American Journal of Kidney Disease

The role of deconditioning in the end stage renal disease (ESRD) myopathy: physical exercise improves altered resting muscle oxygen consumption

--Manuscript Draft--

Manuscript Number:	
Full Title:	The role of deconditioning in the end stage renal disease (ESRD) myopathy: physical exercise improves altered resting muscle oxygen consumption
Article Type:	Original Investigation
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Original investigation

The role of deconditioning in the end stage renal disease (ESRD) myopathy: physical exercise improves altered resting muscle oxygen consumption

Short title: Muscle oxygen consumption in dialysis patients

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INDEX WORDS: Dialysis; ESRD; Exercise; Muscle metabolism; Noninvasive; Near Infrared Spectroscopy; Biomarker; Oxygen consumption; Mobility, Physical functioning

Abstract word counts: 296

Main text word counts: 3040

Support: This work was supported by an Italian government grant from the Health Minister (Ricerca Finalizzata).

Financial disclosures: None

ABSTRACT

Background: Skeletal muscle dysfunction and poor exercise tolerance are hallmarks of end stage renal disease (ESRD). We hypothesized that resting muscle oxygen consumption ($rmVO_2$) by near infra-red spectroscopy (NIRS) is a biomarker of muscle dysfunction useful to non-invasively study both severity and reversibility of ESRD myopathy.

Study design: Multicenter randomized clinical trial.

Setting & Participants: The whole dialysis population (n=59) of two of the eight centres participating into the EXCITE study (Clinicaltrials.gov NCT01255969), was studied. Thirty-one patients were in the exercise group and 28 in the control group. Normative data for $rmVO_2$ were obtained in 19, age and sex matched healthy subjects.

Interventions: Exercise group: two daily 10-min walking sessions, performed at home on the non-dialysis day (every second day for patients on peritoneal dialysis) for six months at a speed weekly increased from 70% to120% of the walking speed at baseline test. Control group: usual care.

Outcomes: Primary: change in $rmVO_2$. Secondary: change in biochemical, mobility and vascular parameters.

Measurements: $rmVO_2$ at gastrocnemius by venous occlusion NIRS technique, biochemical parameters; mobility by the six-minute walk test, vascular function by an oscillometric device.

Results: Among the 54 ESRDs patients who completed the study, $rmVO_2$ was twice higher (P<0.001) (0.083±0.034 ml/100g/min) than in healthy subjects (0.041±0.020 ml/100g/min) indicating substantial skeletal muscle dysfunction in ESRD. $rmVO_2$ correlated with resting heart rate (r=0.34; P=0.009) but was independent of age, dialysis vintage, biochemical and vascular parameters. At the follow-up $rmVO_2$, identical in the control group (0.082±0.032 to 0.082±0.031 ml/100g/min), reduced to 0.064±0.024ml/100 g/min (-23%, P<0.001) in the exercise group indicating the reversibility of muscle dysfunction.

Limitations: Mainly inherent to the NIRS technique.

Conclusions: Deconditioning has a major role in ESRD myopathy. $rmVO_2$ is a marker of physical deconditioning and has potential for monitoring exercise-based re-conditioning programs in the ESRD population.

INTRODUCTION

Skeletal muscle dysfunction and poor exercise tolerance are established determinants of a sedentary lifestyle and physical deconditioning in end stage renal disease (ESRD) patients.[1] Such a myopathy develops during the late stages of chronic kidney disease and is characterized by muscle wasting and weakness, particularly in the lower limbs associated with type II fiber atrophy, internalized nuclei and fiber splitting.[2] Hyperparathyroidism, vitamin D deficiency, altered potassium metabolism, insulin resistance, uremic toxins, malnutrition and physical deconditioning have all been implicated in ESRD myopathy.[1] Studies showing that physical exercise may improve physical performance in ESRD patients [3] suggest that deconditioning may have a relevant role in this myopathy. However, there is no study on the reversibility of this myopathy focusing on major biologic parameters of skeletal muscle function like muscle oxygen consumption. Resting muscle oxygen ($rmVO_2$) consumption, a parameter which quantifies muscle's capacity to extract oxygen from the blood in standardized conditions, can be measured non-invasively by near infra-red spectroscopy (NIRS).[4] $rmVO_2$ is markedly increased in ischemic muscles in patients with peripheral artery disease [5] or in deconditioned patients with disabling chronic diseases like multiple sclerosis.[7] $rmVO_2$ reflects a fundamental biologic function of the skeletal muscle and therefore may represent a biomarker which can be applied to quantify the severity of myopathy and its reversibility in the ESRD population. NIRS has been tested in various chronic conditions.[8-10] In ESRD, it has been used to assess the severity of peripheral artery disease [11] and muscle wasting [12] or to profile skeletal muscle oxygenation during dialysis [13] but to our knowledge it has never been applied to measure the skeletal muscle response to physical reconditioning programs in the same population. We took the opportunity of the EXCITE trial,[14] a randomized trial testing the effect of a home-based exercise program on the functional capacity of dialysis patients, to investigate the $rmVO_2$ pattern in dialysis patients and to evaluate the $rmVO_2$ response to exercise training. These studies embedded into a randomized trial allowed unbiased assessment of the suitability of

$rmVO_2$ as a biomarker of skeletal muscle dysfunction and of the reversibility of such an impairment after a home-based exercise program.

METHODS

Participants

Fifty-nine subjects were enrolled from 2 of the 8 centres participating in the EXCITE study, [14] a randomized controlled trial testing the effect of a structured home-based exercise program on the functional capacity of dialysis patients. The protocol of the present study was approved by the hospital ethics committees of the renal units participating in the present sub-study (Ferrara and Imola) and written informed consent was obtained from all patients. As detailed elsewhere,[15] the exclusion criteria for enrolment included the following: physical limitations to deambulation, clinical conditions limiting or contraindicating exercise execution (severe effort angina or stage IV NYHA heart failure, any intercurrent illness requiring hospitalization) or a high degree of fitness (ability to walk a distance of over 550 m in six minutes during the standard walking test). Enrolled patients were randomized (randomization stratified by NYHA class) to a structured home-based program of walking exercise (exercise group) or to normal physical activity (control group). In order to collect $rmVO_2$ reference values, a group of subjects, matched for age and sex to dialysis patients (n=19, age=64±9 year, males n=15, 79%) recruited at the entry of an exercise class for the elderly patients at a city gym, was studied. The subjects, free from cardiovascular and neurological diseases, had no limitations of mobility and were normally active.

Interventions

Exercise group: Patients randomized to the active group followed a 6-month home exercise program, based on two daily 10-min walking sessions during the off-dialysis days (every second day for patients on peritoneal dialysis) at a prescribed walking speed to be maintained at home by the use of a metronome. The program, semi-personalized according to the baseline

test, was based on a progressive increase of walking intensity at weekly intervals, ranging from 70% to 120% of the patient walking speed at baseline. The number of the sessions performed was reported in a personal diary and, when possible, certified by a caregiver to enable the evaluation of adherence to the prescription. We considered as high compliers those patients who performed ≥ 60% of the prescribed sessions and low compliers those who performed < 60% of the planned sessions.

Control group: The patients in the control group received usual care and general advice to maintain an active lifestyle.

Outcome measures

Biochemical measurements: Blood samples in hemodialysis patients were drawn immediately before the dialysis session, 7-10 days before the testing sessions. For the present study, the following laboratory parameters, mainly related to the nutritional status, were extracted for analysis: creatinine, blood urea nitrogen, serum albumin, ferritin, total proteins, hemoglobin and hematocrit.

NIRS-based measurements (primary): At first skinfold thickness was measured in triplicate according to the international standards [16] at the calf at the level of the largest circumference by using the Holtain-Tanner/Whitehouse plicometer (Holtain Ltd, UK). NIRS measurement to determine the $rmVO_2$ were made at the level of skinfold measurement, along the medial gastrocnemius muscle as detailed elsewhere.[5] The distance between the NIRS sensor and malleolus medialis was measured and recorded for each patient to maintain the correct positioning at 6 months follow-up evaluation. The interoptode distance was set at 40 mm, allowing a maximum light penetration depth of approximately 25 mm. The NIRS sensors were connected to a continuous wave system (Oxymon MKIII, Artinis Medical System, Netherlands) composed of two channels (two equivalent pulsed light sources, two avalanche photodiode detectors, shielded from ambient light). The system uses intensity-modulated light at a frequency of 1 Hz and laser diodes at three wavelengths (905, 850, and 770 nm)

corresponding to the absorption wavelengths of oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) with an auto-sensing power supply (approximately 40 W at 110-240 V). The light generated by the laser diodes and conducted to the tissue, is partly absorbed and partly scattered by the tissues and re-collected by the detector, providing a direct measurement of the O_2Hb and HHb concentrations ([O_2Hb], [HHb]). NIRS measurements were made in resting, supine position. A blood pressure cuff was placed around the thigh and connected to a compressor with a manometer. Venous occlusion was induced by inflating the cuff to a pressure of 60 mmHg in four seconds. The pressure was maintained at a constant level for thirty seconds and then quickly released. The absolute value of $rmVO_2$ was calculated by analyzing the rate of increase in [HHb] ensuing venous occlusion.[17] The concentration changes of HHb were converted from micromolar per second (μM/s) into millilitres of O_2 per 100 grams of tissue per minute (ml/100 g/min). $rmVO_2$ values were measured in both legs and the mean value was considered for data analysis. The data collection and calculations were performed using the Oxysoft 2.0.47 software (Artinis Medical System, Netherlands).

Vascular function measurements: The Toe-Brachial Index (TBI) and the Arterial Stiffness Index (ASI) (calculated as the average value of the values collected from the arms and legs) were measured by an automatic oscillometric 4-channel device (AngE, Sonotechnik Austria).

Functional capacity assessment: Patients performed the six-minute walk test, validated for different chronic populations including ESRD patients.[18,19] They were asked to walk back and forth in a corridor along a 22 m course (two 10 m straight sections connected by two 1 m curves) at their own pace, as quickly and safely as possible, aiming to cover the maximal distance in six minutes. The patients were allowed to rest in case of fatigue or pain and to continue when possible. The final distance covered (six-minute walk distance, 6MWD) by the patients was recorded. Resting heart rate before this test was measured by a heart rate monitor (Polar RS800CX, Polar Electro, Finland) with the patient standing.

In both study groups (the exercise and the control group) NIRS-based measurement, vascular testing, and a functional capacity assessment were carried out (in sequence, separated by a 5 min interval) in a non-dialysis day, in the morning (between 7 AM and 1 PM) according to the dialysis schedule. These measurements were performed at baseline and after 6 months.

Statistical Analysis

The comparison between groups was performed by unpaired Student's *t*-test and the Fisher's exact test, as appropriate. Spearman rank correlation was applied to evaluate the relationship between $rmVO_2$ values and putative functional correlates (age, dialysis vintage, resting heart rate, biochemical parameters), as well the vascular or functional capacity measurements. Between groups differences were tested by the unpaired Student's *t*-tests or Mann-Whitney *U* tests, as appropriate. The proportion of patients with abnormal $rmVO_2$ values among patients with high and low compliance to the exercise program was compared by the χ^2 test. A one-way analysis of variance was used to compare the mean $rmVO_2$ values in presence of different comorbidities. Significance was set at a P-value ≤ 0.05. Statistics were performed using MedCalc 14.8.1 (MedCalc-Software, Mariakerke-Belgium).

RESULTS

Among the 59 patients enrolled into this study 3 in the active and 2 in the control arm failed to complete the testing session and could not be included in the analysis (Fig 1). Thus the final analysis was performed in 54 patients, 28 patients (22 on hemodialysis) randomized to the active arm and 26 (19 on hemodialysis) to the control arm, respectively. Patients in the two arms of the study (Table 1) were comparable for age, gender, BMI, dialysis vintage, type of dialysis treatment (hemodialysis and peritoneal dialysis), blood pressure, comorbidities, smoking habits, pharmacological therapy including erythropoietin treatment as well as for serum creatinine and the main biochemical parameters, and dialysis dose (kt/v). Furthermore, skinfold thickness, $rmVO_2$ and vascular function indexes (TBI, ASI) were also similar in the two groups (Table 1).

NIRS-based measurement: The skinfold thicknesses at the calf were less than 16 mm for all participants, indicating no technical impediment for NIRS measurements, and were unmodified at the follow up. At baseline in the entire study population $rmVO_2$ was higher in the dialysis population than in the healthy subjects (0.083±0.034 ml/100g/min vs 0.041±0.020 ml/100g/min, respectively; $P<0.001$) documenting an abnormally high necessity at rest to extract oxygen from the blood in dialysis patients. The mean $rmVO_2$ values were closely similar for patients undergoing hemodialysis (0.082±0.028 ml/100g/min) or peritoneal dialysis (0.087±0.048 ml/100g/min) and were significantly higher in males than in females (0.089±0.035 vs 0.071±0.026 ml/100g/min, respectively; $P=0.04$). In a categorical analysis $rmVO_2$ was higher than the upper limit of the normal range in 41 patients (76%). No significant differences in the mean $rmVO_2$ were observed in patients with or without peripheral arterial disease ($P=0.42$), diabetes ($P=0.26$) or belonging to the three different NYHA classes ($P=0.51$)

Functional correlates of $rmVO_2$ at baseline: No significant relationship was found between $rmVO_2$ and age, dialysis vintage, anthropometric and biochemical measurements and vascular function (TBI, ASI) measures. Resting heart rate before the walking test was the sole parameter which correlated significantly with $rmVO_2$ ($r=0.32$, $P=0.02$).

Effects of the 6-month exercise program

The biochemical parameters showed comparable values at the follow-up, superimposable in the two groups. Patients in the exercise group reported the safe execution of a median number of 190 (IQ range 83-289) certified walking sessions per patient, with a maximum of 336 sessions. The 6MWD significantly improved in the exercise group but not in the control group (Table 2). In the exercise group the mean $rmVO_2$ decreased significantly, reducing from 0.084±0.036 to 0.064±0.024 ml/100g/min ($P<0.001$) while on average it remained identical in the control group (Table 2, Fig 2). Of note, $rmVO_2$ attained the normal range in 12 patients (39%) of the exercise group. The TBI did not differ at baseline in the study arms and so did after the 6-month training program (6-month: 0.85±0.26 arbitrary units vs 0.82±0.15 arbitrary units). The ASI showed a down-sloped trend in the

exercise group, implying a tendency for arterial stiffness improvement, and an opposing trend in the control group but the between groups difference in ASI changes failed to achieve statistical significance (*P*=0.09) (Table 2).

$rmVO_2$ changes in exercise group correlated significantly with the number of training session reported by patients (r=-0.42, *P*=0.03) (Fig 3). When we grouped patients in the active group according to the pre-specified criterion of adherence to prescribed sessions (high adherence: n=20; low adherence: n=8) and compared $rmVO_2$ changes in these subgroups and in the control group, a graded relationship emerged (χ^2 for trend *P*=0.009), $rmVO_2$ changes being maximal in the high adherence group, intermediate in the low adherence group and minimal (null) in the control group. Remarkably, such pattern closely mirrored physical performance as measured by the 6MWD (Fig 4).

DISCUSSION

In the present study $rmVO_2$ was on average much higher in ESRD patients on chronic dialysis than in coeval healthy subjects indicating substantial muscle function impairment in this population. A home exercise program produced an improvement in physical performance and a clear-cut reduction in $rmVO_2$ which attained the normal range in a substantial proportion (39%) of patients. These findings are compatible with the hypothesis that the ESRD myopathy depends to an important extent by physical deconditioning. $rmVO_2$ by NIRS has been sparsely measured in previous studies in ESRD patients [13] but to our knowledge this parameter has never been applied to investigate the reversibility of ESRD myopathy in these patients. In the present study we took the opportunity of a clinical trial testing the efficacy of a home-based physical exercise program for exploring the effect of exercise on this fundamental parameter of muscle function. Along with our working hypothesis, we found that $rmVO_2$ was much higher in ESRD patients than in coeval healthy subjects. Of note, $rmVO_2$ in these patients (0.083±0.034 ml/100g/min) was also much higher than that we had previously observed -under the same experimental conditions and with the same NIRS device- in patients with peripheral artery disease (0.069 ml/100g/min) [5] and in those

with multiple sclerosis (0.059 ml/100g/min) [7]. The increased muscle oxygen consumption in ESRD patients was unrelated to peripheral artery disease, diabetes or the functional classification of hearth insufficiency pointing to the disease burden of ESRD per se as the main factor underlying the muscle dysfunction in this condition. Overall, findings in this study set ESRD as a condition entailing a risk for muscle function impairment similar or higher than that of other severe chronic disease like peripheral artery disease or a neurologic disease like multiple sclerosis.

Along with higher $rmVO_2$, short-term physical inactivity and sedentarism induce vascular deconditioning, with reduced endothelium dependent vasodilatation and increased arterial stiffness and vasoconstriction, [20,21] alterations which are almost universal in ESRD patients. [22] On the other hand muscle deconditioning attributable to the burden of ESRD -including muscle wasting, anemia and other comorbidities- and the resulting sedentary lifestyle is recognized as a prevalent, major clinical problem in ESRD patients on dialysis. [23] Thus altered oxygen consumption at rest in the ESRD population is a multifactorial problem attributable to the systemic nature and the severity of this condition. The impact of uremic myopathy in ESRD on clinical outcomes in this population appears of major relevance because physical inactivity and poor physical performance represent strong death predictors in this population. [24-26] Therefore studies investigating the reversibility of ESRD myopathy are important to inform clinical trials testing the effect of physical exercise programs in ESRD. Along with observations made in other chronic conditions [5,7] and considering the potential benefits of exercise on these population [27] we hypothesized that an exercise program may induce a measurable improvement in the myopathy of ESRD patients. In the present study we document for the first time that physical training in these patients produces a parallel improvement in physical performance (as measured by the 6MWD) and in $rmVO_2$. Indeed this parameter substantially decreased in patients in the active arm of the trial and normalized in about the 39% of patients. Furthermore such an improvement paralleled the adherence to the exercise program being more marked in patients with a high compliance to the same program. Improved oxygen utilization promoted by an increase in mitochondrial volume and in capillary density following exercise [28]

likely explains the reduction in $rmVO_2$ we registered in ESRD patients after physical training. Aerobic exercise training ameliorates endothelial function in dialysis patients [29] and improved control of vascular tone might contribute to the exercise-induced improvement in $rmVO_2$ we observed in these patients. In the present study neither the TBI nor the ASI showed significant changes in the exercise group, even though the second parameter showed a favorable time trend. More sensitive indicators of endothelial function and arterial stiffness and longer observations periods may be needed to detect the hypothetic favorable effect of exercise on vascular deconditioning in ESRD. It was recommended that biomarkers of muscle function related to clinical status be tested and applied to develop biological models of recovery in severe, disabling diseases like stroke. [30] Findings in the present study in ESRD patients and observations on other chronic conditions [5,7] concur in supporting $rmVO_2$ as a biomarker of peripheral deconditioning in ESRD patients. In the present study we document that $rmVO_2$ is not a mere surrogate of other risk factors or disease markers. Indeed this parameter was largely independent of age, dialysis vintage, biochemical, vascular, functional and nutrition factors and effectively captured not only the severity of muscle dysfunction but also the improvement in muscle performance brought about by a physical rehabilitation intervention. Unlike circulating biomarkers of deconditioning-reconditioning previously studied by us in dialysis patients, [31,32] $rmVO_2$ seems to be an easily and quickly measured biomarker giving an insight into the local muscle metabolism. [4]

The main limitations of the present study are inherent to the NIRS technique. [33] The limited region of muscle evaluated, the technical variability of $rmVO_2$ measurements attributable to probe position and to the thickness of tissues overlying muscles may affect the interpretation of muscle oxygen consumption by NIRS. However, these potential shortcomings can be overcome by appropriate standardization, as we did in the present and in previous studies in patients with chronic diseases. [5,7] The technicians collecting NIRS parameters were not blinded to the group assignment of participants, although this assessment is not operator dependent. Finally, the reproducibility of the device to measure ASI was not preliminarily tested by the investigators.

Future studies testing this biomarker in larger trials will establish the usefulness of this technique for monitoring re-conditioning programs based on physical exercise and other potential implementations of the same technique in ESRD.

Contributions: Research idea and study design: FMan, CZ, FMal; data acquisition: MF, AZ, LC; data analysis/interpretation: FMan, CZ, FMal, NL, GT, GT, AMM; statistical analysis: NL, GT; supervision or mentorship: CZ, FMan. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. FMan and CZ take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Demographic, clinical and functional measurements in the patients of the two study arms at baseline.

	Exercise group (n = 28)	**Control group (n = 26)**
Demographics		
Males, n (%)	20 (71)	15 (58)
Age (years)	66 ± 14	68 ± 13
Dialysis vintage (years)	7 ± 8	7 ± 8
Body Mass Index (kg/m^2)	27.6 ± 6.5	25.4 ± 3.2
Hemodialysis, n (%)	22 (79)	19 (73)
Heart failure, (n, %)	12 (43)	16 (61)
NYHA Class I	12 (43)	11 (42)
NYHA Class II	0 (0)	5 (19)
NYHA Class III	0 (0)	0 (0)
NYHA Class IV	0 (0)	0 (0)
Peripheral arterial disease, n (%)	2 (7)	3 (12)
Diabetes, n (%)	6 (21)	2 (8)
Smokers, n (%)	10 (36)	10 (38)
Blood pressure (systolic/diastolic, mmHg)	128 / 71	128 / 73
Biochemical measurements		
kt/v (fractional urea clearance)	1.58 ± 0.41	1.66 ± 0.48
Creatinine (mg/dl)	10.1 ± 3.0	9.6 ± 2.2
Serum albumin (g/dl)	3.7 ± 0.3	3.6 ± 0.5
Serum cholesterol (mg/dl)	172 ± 42	170 ± 35
Serum phosphate (mg/dl)	5.3 ± 1.4	5.2 ± 1.5
Hemoglobin (g/dl)	11.5 ± 1.2	11.7 ± 1.8
NIRS measurements		
$rmVO_2$ (ml/100g/min)	0.084 ± 0.036	0.082 ± 0.032
Skinfold thickness (mm)	12.3 ± 4.2	11.7 ± 5.0
Vascular and functional measurements		
[#]TBI (arbitrary unit)	0.87 ± 0.16	0.82 ± 0.21
[#]ASI (m/s)	8.87 ± 4.46	7.05 ± 1.57
6MWD (m)	347 ± 87	333 ± 118
Resting heart rate (bpm)	74 ± 9	74 ± 8

NYHA, New York Heart Association; NIRS, near infra-red spectroscopy; $rmVO_2$, resting muscle oxygen consumption; TBI, toe-brachial index; ASI, arterial stiffness index; 6MWD, six-minute walk distance. [#]TBI and ASI measurements were performed in 21 patients in the exercise group and in 16 patients in the control group.

Table 2. Near infra-red spectroscopy (NIRS), vascular and functional measurements in the two study arms.

	Exercise group		Control group	
	Baseline	**6 months**	**Baseline**	**6 months**
NIRS measurements				
Mean $rmVO_2$ (ml/100g/min)	0.084 ± 0.036	0.064 ± 0.024*	0.082 ± 0.032	0.082 ± 0.031
Vascular measurements				
TBI (arbitrary unit)	0.87 ± 0.16	0.85 ± 0.26	0.82 ± 0.21	0.82 ± 0.15
ASI (m/s)	8.87 ± 4.46	7.67 ± 2.15	7.05 ± 1.57	8.70 ± 3.61*
Functional measurements				
Resting heart rate (bpm)	74 ± 9	73 ± 9	74 ± 8	73 ± 9
6MWD (m)	347 ± 87	397 ± 101*	333 ± 118	331 ± 115

Paired sample t-test (* $P<0.05$).
NIRS, Near infra-red spectroscopy; $rmVO_2$, resting muscle oxygen consumption; TBI, toe-brachial index; ASI, arterial stiffness index; 6MWD, six-minute walk distance.

Legends to Figures

Figure 1. Flow diagram of study participants.

Figure 2. Box and whisker plots of resting muscle oxygen consumption ($rmVO_2$) at baseline and after 6 months in the two experimental groups.

The upper and lower dashed lines correspond to the 25^{th} and 75^{th} percentiles of the values of the healthy group.

Figure 3. Correlation between number of training sessions and resting muscle oxygen consumption ($rmVO_2$) changes.

Figure 4. Trends of resting muscle oxygen consumption ($rmVO_2$), vascular and functional changes for the High, Low and Control groups.

Figure
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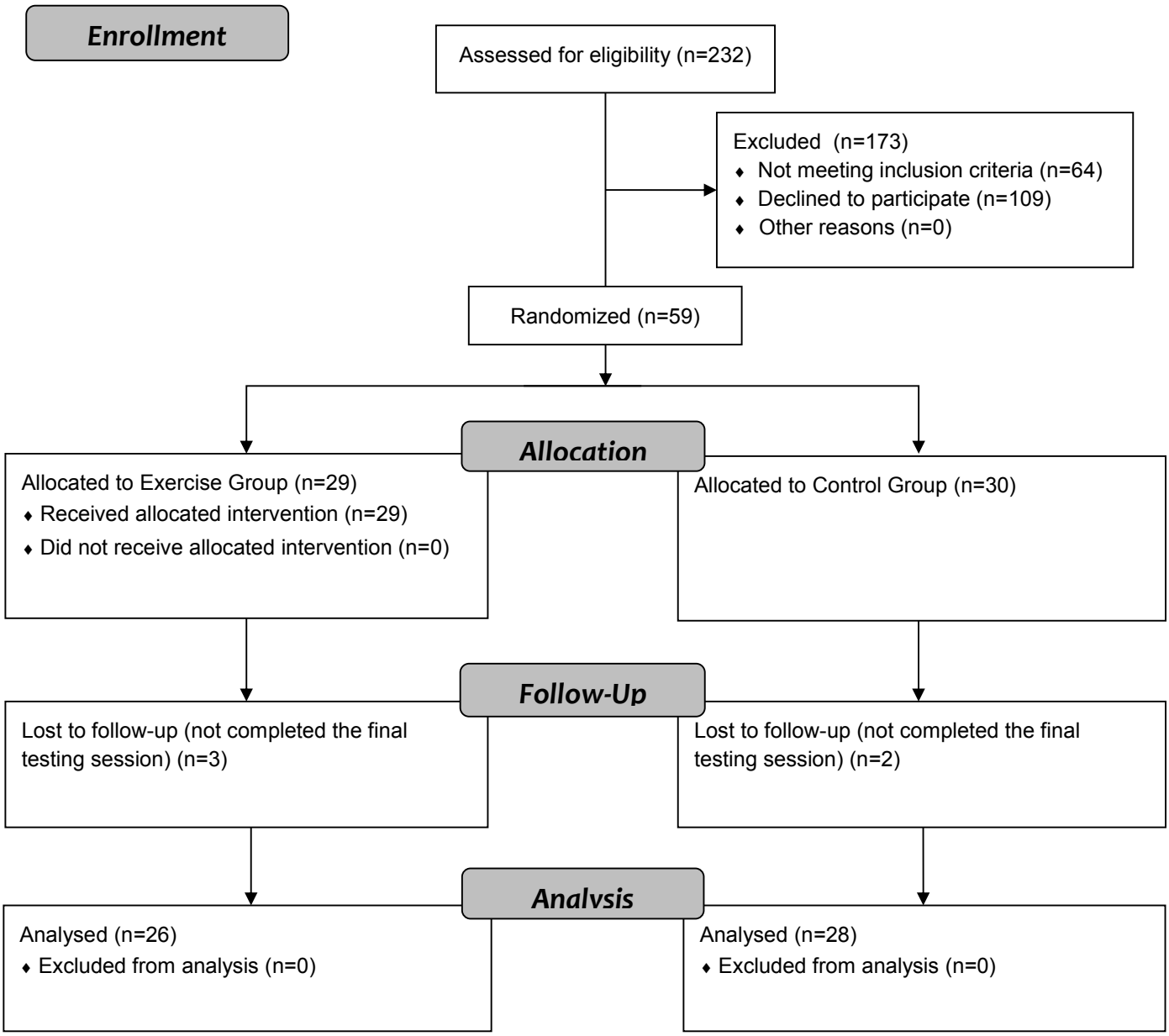

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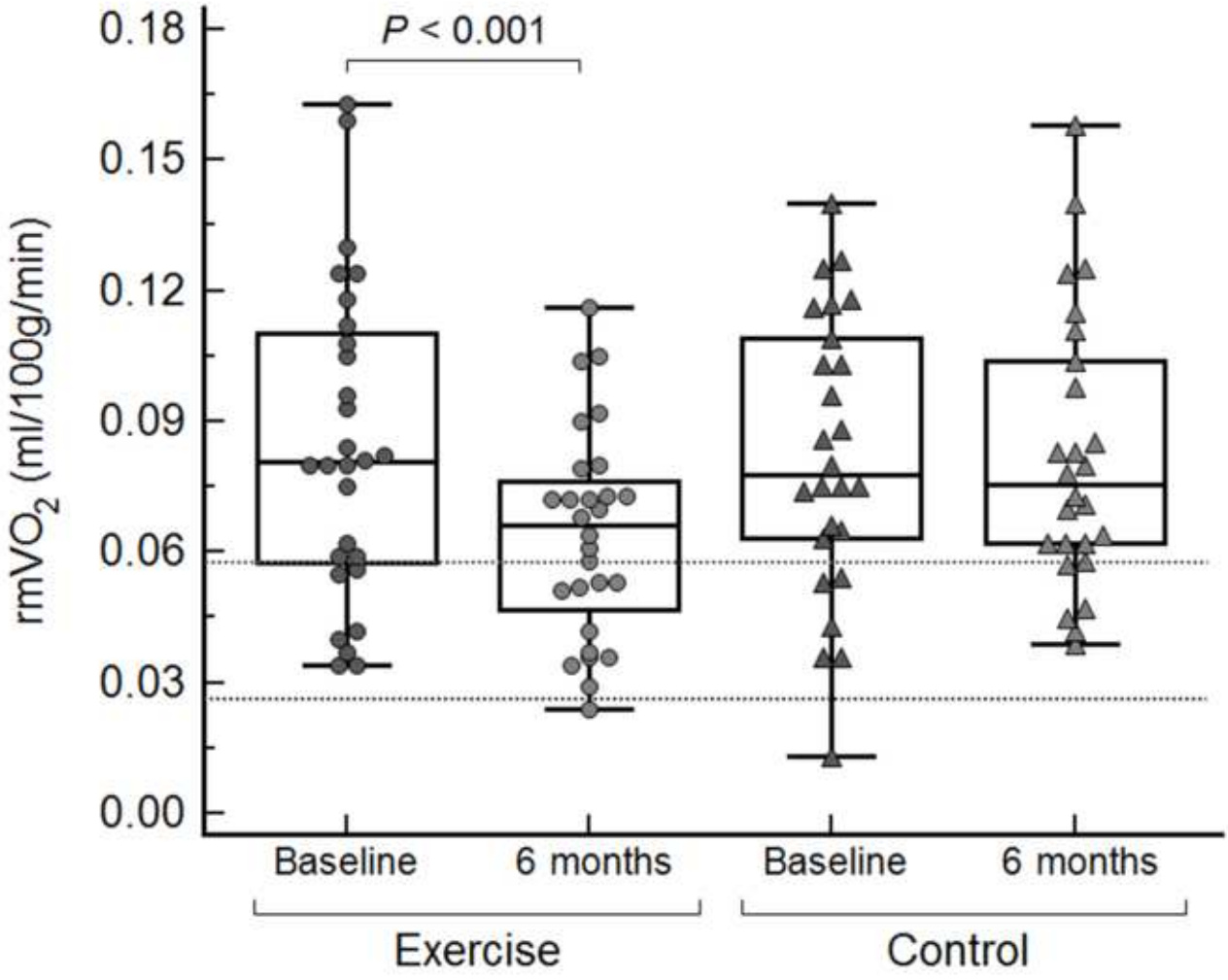

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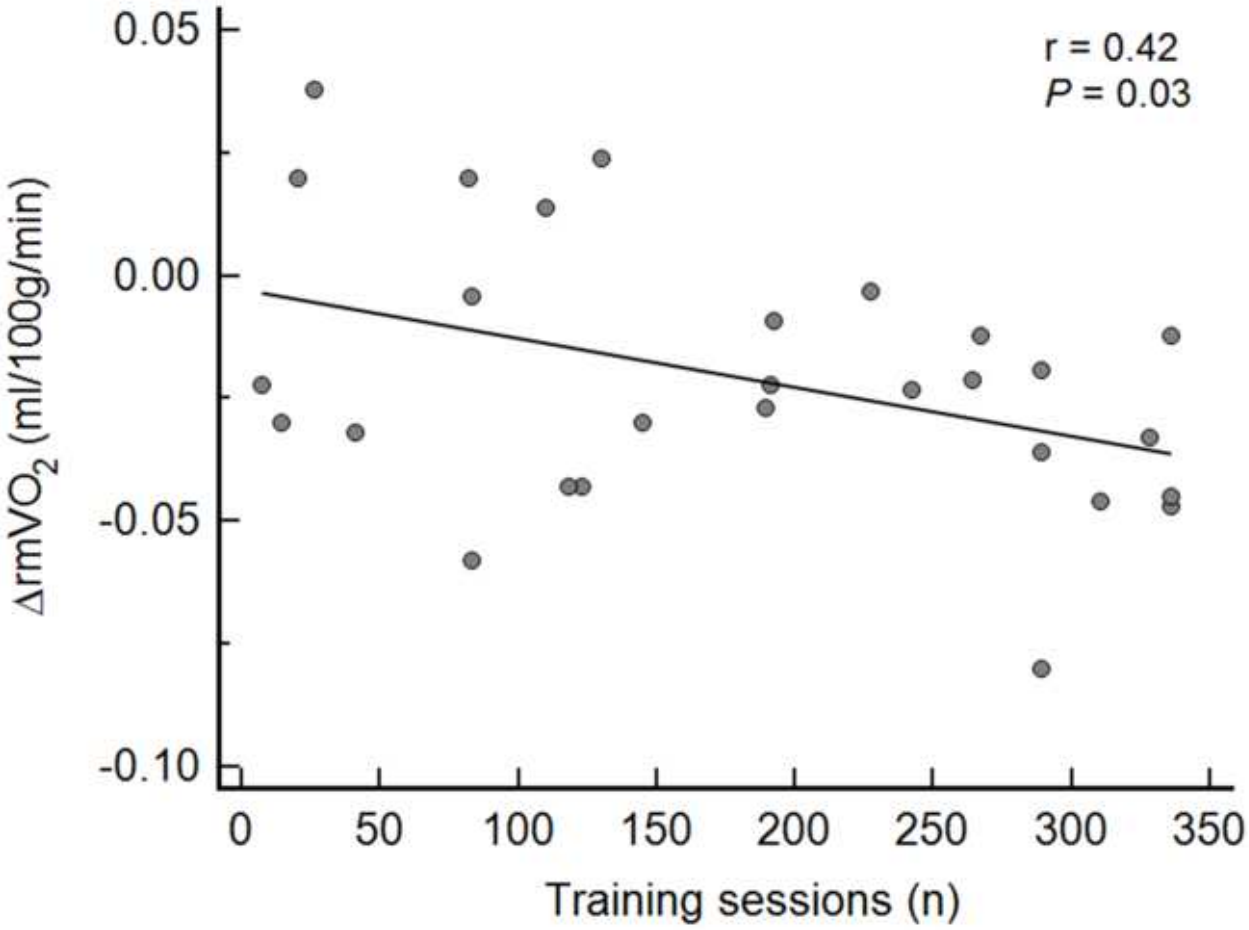

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