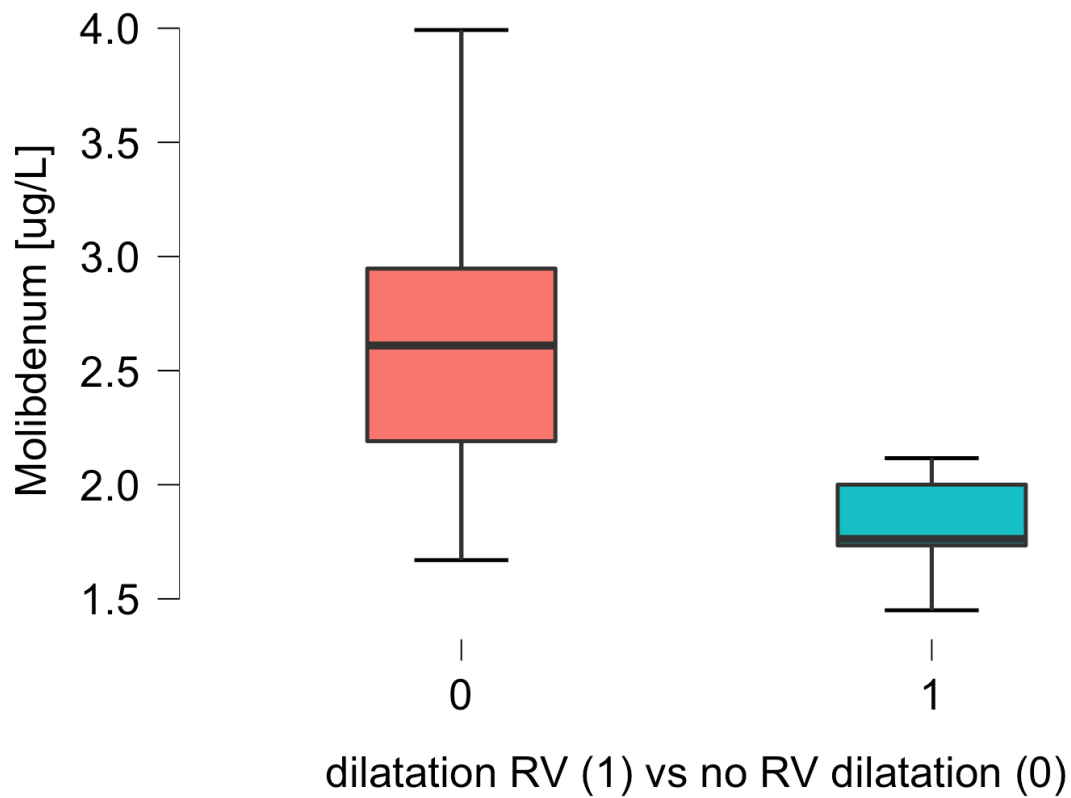
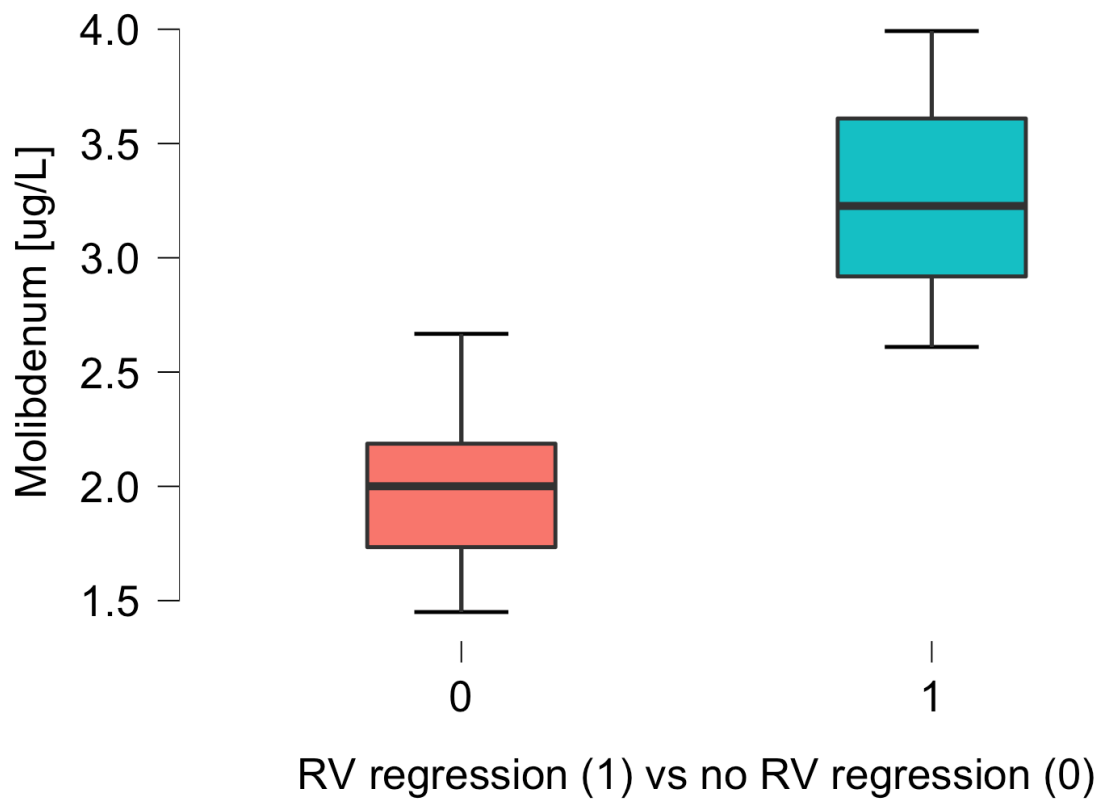


Figure 2.

Molybdenum concentration [$\mu\text{g L}^{-1}$] in group 3 (right ventricular (RV) postoperative regression) vs group 4 (no RV regression in postoperative course).



4. Discussion

Our analysis points out the possible role of molybdenum (Mo) body concentration on the right ventricular dimensions after left ventricular assist device implantation. Our initial report suggests the relationship between low Mo concentration and postoperative right ventricular dilatation, contrary to RV postoperative diameter decrease related to high Mo content.

The fully levitated magnetic support confirmed its safety and improved patients' clinical status, though not significantly impacting the function measured by the 6MWT test [25]. Previous reports revealed LVAD patients perform daily activities at next-to-peak oxygen uptake levels [26]. Postoperative right ventricular dysfunction is among the possible complications that deteriorate the clinical status of implantable LVAD recipients. It must be underlined that in the majority of cases, occult intrinsic RV dysfunction is demonstrated. The RV contractility depression was found to be partially related to left ventricular unloading, which reduces septal contractility [27]. Various predictive scoring systems for post-LVAD RV dysfunction were proposed [28], but they still do not reach optimal levels of clinical efficiency. Therefore, additional strategies are required to assess preoperative RV function or improve its post-LVAD characteristics.

The MOMENTUM-3 trial confirmed satisfactory LVAD long-term results [4]. In TriNetX database analysis, the co-existence of diabetes mellitus, pulmonary and kidney disease, and rhythm disturbances were pointed out as possible ominous long-term survival factors. Though post-LVAD development of right-heart failure heralds an excess in mortality rates and echocardiographic parameters of right ventricular systolic function are considered inconclusive, right heart catheterization frequently offers additional support for the assessment and optimization of RV function [29].

Based on pathophysiological mechanisms resulting in post-LVAD RHF, developing new biomarkers and possible targeted therapies is a prerequisite. The question arises as to whether we can modify the RV function in LVAD recipients. Despite RV phenotyping before the procedure and meticulous perioperative RV evaluation, The postoperative factors contributing have not been fully captured and evaluated [30].

Our analysis focused on the possible role of trace elements as enzymatic co-factors in post-LVAD right ventricular characteristics. We compared the serum elements concentration between LVAD patients with RV diameter regression and dilatation. The possible link between

RV characteristics and molybdenum concentration was noted. Molybdenum (Mo) regulates necroptosis and apoptosis via NF- κ B/TNF- α axis. In animal studies, mitochondria-mediated heart cell apoptosis was activated by excessive Mo [31]. In human studies, the reduction of systemic inflammatory activation, reactive oxygen species, and uric acid about molybdenum's concentration was noticed [32]. The study could explain the association presented in the survey between molybdenum concentration in RV characteristics, linking the results with our previous study, where uric acid accumulation and RV dysfunction in LVAD patients were reported [33]. The National Health and Nutrition Examination Survey [34] revealed a negative correlation between molybdenum and cardiovascular risk. In previous studies [35], the efficiency of molybdenum dietary supplementation linked to molybdoenzymes activation was noted in iron-deficiency anemia and arthritis pain therapy. In Vasto et al. study [36], the molybdenum supplementation by molybdenum biofortified lettuce consumption improved glucose homeostasis by Glucagon-Like Peptide (GLP) and Peptide YY (PYY). In animal analysis by Li et al. [37], higher serum molybdenum concentration reduced oxidative stress and improved immune function. The mentioned reports indicate the beneficial role of molybdenum as an anti-oxidant agent that, through enzymatic processes, may play a pivotal role in human organisms.

Our analysis points out the possible modulatory role of molybdenum serum concentration on right ventricular function. The presented results are in co-ordinance with previous reports suggesting the beneficial role of these trace elements in human organism hemostasis. Molybdenum supplementation could be a future therapeutic target in heart failure patients, especially LVAD patients.

Study limitation

The study was performed on a limited number of patients as a single-center prospective study. The trace elements concentration was estimated only in the post-LVAD period and related to RV postoperative characteristics. The results suggest a hypothetical relation between trace elements serum concentration and RV performance. Further studies are required on high-volume groups, including multivariable model creation.

5. Conclusions

The low serum molybdenum concentration can be related to adverse right ventricular performance after LVAD implantation, contrary to higher molybdenum values related to right ventricular regression.

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Data availability statement:

Data supporting the manuscript's results is restricted due to privacy and ethical reasons and can be obtained by contacting the corresponding author (turbanowicz@ump.edu.pl) by presenting a reasonable request.

Conflicts of Interest:

The authors declare no conflicts of interest.

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