

Correlation between intradialytic aerobic exercise, associated or not with neuromuscular electrical stimulation, and the quality of hemodialysis in patients with chronic kidney disease

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ABSTRACT

Introduction: Individuals with Chronic Kidney Disease (CKD) on hemodialysis (HD) have impaired functional capacity. Therefore, to alleviate these complications, intradialytic exercises have been implemented. **Objective:** To evaluate the correlation between intradialytic aerobic exercise, associated or not with neuromuscular electrical stimulation (NMES), and the quality of HD. **Methods:** Randomized clinical trial that submitted individuals with CKD to an intradialytic exercise using a cycle ergometer in the lower limb and active upper limb NMES in the intervention group (IG) or placebo in the control group (CG). The outcomes evaluated were Kt/V index (an index that evaluates the adequacy of HD), number of cycles cycled, distance covered, and heart rate (HR). The groups were compared, and correlation was made between Kt/V and variables: cycles cycled, distance covered, delta HR_{F-I} (difference between final HR and initial HR of the intervention), delta HR_{cycle} (difference between final HR and initial HR of the cycle ergometer), and HR_{peak} (highest HR value during the cycle ergometer). **Results:** Five participants were included in the IG and 4 in the CG. During exercise, there was an increase in HR in IG and a reduction in systolic blood pressure in the CG. Furthermore, the CG performed a greater number of pedaling cycles and a greater distance covered ($p < 0.05$). Furthermore, delta HR_{F-I} and HR_{peak} were higher in the IG. There was a weak positive correlation in the IG ($r = 0.21$; $p = 0.03$) between delta HR_{cycle} and Kt/V. **Conclusion:** Intradialytic aerobic exercise associated with NMES had a weak positive correlation between Kt/V and delta HR_{cycle}.

Keywords: Renal Insufficiency, Chronic; exercise; electric stimulation; renal dialysis.

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INTRODUCTION

Chronic kidney disease (CKD) is defined as damage to kidney function, with or without reduced glomerular filtration rate, present for at least three months¹ and affecting approximately 8.54% of people worldwide². In the most advanced stage of the disease, patients progress to end-stage CKD, requiring some form of renal replacement therapy, the most common being hemodialysis (HD)³.

Patients with CKD on HD have impaired quality of life and functional capacity, the cause of which is multifactorial. Factors such as age, sex, body mass index, peripheral muscle strength, and nutritional status are associated with this reduction⁴. Impairments in physical fitness in these patients also interfere with their ability to perform activities of daily living and occupational tasks, which are directly related to loss of muscle strength and mass⁵⁻⁷. In addition, the incidence of cardiovascular disease is high in this population, thus increasing their morbidity and mortality⁸.

To mitigate these adverse effects on CKD patients undergoing HD, many types of intradialytic exercise have been studied^{9,10}. According to recent research, lower limb (LL) cycle ergometer exercise and muscle strengthening exercises increase physical performance, walking distance, and muscle strength in patients undergoing hemodialysis¹⁰⁻¹². They also bring other benefits, such as improved cardiovascular function¹³, reduced systemic inflammation¹⁴, improved depression¹⁵ and improved quality of life¹⁶.

In addition to aerobic and strength exercises, neuromuscular electrical stimulation (NMES) has also been used during HD, suggesting benefits such as improved muscle strength, functional capacity, and quality of life¹⁷, likely caused by increased muscle oxidative capacity and increased muscle capillarization¹⁸. In addition to being easy to perform, feasible, and safe, NMES has been shown to improve muscle strength and functional capacity in patients with chronic kidney disease¹⁷.

It is known that one of the most widely used methods for measuring HD adequacy, based on urea clearance, is Kt/V. This was prescribed by the National Cooperative Dialysis Study (NCDS) and corresponds to the result of urea clearance (K) of the dialyzer and treatment time (t) divided by body urea volume (V). Guidelines recommend a Kt/V of at least 1.2 as the minimum dose for HD three times a week, to assess that HD was adequate¹⁸. It is therefore important to evaluate the Kt/V index in all HD sessions, since if it is adequate, it contributes to lower morbidity and mortality rates¹⁹.

Although the Kt/V index is an important parameter for measuring HD efficiency, there are still few studies demonstrating whether intradialytic exercise interferes with HD quality. It has been hypothesized that aerobic exercise during HD sessions appears to be a good alternative because, in addition to the general benefits of exercise and easy patient adherence, it may be directly related to HD outcomes as assessed by Kt/V. In addition, it is expected that the combination of UL NMES and intradialytic aerobic exercise will bring additional benefits to the quality of hemodialysis.

Therefore, this study aims to evaluate the correlation between intradialytic aerobic exercise with a cycle ergometer in LL, associated or not with NMES of upper limbs (UL), and HD quality, measured by Kt/V, in adult patients with CKD.

METHODS

Study design and setting

This is a randomized clinical trial conducted from May 2022 to July 2023. Adult individuals undergoing HD at the Hemodialysis Center of the Cassiano Antônio de Moraes University Hospital (HUCAM) in Vitória, Espírito Santo, Brazil, were included and randomly assigned to the intervention group (IG) and control group (CG). The study was approved by the HUCAM Research Ethics Committee (CEP-HUCAM), with CAAE 27067819.1.0000.5071 and approval protocol number 5.614.016. The prospective registration of the clinical trial was performed at ClinicalTrials.gov (Registration: NCT05374863).

Participants

Individuals diagnosed with CKD, aged over 18, of both sexes, who had undergone hemodialysis for at least 3 months at HUCAM, with a hemoglobin concentration greater than or equal to 9g/dL, clinically stable for a minimum of 3 months, not involved in another physical activity program, able to perform the assessment tests adequately, and who agreed to the Informed Consent Form (ICF). Exclusion criteria included patients who had signs and/or health problems (neurological, cardiovascular, cognitive, respiratory) that made it difficult to perform the assessment tests and engage in the physical activity program.

On Mondays, Wednesdays, and Fridays, during the morning and afternoon shifts, the service where the study was conducted had 19 HD patients. When performing the screening process, according to the eligibility criteria, one patient refused, and nine had exclusion criteria (one with anemia, three with LL amputation, and five with severe heart disease). Thus, 9 volunteers were included in the study, and after agreeing and signing the ICF, they were randomized to the IG (5 participants) and CG (4 participants). Patients on Tuesdays, Thursdays, and Saturdays, in the morning and afternoon shifts, did not participate in the screening process because, on those days, no research team was available to conduct the study and perform the exercise protocol.

The IG participants had a mean age of 37.80±15.92 years, with 3 male participants (60%). The CG had a mean age of 39.75±13.22 years, with 3 male volunteers (75%). The other characteristics of the study population can be seen in table 1.

Research protocol

It consisted of performing intradialytic exercise three times a week, on alternate days (Monday, Wednesday, and Friday), for

eight weeks, during the first two hours of HD, due to the higher risk of cardiovascular instability after the third hour of HD, which could compromise the regularity of the training²⁰.

The intervention protocol included aerobic exercise on a cycle ergometer at LL for all participants for 30 minutes, followed by 20 minutes of active NMES (IG) or placebo (CG) on the upper limb that did not contain the HD fistula, targeting the biceps and flexor muscles of the wrist and fingers.

On each day of the exercise session, the following variables were recorded: Kt/V index (recorded by the HD machine at the end of each session); number of cycles pedaled and distance traveled (both recorded on the cycle ergometer); the delta of HR_{F-1} (difference between HR immediately at the end and initial HR (immediately pre-intervention) – cycle ergometer + NMES); delta of HR_{cycle} (difference between HR immediately after and HR immediately pre-cycle ergometer) and peak HR (maximum HR reached during the cycle ergometer). In addition, at the beginning and immediately at the end of each day of intervention (cycle ergometer + NMES), the following variables were assessed: blood pressure (BP), peripheral oxygen saturation (SpO₂), heart rate (HR), and respiratory rate (RR) (measured for 1 minute by observing chest movements with each breath). The weight (kg) of the participants was also recorded each day before hemodialysis and after HD. Finally, complications, complaints, and other relevant information were recorded.

Thus, if each participant performed 3 days of exercise per week for 8 weeks, at the end of the research protocol, each should have 24 records of the variables described above. For intra- and intergroup analysis and correlation between exercise variables and Kt/V, each day of assessment of these variables was considered as a sample.

Table 1: Characterization of participants in the intervention and control groups

Variables	Intervention Group (n=5)	Control Group (n=4)
Age (years)	37.80 ± 15.92	39.75 ± 13.22
Sex		
Male	3 (60%)	3 (75%)
Female	2 (40%)	1 (25%)
Ethnicity		
Black	2 (40%)	2 (50%)
Mixed-race	2 (40%)	1 (25%)
White	1 (20%)	1 (25%)
Hemodialysis duration (months)	56.20±29.15	78.00±49.67
Average number of visits/patient	20.40±2.88	19.00±2.58
Health Conditions		
Hypertension	3 (60%)	4 (100%)
Diabetes Mellitus	1 (20%)	1 (25%)
Lung Disease	0	1 (25%)
Heart disease	2 (40%)	0
Dyslipidemia	0	1 (25%)
Hepatitis	0	1 (25%)

Safety criteria were adopted for the start and/or suspension of exercise²¹. The criteria indicated for the start of exercise were: blood pressure (BP) <180/100 mmHg or >100/50 mmHg, resting HR <100 bpm (beats per minute), SpO₂>90%, absence of abnormal symptoms such as fever, cold, headache, chills, dizziness, nausea, and chest pain. The criteria for stopping the exercise were: SpO₂ 88%, BP >180/105 mmHg, patient refusal, and symptoms of chest pain, dyspnea, palpitations, bronchospasm, exercise intolerance, mental confusion, dizziness, pallor, or cyanosis²¹. In the presence of any of these symptoms, the intervention was interrupted and, after evaluation by the multidisciplinary team, the intervention could be resumed or not.

Aerobic exercise (LL cycle ergometer)

The exercise lasted 30 minutes, divided into warm-up (5 minutes), conditioning (20 minutes), and cool-down (5 minutes). Participants in the IG and CG groups were verbally encouraged to cycle at a speed sufficient to achieve an exercise intensity between levels 4 and 7 on the modified Borg Scale during the conditioning phase. In addition, the resistance on the cycle ergometer (non-measurable load) was mechanically increased, and ankle weights were added to achieve the desired intensity. Thus, every 5 minutes, the patient was assessed for symptoms of dyspnea and LL fatigue using the modified Borg Scale, with the goal in the warm-up and cool-down phases being to maintain a lower exercise intensity, between levels 1 and 3 on the scale. Also, every 5 minutes, HR and SpO₂ values were collected to control exercise intensity and the patient's general condition. The Mini Bike E5 Acte Sports® (São Paulo, Brazil) was the cycle ergometer used for the intervention and was positioned in front of the HD chair.

Neuromuscular electrical stimulation (NMES) of the upper limb

NMES was performed for 20 minutes on the biceps brachii and wrist and finger flexor muscles, only on the limb that did not contain the HD fistula. Two electrodes were placed longitudinally on the muscle bellies of the biceps (5x5 cm), and two on the wrist and finger flexors (5x3 cm). The limbs were positioned alongside the body with slight flexion of the elbows and supination of the forearms. The parameters used were: frequency of 80Hz, pulse width of 350ms, on time of 5s (rise time 1s, hold time 3s, and fall time 1s), and off time of 10s.

The intensity was adjusted according to each individual's tolerance level so that it reached the greatest vigorous contraction without pain (IG). Patients were instructed to perform concentric isotonic contraction of the elbow flexor muscles and to contract the wrist and finger flexors isometrically during the NMES on time. Placebo NMES (CG) included the same parameters and electrode placements, but the intensity only reached the sensory threshold (intensity sufficient only for the patient to perceive

the electrical stimulus, without performing muscle contraction). The intervention was performed with the patient seated in the HD chair, and the equipment used was the Neurodyn II Ibramed® (São Paulo, Brazil).

Outcomes Evaluated

KT/V

The Kt/V index (a parameter used to assess the adequacy of dialysis) was recorded from the HD machine at the end of each session.

Cycle rides and distance traveled (km)

The number of cycles pedaled and the distance traveled, in kilometers (km), were recorded on the Mini Bike E5 Sports® cycle ergometer (São Paulo, Brazil) and collected at the end of each activity. The researchers recorded this data and then reset the device's records for later use.

Heart Rate (HR)

Based on HR recordings at different times, the following outcomes were evaluated: HRF-I delta (difference between final HR and initial HR in each session, including all exercises: cycle ergometer and NMES); HRcycle delta (difference between HR after and HR before cycle ergometer), peak HR reached during exercise (highest HR value reached during cycle ergometer, among the values collected every 5 minutes of activity). The values of these heart rates in beats per minute (bpm) were obtained by the device that monitors peripheral blood oxygen saturation (SpO₂) and heart rate per minute (HR), the G-TECH LED finger oximeter.

Statistical analysis

Participants were randomized into the IG and CG groups in blocks using a table generated by computer software. In addition, to reduce the risk of bias, an intention-to-treat analysis was performed, and the researchers involved in recording the outcomes and performing the statistical analysis were blinded to the allocation of participants to the groups.

The results are shown as mean \pm standard deviation (SD). The Kolmogorov-Smirnov test confirmed the normality of the data, as the sample size was greater than 50, verifying that the data were parametric. Therefore, the groups (IG and CG) were compared using Student's t-test for independent samples. For intra-group comparison, the paired Student's t-test was used at pre- and post-exercise moments. Correlations between Kt/V and variables (pedaling cycles, distance traveled, delta HR_{F-I}, delta HR_{cycle}, peak HR) per group were performed using Pearson's test. Results were considered significant when $p < 0.05$.

RESULTS

According to the research protocol, each participant was supposed to attend 24 sessions over the 8 weeks of the intervention, considering that they were held three times a week. However, some were unable to attend all sessions. In the IG, composed of 5 participants, the total number of scheduled sessions was 120. However, a total of 102 sessions were attended, with an average of approximately 20.40 ± 2.88 sessions per patient. In the CG, composed of 4 volunteers, the total number of scheduled sessions was 96. However, 76 sessions were performed, with an average of 19.00 ± 2.58 sessions per patient (Table 1).

The reasons for not performing or interrupting IG treatments were: BP higher than the acceptable limit (2); personal problems (2); malaise/illness (3); holidays (2); undergoing tests (1); no record (6); interruption due to increased fatigue caused by flu symptoms (1); Interruption due to a drop in BP during exercise (1). In the CG, the reasons were: Holidays (9); Malaise/illness (3); Patient absent because they underwent HD during the project's off-hours (2); No record (3).

Table 2 presents a comparison of the variables assessed before and after exercise (immediate), on each day of care, for each of the two groups studied, IG and CG. The variables analyzed here for each individual were: weight in kilograms (kg), systolic blood pressure (SBP) and diastolic arterial pressure (DAP) (mmHg), HR (bpm), SpO₂ (%), and RR (bpm). Thus, it can be verified that

Table 2: Evaluation of pre- and post-exercise variables in the intervention (IG) and control (CG) groups

Variables	Intervention Group (n=102)		Control Group (n=76)	
	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
Weight (kg)	72.03 \pm 11.13	69.50 \pm 11.08 ^{H*}	67.66 \pm 5.41	65.06 \pm 5.01 ^{H*}
SBP (mmHg)	138.86 \pm 16.34	134.15 \pm 17.10 ^{Ex}	135.07 \pm 12.40	130.66 \pm 12.11 ^{Ex*}
DAP (mmHg)	78.62 \pm 11.32	76.49 \pm 9.57 ^{Ex*}	81.11 \pm 10.74	79.21 \pm 10.98 ^{Ex*}
HR (bpm)	75.19 \pm 11.98	83.09 \pm 12.16 ^{Ex*}	70.96 \pm 7.82	76.09 \pm 12.12 ^{Ex*}
SpO ₂ (%)	98.13 \pm 1.09	98.31 \pm 0.74 ^{Ex*}	98.24 \pm 1.02	98.43 \pm 0.75 ^{Ex}
RR (bpm)	17.79 \pm 2.67	18.54 \pm 2.32 ^{Ex*}	16.13 \pm 1.50	17.12 \pm 2.04 ^{Ex*}

SBP – Systolic Blood Pressure; DAP – Diastolic Blood Pressure; HR – Heart Rate; SpO₂ – Peripheral Oxygen Saturation; RR – Respiratory Rate

^H – after total hemodialysis time

^{Ex} – after exercise

* - statistically significant difference ($p < 0.05$) between pre and post.

there was a reduction in weight (kg) in all individuals in both groups after the hemodialysis session. Similarly, there was also a statistically significant reduction in DAP values post-exercise in both groups ($p < 0.05$). Furthermore, SBP values also decreased after exercise, but only in the CG was this statistically significant ($p < 0.05$). In addition, both HR and RR in the IG and CG increased significantly after exercise.

When comparing the IG and CG groups, there was no difference between the Kt/V values. However, a statistically significant difference ($p < 0.05$) was observed in the number of cycles pedaled, distance traveled, delta HR_{F-I}, and peak HR, as shown in Table 3. It was found that the CG performed a greater number of pedaling cycles, as well as a greater distance traveled ($p < 0.05$). On the other hand, the delta HR_{F-I} and peak HR of the IG were higher than those of the CG.

When performing the correlation analysis between Kt/V and exercise variables (pedaling cycles, distance traveled, delta HR_{F-I}, delta HR_{cycle}, peak HR), a weakly significant positive correlation was observed in the IG ($r = 0.21$; $p = 0.03$) between delta HR_{cycle} and Kt/V. However, there was no statistical significance for any other correlation between Kt/V and the other variables evaluated. The mean values and standard deviation of Kt/V and the variables evaluated are described in table 3.

DISCUSSION

The results showed that intradialytic exercise using a cycle ergometer in the lower limbs combined with active NMES in the upper limbs had a weak but statistically significant positive correlation between Kt/V and delta HR_{cycle}. However, for the other variables (cycles pedaled, distance traveled, delta HR_{F-I}, and peak HR) there was no statistically significant correlation with Kt/V in either group. In addition, UL NMES, when associated with the cycle ergometer, does not seem to have an additional effect on Kt/V; however, it seems to improve the HR response to exercise with the LL cycle ergometer.

Regarding the characteristics of the population, the mean age was 38.67 ± 13.91 years, indicating that these are younger patients, since the mean age was lower when compared to studies such as those

by Bogataj et al.²², Desai et al.¹² and Guio²⁰, whose mean ages were over 50 years. However, it is worth noting that the present study was similar to the studies mentioned above and to the 2023³ Brazilian Dialysis Census, as most participants were male, and the most prevalent comorbidities were hypertension and diabetes mellitus.

When comparing the variables before and after exercise within each group, a drop in BP was identified for both the GI (DBP) and the CG (SBP and DAP). Intradialytic hypotension may be associated with factors related to dialysis (ultrafiltration volume and rate) and to the patient (hypovolemia, cardiac dysfunction, vasodilation)²³. However, the drop in blood pressure recorded in the participants of this study remained within the safety criteria for exercise and was not considered intradialytic hypotension, since this requires a reduction in SBP greater than 20 mmHg or MAP greater than 10 mmHg, associated with the presence of symptoms and/or the need for intervention²³.

An increase in HR and RR was also observed for both the IG and CG after exercise (immediate). This result corroborates the findings of Thompson et al.²⁴, since they also observed an increase in HR in all IG subgroups during intradialytic exercise, even though they returned to baseline values after completion. This can be explained by the increase in sympathetic flow and circulating catecholamine levels, combined with a decrease in vagal tone of the heart during exercise, which leads to an increase in HR²⁵. Even so, it should be noted that the increase in HR may have been attenuated, since three participants in the IG and two participants in the CG regularly used beta-blocker medications, and, as is already known, this drug acts to reduce HR both at rest and during exercise²⁶. As with the increase in HR, an increase in RR during exercise is also expected, since this variable plays an important role as a marker of physical exertion and, according to Cheng²⁷, may reflect the ability of the heart and lungs to supply oxygen to the muscles during continuous physical activity.

In addition to the well-established physiological responses to exercise, the effect of intradialytic exercise on the Kt/V index, which measures the quality of HD, remains uncertain^{28,29}. Patients with CKD have complications that interfere with solute removal due to peripheral circulation constriction that occurs during HD, retaining most uremic toxins in low-perfusion organs, such as muscles, thus hindering solute removal and leading to a worse Kt/V outcome^{30,31}. This condition can be mitigated by intradialytic exercise, as it promotes an increase in body temperature, cardiac output, and blood flow, resulting in peripheral vasodilation, accelerating muscle and systemic circulation, and promoting the elimination of waste products^{31,32}.

This is the most likely explanation for the improvement in Kt/V with intradialytic exercise. Some studies, such as that by Kirkman et al.³³, believe that what really influences dialysis adequacy is HD time, and intradialytic exercise is only an aid, with no significant effect on urea clearance. However, the meta-analysis by Pu et al.³⁴ contradicts these

Table 3: Comparison of variables assessed between the intervention group (IG) and control group (CG)

Variables	Intervention Group (n=102)	Control Group (n=76)
Kt/V	1.34 ± 0.15	1.29 ± 0.17
Number of cycles ridden	2467.82 ± 475.06	2753.86 ± 352.09*
Distance traveled (km)	0.474 ± 0.10	0.531 ± 0.07*
Delta HR _{F-I}	8.32 ± 9.66*	6.18 ± 10.72
Delta HR _{cycle}	15.65 ± 10.99	14.92 ± 9.23
Peak HR	103.09 ± 12.30*	91.69 ± 9.43

Data presented as mean ± standard deviation, p-value obtained by Student's t-test
* - statistically significant difference ($p < 0.05$) between IG and CG.

findings, since intradialytic exercise protocols lasting at least 8 weeks have been shown to increase dialysis adequacy and reduce the risk of death. However, in this study, no robust correlations were found between exercise and Kt/V, suggesting that the proposed intradialytic exercise protocol does not appear to influence HD efficiency. Only a statistically significant positive correlation between Kt/V and delta HR_{cycle} was found in the IG; however, it was of weak magnitude ($r=0.21$), which may indicate that a greater variation in HR during exercise may improve the quality of HD as measured by Kt/V.

However, even though the IG performed less aerobic exercise (number of cycles pedaled and distance traveled) than the CG, the variation in HR was greater in the former. Therefore, it is possible to hypothesize that NMES used in the IG may have contributed to a greater HR response to exercise in this group. In view of the above, Figoni³² addresses in his publication the role of LL muscle contraction in activating the venous pump, particularly the increase in stroke volume and cardiac output. In addition, Banerjee et al.³⁵ concluded that NMES in LL was able to generate a physiological response compatible with cardiovascular exercise at light to moderate intensities, similar to walking at 3 to 3.5 mph. This finding corroborates the research of Harris et al.³⁶ and Dobsak et al.³⁷. That said, it is possible to suggest that NMES appears to be a useful tool, evidenced by the greater HR response in the IG, especially for patients undergoing HD who cannot perform high-amplitude exercises, particularly of the UL, at the time of the procedure.

Strengths and limitations

The strengths of this study include the existence of several studies on the effects and benefits of intradialytic exercise on functional capacity, muscle strength, BP control, and quality of life in patients with CKD. However, there are still a few studies that relate exercise intensity to HD quality, as assessed by Kt/V. Furthermore, the

association with NMES in the UL is also difficult to find in the literature, since most studies using NMES have been applied in the LL.

One limitation is the sample size, which has a very small number of participants due to refusal or ineligibility of guests. This makes analysis and statistical results more difficult, given that the amount of data collected may not have been sufficient to generate a statistical difference between the GI and CG or in the analysis of the correlation between variables. Another problem that may have influenced the results was the lack of human resources, i.e., physical therapists and students, to perform the assessment and intervention procedures in other shifts of the hospital's HD, restricting data collection to only 2 of the 4 possible shifts.

Conclusion

Based on the results obtained in this study, a weak but statistically significant positive correlation was found between Kt/V and delta HR_{cycle}. When intradialytic exercise was performed using the cycle ergometer in LL associated with active NMES in UL. However, for the other variables evaluated to measure exercise intensity (pedaled cycles, distance traveled, delta HR_{F.I.}, and peak HR), there was no statistically significant correlation with Kt/V for either the IG or the CG. In addition, active NMES of the UL, when associated with the cycle ergometer, does not seem to have an additional effect on Kt/V, but it does seem to improve the HR response to exercise with the LL cycle ergometer. Therefore, the findings suggest that the effect on cardiac function of active NMES of the UL, associated with the LL cycle ergometer, seems to contribute to greater HD adequacy. However, these results should be interpreted with caution, considering the small number of participants included in the study. Thus, further studies are needed to clarify the influence of NMES associated with the cycle ergometer on HD quality as assessed by Kt/V.

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