

Chronic nimesulide use impairs exercise-induced cardiac hypertrophy ***O uso crónico de nimesulida prejudica a hipertrofia cardíaca induzida pelo*** ***exercício***

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Abstract

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of pain and inflammation. This exploratory study evaluated whether nimesulide administration concomitant with resistance training (RT) was associated with differences in performance, the heart mass-to-body mass ratio, and ex vivo cardiac function. Male Wistar rats were allocated to three groups: CTRL (control, n = 4), TR (8 weeks of RT, n = 7), and COMB (the same RT protocol associated with nimesulide, 2.5 mg/kg, n = 7). After the intervention, hearts were studied using a Langendorff preparation during baseline stabilization, 30 min of global ischemia, and 60 min of reperfusion. TR and COMB significantly increased load-carrying capacity compared with pre-intervention values ($p < 0.0001$), with no difference between the trained groups at the end of the protocol. The heart mass-to-body mass ratio was higher in TR than in CTRL and showed a distinct response in COMB. Infarct size did not differ significantly among groups, and there was no conclusive evidence of improved recovery of left ventricular developed pressure after ischemia-reperfusion. Thus, concomitant nimesulide administration did not alter strength gain, whereas the morphometric response differed from that observed with training alone. Because of the small sample size and the absence of a sedentary nimesulide-treated group, these findings should be considered exploratory and do not allow causal attribution of the observed differences to nimesulide.

Keywords: Cardiac Function; Cardiac Hypertrophy; Nimesulide; Resistance Training.

Resumo

A nimesulida é um anti-inflamatório não esteroide (AINE) utilizado para o tratamento de dor e inflamação. Este estudo exploratório avaliou se a administração de nimesulida concomitantemente ao treinamento resistido (TR) estava associada a diferenças no desempenho, na razão massa cardíaca/massa corporal e na função cardíaca ex vivo. Ratos Wistar machos foram distribuídos em três grupos: CTRL (controle, n = 4), TR (treinamento resistido por 8 semanas, n = 7) e COMB (mesmo protocolo de TR associado à nimesulida, 2,5 mg/kg, n = 7). Após a intervenção, os corações foram estudados em preparação de Langendorff durante estabilização basal, 30 min de isquemia global e 60 min de reperfusão. O TR e o COMB aumentaram significativamente a capacidade de carga em relação ao período pré-intervenção ($p < 0,0001$), sem diferença entre os dois grupos treinados ao final do protocolo. A razão massa cardíaca/massa corporal foi maior no TR em comparação ao CTRL e apresentou

resposta distinta no COMB. O tamanho do infarto não diferiu significativamente entre os grupos, e não houve evidência conclusiva de melhora da recuperação da pressão desenvolvida do ventrículo esquerdo após isquemia-reperusão. Assim, a associação com nimesulida não alterou o ganho de força, enquanto a resposta morfométrica diferiu daquela observada com treinamento isolado. Devido ao pequeno tamanho amostral e à ausência de um grupo sedentário tratado com nimesulida, estes achados devem ser considerados exploratórios e não permitem atribuir causalmente ao fármaco as diferenças observadas.

Palavras-Chave: Função Cardíaca; Hipertrofia Cardíaca; Nimesulida; Treinamento Resistido.

1. Introduction

One of the best-selling nonsteroidal anti-inflammatory drugs (NSAIDs) in Brazil is nimesulide (Secretaria Executiva da Câmara de Regulação do Mercado de Medicamentos, 2025), which is commercially available without a prescription. Its accessibility has led to widespread use, particularly among individuals engaged in physical activity. Abusive use has been reported in the search for pain relief associated with sports practice, especially in gyms and among those performing resistance exercises (Brewer et al., 2014a; Sethi & Talvelkar, 2024).

However, NSAIDs exert significant effects on the cardiovascular system, being associated with vascular dysfunction and increased cardiovascular risk (Liang et al., 2024). This evidence raises a relevant question, since exercise—particularly resistance training (RT)—acts as a protective factor against cardiovascular diseases, improving cardiac morphology and function (Momma et al., 2022). In contrast, the chronic or indiscriminate use of NSAIDs may counteract these benefits, as several studies demonstrate their deleterious cardiovascular effects (Marsico et al., 2017; McGettigan & Henry, 2011; Trelle et al., 2011).

RT is widely used to develop strength and enhance performance in most sports. Beyond its musculoskeletal benefits, RT is a non-pharmacological strategy capable of inducing relevant cardiovascular adaptations, such as increased left ventricular end-diastolic diameter, wall thickness, and improved diastolic function (FLECK, 1988; Soares et al., 2022; Suchomel et al., 2018; Westcott, 2012). During the initial weeks of RT, however, exercise-induced muscle damage leads to delayed onset muscle soreness (DOMS) (Cheung et al., 2003; Clarkson & Hubal, 2001). To alleviate this discomfort, many individuals resort to analgesic and anti-inflammatory drugs—particularly nimesulide, a potent COX-2 inhibitor (Brewer et al., 2014; Corrigan & Kazlauskas, 2003).

While RT confers functional and structural cardiac benefits (Barauna et al., 2007), its cardioprotective effects remain less explored compared to aerobic training. Moreover, the interaction between RT and chronic NSAID administration is poorly understood, despite the high prevalence of their combined use among active individuals. From a cardiovascular physiology standpoint, RT imposes transient hemodynamic overloads that stimulate adaptive remodeling of the myocardium, improving left ventricular compliance, diastolic filling, and vascular reactivity through repeated mechanical stress and controlled inflammatory signaling (Alves et al., 2014; Lekavich et al., 2021). These adaptive responses depend on the integrated action of endothelial nitric oxide (NO) synthesis, prostaglandin-mediated vasodilation (particularly PGI₂ and PGE₂), and modulation of oxidative balance—all of which contribute to enhanced myocardial perfusion and ischemic tolerance (Green et al., 2017; Kingwell, 2000). However, chronic inhibition of cyclooxygenase-2 (COX-2) by nonsteroidal anti-inflammatory drugs (NSAIDs), such as nimesulide, disrupts prostaglandin biosynthesis, shifting the vascular equilibrium toward a pro-constrictive and pro-thrombotic state characterized by reduced prostacyclin availability and unopposed thromboxane A₂ activity (Grosser et al., 2006; Ik Dahl et al., 2024). This pharmacological interference could blunt the beneficial remodeling induced by RT, attenuating both vascular and myocardial adaptive responses. Nonetheless, the magnitude and direction of these effects likely depend on dosage, duration, and physiological context—raising the hypothesis that chronic COX-2 blockade may hinder exercise-induced cardioprotection while acute or therapeutic exposure exerts minimal interference.

Given that human studies are limited by ethical and methodological constraints, making direct assessment of cardiac function difficult, animal models provide a unique advantage. They enable controlled conditions, precise

monitoring of physiological variables, and direct evaluation of myocardial performance, offering valuable insights into mechanisms underlying exercise-induced cardioprotection and drug interactions. Chronic administration of nimesulide during RT attenuates the myocardial and vascular adaptations normally induced by exercise by reducing prostaglandin-dependent signaling, thereby impairing cardiac function and post-ischemic recovery. Conversely, isolated resistance training promotes cardioprotective adaptations that enhance myocardial performance and resilience to ischemic stress.

Therefore, the present exploratory study asked whether nimesulide administration during RT was associated with differences in load-carrying performance, heart mass-to-body mass ratio, and post-ischemic cardiac recovery compared with RT alone. Because the experimental design did not include a sedentary nimesulide-treated group, the study was not designed to estimate an independent drug effect or formally test a drug × exercise interaction.

2. Background

Nimesulide is a preferential COX-2 inhibitor widely used for musculoskeletal and postoperative pain, showing comparable or superior efficacy to other NSAIDs, rapid onset of action, and, in several scenarios, better gastrointestinal tolerability (Binning & Chb, 2007; Famaey, 1997; Pohjolainen et al., 2000). In acute low back pain, nimesulide improved function and flexibility with fewer gastrointestinal effects than ibuprofen (Pohjolainen et al., 2000). In periodontal pain, preemptive analgesia with nimesulide outperformed ibuprofen in the first 48–72 hours (Santos et al., 2021).

Mechanistically, its effects extend beyond COX-2 blockade. Nimesulide inhibits phosphodiesterase type IV (PDE4), modulates tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) production, reduces reactive oxygen species (ROS) formation, and suppresses neutrophil migration (Famaey, 1997; Rainsford, 2006). These pleiotropic effects contribute to its broader anti-inflammatory and cytoprotective actions, including neuroprotection (Dhir et al., 2007) and anti-nociceptive synergy with opioids and nefopam (Saghaei et al., 2012).

Experimental findings from rat models confirm that nimesulide decreases PGE₂ levels without causing gastric ulceration, even under inflammatory or stress conditions (Nakatsugi et al., 1996). These properties explain its favorable gastrointestinal safety profile and relative cardiovascular neutrality compared to potent COX-2 inhibitors like rofecoxib or celecoxib (Bianchi & Broggin, 2003).

Although NSAIDs share a class risk for cardiovascular events, differences in COX selectivity and prostanoid balance determine individual safety profiles. Inhibition of endothelial PGI₂ synthesis by COX-2 blockade removes a crucial vasodilatory and anti-thrombotic mediator, allowing unopposed TXA₂ activity and platelet aggregation (Grosser et al., 2006; Wang & Li, 2022). Chronic NSAID exposure can lead to sodium retention, hypertension, and impaired renal function, further compounding cardiovascular risk (Bally et al., 2017; Ikdaahl et al., 2024).

However, data from epidemiological studies suggest that nimesulide exhibits moderate COX-2 selectivity and minimal interference with COX-1-dependent PGI₂ production, resulting in a milder impact on vascular homeostasis compared with other NSAIDs (Liang et al., 2024; Varas-Lorenzo et al., 2013). Case reports and pharmacovigilance reviews reinforce this profile, indicating no disproportionate increase in myocardial infarction incidence when used at therapeutic doses (Rainsford, 2006).

Recent systematic analyses (Ikdaahl et al., 2024; Trelle et al., 2011) have confirmed that while all NSAIDs elevate cardiovascular risk to some extent, nimesulide remains among the least hazardous options when prescribed acutely and within dosage limits. Chronic or high-dose exposure, however, is inadvisable, especially in patients with existing cardiac pathology or hypertension.

RT imposes transient hemodynamic overloads that induce structural and functional adaptations in both skeletal muscle and the cardiovascular system. These overloads increase myocardial wall stress, venous return, and intraventricular pressure, stimulating cardiomyocyte hypertrophy and improved diastolic function (FLECK, 1988; Pluim et al., 2000; Silva et al., 2021).

RT also enhances endothelial function through shear-stress-mediated upregulation of nitric oxide synthase (eNOS) and prostaglandin release (Green et al., 2017; Kingwell, 2000). Exercise promotes the synthesis of NO and prostacyclin (PGI₂), both key in vasodilation and perfusion regulation. Studies in hypertensive models show that RT can restore endothelial-dependent vasodilation, improve baroreflex sensitivity, and reduce collagen deposition in cardiac tissue (Alves et al., 2014; Correia et al., 2023).

These beneficial effects are closely tied to controlled inflammatory signaling, where COX-derived prostaglandins, NO, and ROS act as integrated mediators of vascular remodeling and metabolic adaptation. Thus, pharmacological inhibition of COX-2 may interfere with these adaptive pathways, particularly when sustained. During the initial weeks of RT, delayed onset muscle soreness (DOMS) is frequent, leading athletes to use NSAIDs to maintain training volume (Brewer et al., 2014; Corrigan & Kazlauskas, 2003). Recent research indicates heterogeneous effects of NSAIDs on skeletal muscle adaptations: Chronic use may attenuate hypertrophy and myogenesis in young individuals, as well as reduce satellite cell activation and protein synthesis signaling (e.g., the mTOR and COX-2-derived PGF₂α pathways) (Ashton et al., 2020; Cardinale et al., 2017), while in older adults, results are neutral or mildly favorable (Cardinale et al., 2017; Krentz et al., 2008; Schoenfeld, 2018). Thus, when adaptation to RT is the priority, chronic or prophylactic NSAID use should be avoided, but acute use for pain control may improve adherence and recovery.

Therefore, for athletes or physically active individuals, nimesulide may offer short-term analgesic and anti-inflammatory relief without significantly impairing cardiovascular function, provided it is used acutely and within therapeutic doses (Patil et al., 2024). Nonetheless, long-term studies combining RT and NSAID exposure with cardiac outcomes are lacking. Controlled animal models provide essential insight, allowing direct cardiac evaluation (e.g., Langendorff perfusion) under well-controlled conditions (Nakatsugi et al., 1996). The literature provides robust evidence that nimesulide exhibits potent anti-inflammatory and analgesic properties, a favorable gastrointestinal profile, and potentially lower cardiovascular interference than other NSAIDs when used acutely. chronic COX-2 inhibition during exercise may reduce the expression of heat-shock proteins, NO bioavailability, and endothelial progenitor cell activation, potentially limiting exercise-induced cardioprotection (Grosser et al., 2006; Ikdahl et al., 2024). However, short-term or intermittent NSAID use—particularly with nimesulide—appears less likely to disrupt adaptive remodeling, as indicated by experimental and clinical findings (Binning & Chb, 2007; Rainsford, 2006).

3. Methods

Drug preparation and administration

The drug used for pharmacological therapy was Nimesulide (Cimed®), at a therapeutic dose of 2.5 mg/kg, with a concentration of 50 mg/mL (Dhir et al., 2007; Saghaei et al., 2012). The industrialized form of Nimesulide is marketed in liquid form, containing 50 mg/mL, therefore requiring a 20-fold dilution to obtain the dose selected for the study. The administration dose was prepared with 1 mL of the Nimesulide concentration, added to 19 mL of 0.9% saline solution (NaCl), and diluted in a 50 mL beaker using an INTLAB™ magnetic stirrer.

The drug was administered daily after the training session for the COMB group, throughout the study (8 weeks). The orogastric (gavage) route of administration was chosen because it presents a lower risk of injury to the animals, given the length of the study and the total number of administrations performed.

To ensure the reliability of the drug's effect, the animals were weighed weekly and the dose adjusted according to their weight.

All groups received gavage administration on training days. The treated group received the drug, and the control and trained groups received 0.9% saline, thus mitigating the potential interference of stress caused by orogastric administration during the 8-week protocol.

Animals

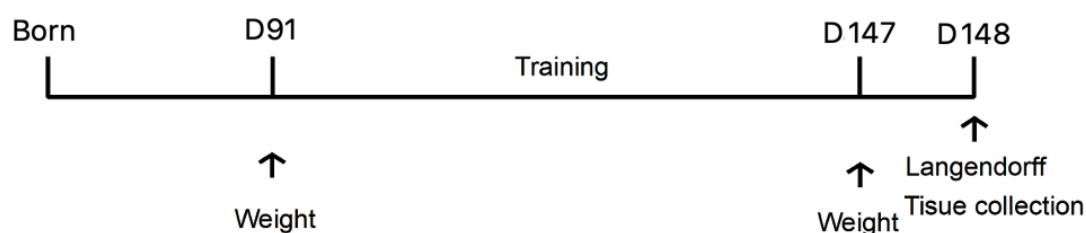
The animals were obtained from the Laboratory Animal Nucleus at the Fluminense Federal University (NAL-UFF) and were housed in collective cages under controlled temperature (23 °C + 1°C), and kept in collective cages on a 12-hour light-dark cycle (light at 6:00 am – 17:59h, dark from 18:00h – 05:59h). The animals had access to granulated feed and water ad libitum. The animals were weighed on a semi-analytical scale (Model SF400, YDTECH, Brazil) with a precision of 0.1 g. Reporting was revised with attention to ARRIVE 2.0 principles. Experimental details not documented in the available study record (including allocation concealment, blinding procedures, cage-position control, and prespecified humane endpoints) are not inferred here and should be supplied from the original protocol before final submission.

Male Wistar rats, 91 days old, with a body weight of 331.2 g ($\pm$ 4.94), were divided into the following groups: CTRL (sedentary controls, n = 4), TR (rats subjected to RT for 8 weeks, n = 7), and COMB (rats subjected to the same RT protocol combined with nimesulide administration at a dose of 2.5 mg/kg, n = 7). At the end of trials, animals were euthanized, and hearts were excised for mounting in the isolated heart apparatus, where they were perfused with modified Krebs-Henseleit solution. Ventricular function was recorded for 20 minutes, followed by 30 minutes of ischemia and, finally, 60 minutes of reperfusion. The recordings were digitized via an analog-to-digital interface (PowerLab 400, ADInstruments, USA) and stored for offline analysis of hemodynamic variables using LabChart 8 Pro software (ADInstruments, USA). The hearts were weighed after isolated heart procedures. Data are presented as mean $\pm$ standard error of the mean. No sedentary nimesulide-treated group was included; therefore, the design does not permit estimation of an isolated nimesulide effect or a formal drug $\times$ training interaction.

Experimental Design

The animals were monitored from birth until the 148th day of life, as can be seen in Figure 1. On day 91 (D91), the first body weighing was performed, followed by the start of the training protocol. After 56 days of intervention, on day 147 (D147), the animals were weighed again to assess body growth. On the following day (D148), isolated hearts were prepared in a Langendorff perfusion system, followed by tissue collection for further analysis.

Figure 1: Experimental design timeline.

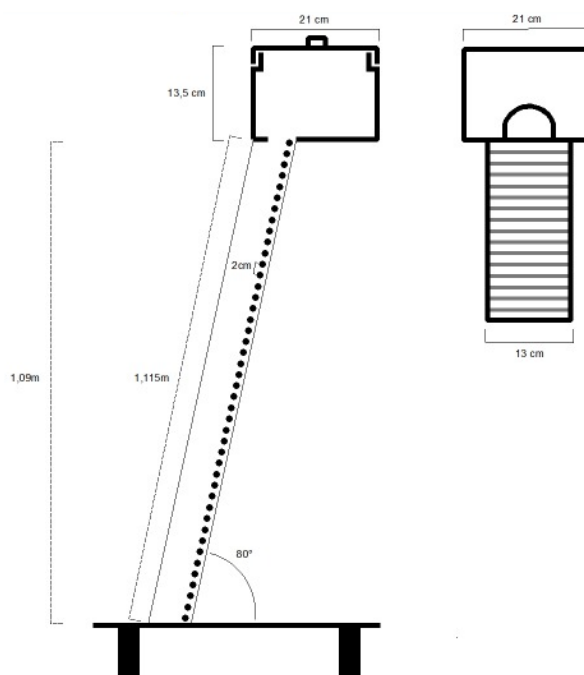


Source: Archive of the Laboratory of Cardiovascular Physiology and Pharmacology - UFRJ.

Resistance Exercise Apparatus

The training apparatus is shown in Figure 2. The resistance exercise apparatus consists of a ladder with an extension of 110 cm and a housing chamber at the top with an entrance hole at the base. The animal was trained to climb the ladder by pulling a load attached to the tail. At the end of the climb, the animal recovered between climbs in the housing chamber.

Figure 2: Training apparatus. Rat ladder.



Source: Archive of the Laboratory of Cardiovascular Physiology and Pharmacology - UFRRJ.

Recognition of training and loading apparatus

Before the maximum load test, the animals underwent a familiarization period with the experimental apparatus. During seven consecutive days, each animal performed three attempts to climb the ladder per session, using a tail-mounted load apparatus. This apparatus consisted of a fabric bag into which lead pieces were inserted to adjust the ideal load during training sessions. The bag had two straps that were attached to the proximal portion of the animals' tails.

Maximum Load Carried Test (MLCT)

On the first attempt, the animals supported an overload of 75% of their body weight (BW) according to . Each subsequent attempt added 30 g, corresponding to $10 \pm 2\%$ of body mass, until the animal failed and did not complete the climb. The maximum load carried was considered the largest load the animal could complete a climb. The maximum capacity test was performed in the first and 20th sessions. MLCT was conducted as outlined in Table 1. A 2-minute rest interval was proposed between each attempt, as recommended by Hornberger and Farrar (2004) for maximum strength tests. The test was interrupted when the rat failed or refused to climb. (Hornberger & Farrar, 2004)

Table 1: Maximum Load Carried Test protocol.

Attempt	Load
1	75% of BW
2	75% do BW + 30g
3	75% do BW + 60g
4	75% do BW + 90g
Consecutive attempts	+30g

Resistance Training Procedure

From the 91 days of life, the TR animals were trained 3 times a week for 8 weeks. Training sessions consisted of 4 to 9 stair climbs. Upon reaching the chamber at the top of the ladder, the animals were given a 2-minute rest break. During the first 4 climbs, the rats carried 50%, 75%, 90%, and 100% of their maximum capacity,

respectively. During subsequent climbs, an additional 30 g load was progressively added until the new maximum capacity was reached. Thus, the rats' new maximum load capacity was calculated for each training session. This training regimen was repeated once every 3 days for 8 weeks, totaling 20 training sessions (Hornberger & Farrar, 2004).

Morphometry

Rats were weighed (Toledo Prix 3, Toledo, Brazil) once a week throughout the study. The hearts were weighed after isolated heart procedures (AD 500, Marte, Brazil).

Isolated Heart Protocol (Langendorff)

Morphofunctional analysis was performed after euthanasia by decapitation, followed by immediate removal of the hearts. The hearts were placed in a Petri dish with enough perfusate to cover the heart and at a temperature between 0 and 3°C, then they were cannulated through the aorta to a Langendorff apparatus (Panlab, ADInstruments, United States of America) and submitted to cleaning, removing the largest surrounding structures that remain with the sample. The cannula was inserted and fixed until close to the coronary ostia. The perfusion flow from the time of aortic cannulation until the first minute was 5 mL/min and was increased to 10 mL/min during the second minute. The artificial perfusion solution used was the modified Krebs-Henseleit Solution (KHS), containing (in mM): 118 NaCl, 4.7 KCl, 1.2 MgSO₄, 1.2 KH₂PO₄, 25 NaHCO₃, 10 glucose, 1.8 CaCl₂, saturated with a carbogenic mixture of 95% O₂ and 5% CO₂. The solution was prepared without CaCl₂ and this was added fractionally with the already gasified mother solution. The solution was adjusted to pH 7.4 and kept warm at 37 °C, being pumped through the circuit through the perfusion pump.

Next step was to insert, through an incision in the left atrium, a latex balloon in the LV connected to a cannula and this to a pressure transducer. The balloon was previously filled with distilled water and adjusted to maintain the end-diastolic pressure (EDP) at 10 mmHg. The pressure transducer was connected to an ML110 amplifier (ADInstruments, United States of America) to record the intraventricular pressure developed by the left ventricle. The pressure recordings were digitized using an analog-digital interface (PowerLab 400, ADInstruments, United States of America) and stored on a computer for off-line analysis with the Lab Chart 8 Pro software (ADInstruments, United States of America).

Ischemia-reperfusion injury (IRI) was performed after the heart accommodation period (baseline recording). Perfusion was stopped for 30 minutes, followed by reperfusion for 60 minutes. At the end of the isolated heart protocol, the hearts were collected and properly weighed on a semi-analytical electronic scale (AD 200, Marte Científica, Brazil).

4. Data Analysis

Data were analyzed with the individual animal or isolated heart as the experimental unit; repeated time points from the same heart were not considered independent observations. Results are presented as mean $\pm$ standard error of the mean (SEM), consistent with the original analysis. Group and time were treated as factors for outcomes measured repeatedly, and multiple-comparison procedures were applied only after the corresponding omnibus analysis. Bonferroni correction, when used, was considered a multiple-comparison adjustment and not a test of normality. Given the small and unequal group sizes (CTRL, $n = 4$; TR, $n = 7$; COMB, $n = 7$ at allocation), all inferential results should be interpreted as exploratory. GraphPad Prism software (version 10.1.1, San Diego, CA, USA) was used for statistical analysis. Exact n values available for each outcome are reported in the corresponding results/figure legends. A complete reanalysis of the longitudinal Langendorff data using a mixed-effects model with heart as a random effect, together with effect sizes and 95% confidence intervals, requires the original heart-level dataset and should be performed before confirmatory inference.

4.1. Quantitative Analysis

Maximum Load Carried

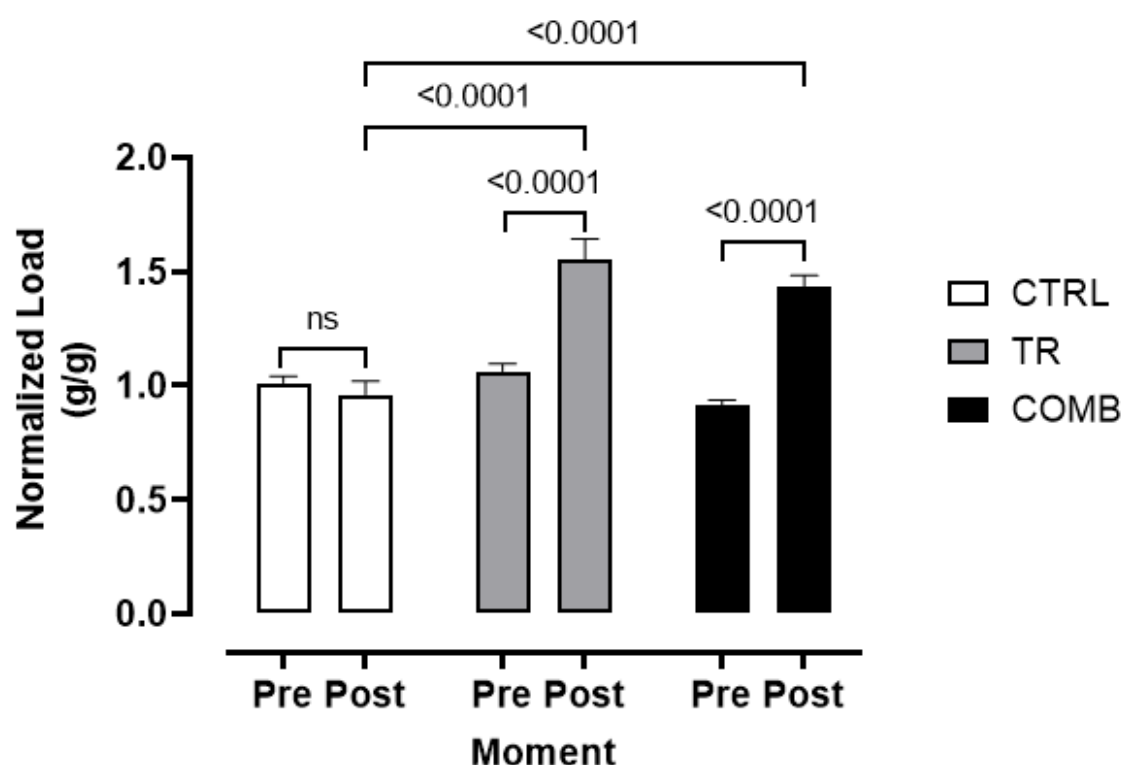
When evaluating maximum strength normalized by the animal's body mass, statistical differences were observed for intragroup comparisons before and after 8 weeks of the resistance training protocol for TR (TRPre: 1.063 ± 0.03309 vs TRPost: 1.553 ± 0.09037 ; $p < 0.0001$) and COMB (COMBPre: 0.9135 ± 0.0232 vs COMBPost: 1.433 ± 0.05072 ; $p < 0.0001$). However, without no statistical difference for CTRL (CTRLPre: 1.012 ± 0.02896 vs CTRLPost: 0.9606 ± 0.05898 ; $p = 0.9379$).

As for the intergroup comparisons before the resistance training protocol, no statistical differences were observed when comparing CTRL with TR (CTRLPre: 1.012 ± 0.02896 vs TRPre: 1.063 ± 0.03309 ; $p = 0.8279$) or COMB (CTRLPre: 1.012 ± 0.02896 vs COMBPre: 0.9135 ± 0.02325 ; $p = 0.4958$). Likewise, no statistical difference was found between TR and COMB (TRPre: 1.063 ± 0.03309 vs COMBPre: 0.9135 ± 0.02325 ; $p = 0.1226$).

However, intergroup analyses after 8 weeks of the resistance training protocol were statistically different when CTRL was compared to TR (CTRLPost: 0.9606 ± 0.05898 vs TRPost: 1.553 ± 0.09037 ; $p < 0.0001$) or COMB (CTRLPost: 0.9606 ± 0.05898 vs COMBPost: 1.433 ± 0.05072 ; $p < 0.0001$). However, without any statistical difference between TR and COMB (TRPost: 1.553 ± 0.09037 vs COMBPost: 1.433 ± 0.05072 ; $p > 0.05$).

Figure 3 shows a significant increase in load in the TR and COMB groups after the intervention ($p < 0.0001$), while the control group showed no change (ns). Comparisons between groups at the post-intervention moment demonstrate significantly higher values in TR and COMB in relation to CTRL ($p < 0.0001$), with no difference between TR and COMB (ns).

Figure 3: Normalized load (g/g) at pre- and post-intervention moments in the control (CTRL), trained rats (TR), and combined training (COMB) groups. Data are expressed as mean $\pm$ S.E.M.



Hemodynamics

Figure 4 shows left ventricular developed pressure (LVDP), defined as left ventricular systolic pressure (LVSP) minus left ventricular end-diastolic pressure (LVEDP), throughout the protocol. During the pre-ischemic phase,

the groups showed broadly similar LVDP profiles and reached a stabilization plateau between 15 and 20 min. Global ischemia (30 min, shaded area) caused the expected marked reduction in developed pressure. During reperfusion, the curves did not provide conclusive evidence that either trained group had superior LVDP recovery compared with CTRL. Because measurements were repeatedly obtained from the same heart, interpretation should be based on heart-level repeated-measures analysis rather than treating individual time points as independent observations.

Figure 4: Left ventricular developed pressure (LVDP, mmHg) in isolated hearts subjected to an IRI induction protocol. The animals were divided into three groups: control (CTRL), trained rats (TR), and trained rats + nimesulide (COMB). LVSP: $F(2, 9) = 8.372$; $p = 0.0088$. LVDP: $F(2, 9) = 10.78$; $p = 0.0041$. Data are expressed as mean $\pm$ S.E.M.

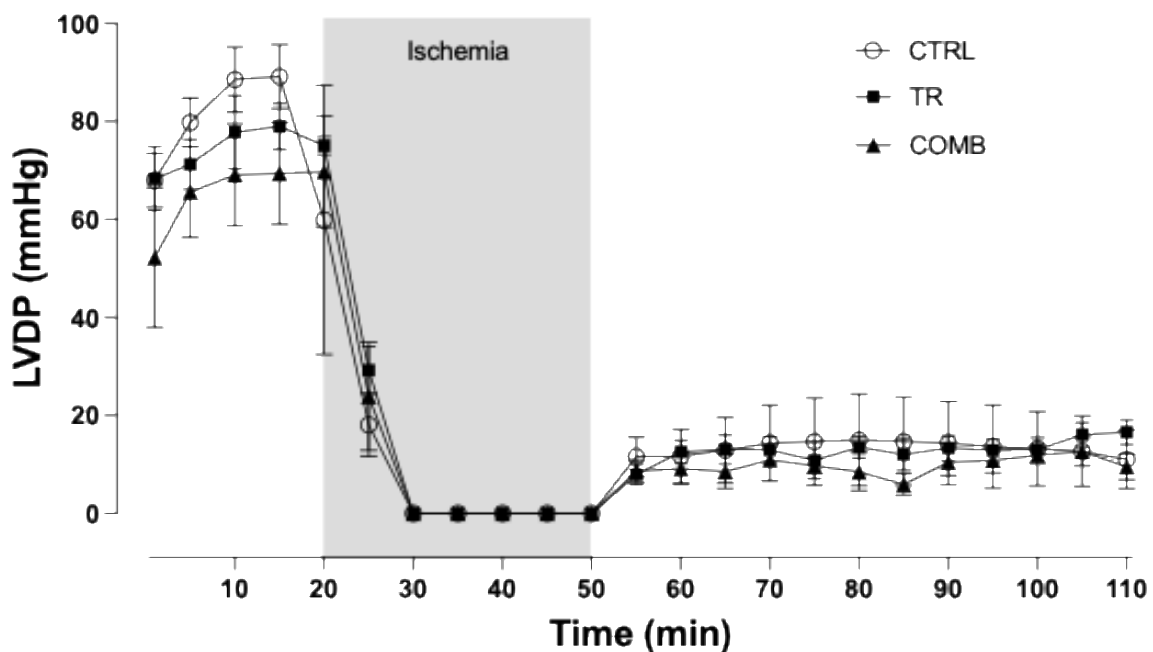
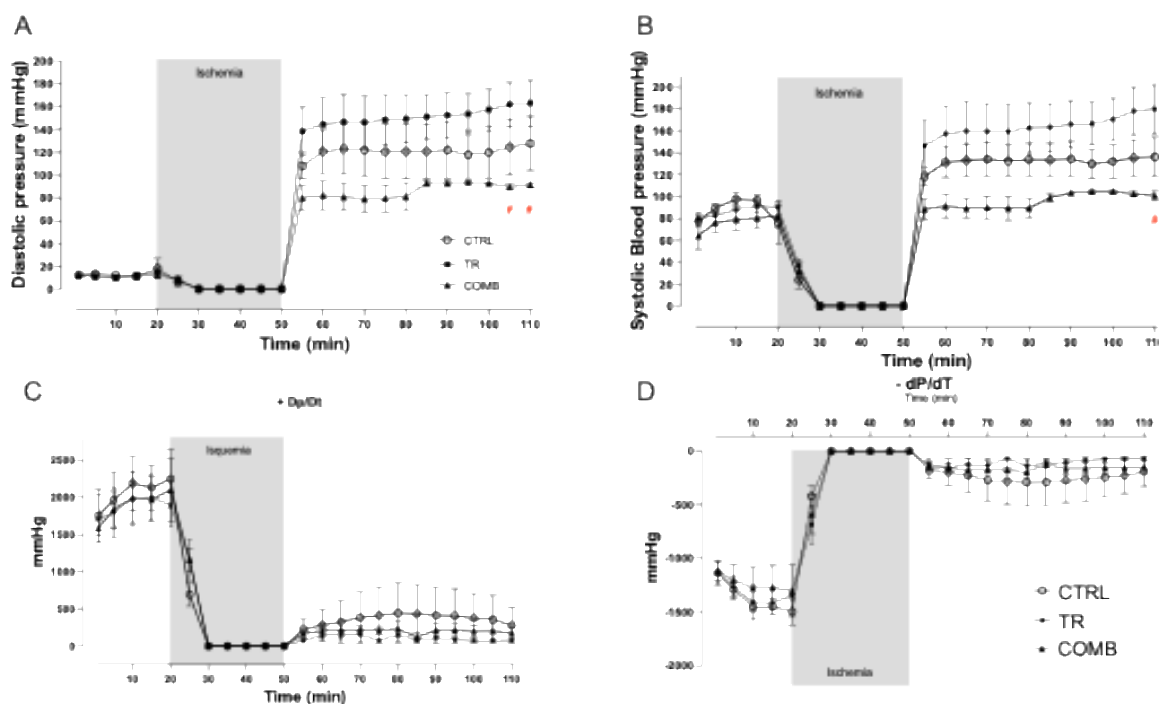


Figure 5 presents LVEDP, LVSP, maximum contraction rate (+dP/dt), and maximum relaxation rate (-dP/dt) during global ischemia and reperfusion. Post-ischemic increases in LVEDP are compatible with impaired ventricular relaxation/ischemic contracture; however, the present study did not include histological or biochemical measurements that would allow this response to be attributed directly to cell death. The +dP/dt and -dP/dt profiles did not provide conclusive evidence of between-group differences in contractile or relaxation recovery.

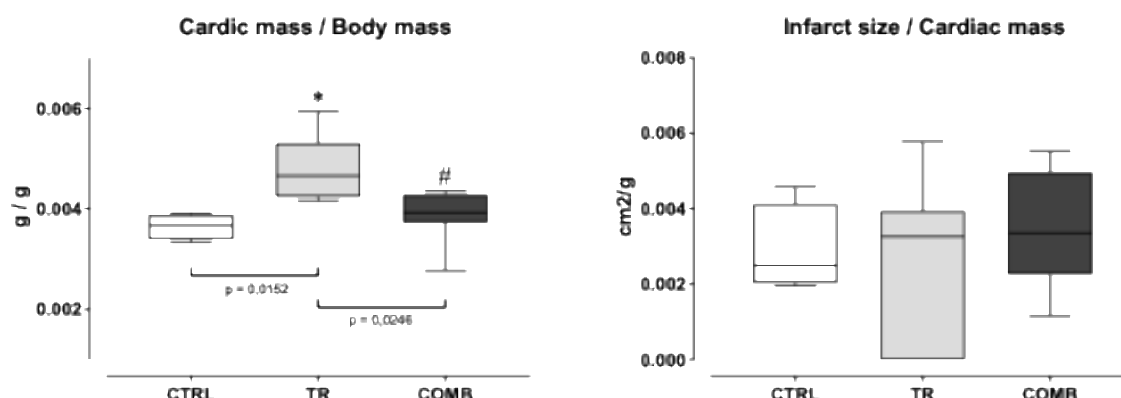
Figure 5: Hemodynamic parameters in isolated hearts subjected to global ischemia (30 min, shaded area) followed by reperfusion (60 min). Three experimental groups were analyzed: control (CTRL), trained rats (TR), and trained rats + nimesulide (COMB). (A) Left ventricular diastolic pressure. (B) Left ventricular systolic pressure. (C) Maximum contraction rate ($+dP/dt$). (D) Maximum relaxation rate ($-dP/dt$).



Cardiac Morphometry

Figure 6 shows the heart mass-to-body mass ratio and the infarct outcome normalized as reported in the original dataset. (A) The heart mass-to-body mass ratio was higher in TR than in CTRL ($p = 0.0152$), and COMB also differed from CTRL ($p = 0.0246$). These findings indicate differences in the post-protocol cardiac mass-to-body mass ratio but, by themselves, do not establish physiological cardiac hypertrophy, because heart mass was obtained after prolonged ex vivo perfusion and ischemia-reperfusion and no cellular, histological, ventricular-mass, tibia-length, or echocardiographic measurements were available. (B) The infarct outcome did not differ significantly among CTRL, TR, and COMB. Therefore, the available data do not provide conclusive evidence that either protocol reduced tissue injury after global ischemia-reperfusion.

Figure 6: Cardiac Morphometry. Cardiac mass and infarct size. CTRL, control; TR, 8-week RT; COMB, 8-week TR and nimesulide. *Comparison of TR vs. CTRL ($P < 0,05$). # Comparison between TR and COMB ($P < 0,05$). Data expressed as mean $\pm$ S.E.M.



5. Discussion

During reperfusion, the LVDP profiles did not provide conclusive evidence of superior mechanical recovery in either trained group. Accordingly, the present data should be interpreted as an absence of evidence for cardioprotection under this protocol rather than evidence that cardioprotection is absent. Studies of exercise preconditioning have described enhanced mitochondrial efficiency, antioxidant capacity, and cell-survival signaling after training (Powers et al., 2014; Quindry & Hamilton, 2013), but these mechanisms were not measured here. Differences in training frequency, cumulative volume, and timing may contribute to divergent findings across experimental models (Demirel et al., 2001; Starnes et al., 2005). (Powers et al., 2014; Quindry & Hamilton, 2013)(Demirel et al., 2001; Starnes et al., 2005)

In this study, resistance training increased the heart mass-to-body mass ratio. This observation is compatible with cardiac remodeling after training, but it should not be interpreted as definitive evidence of physiological hypertrophy because cardiac mass was measured after the Langendorff ischemia-reperfusion protocol and no cardiomyocyte morphometry, ventricular wall measurements, fibrosis analysis, molecular markers, or echocardiography were performed. Pathways such as IGF-1–PI3K–Akt and mediators including PGC-1 α , SOD, and HSP70 have been associated with exercise-induced cardiac adaptation in previous studies (Maillet et al., 2013; Nakamura & Sadoshima, 2018; Finck & Kelly, 2007; McMullen et al., 2003), but their involvement in the present experiment remains hypothetical because they were not measured. (Maillet et al., 2013; Nakamura & Sadoshima, 2018)(Dorn, 2007; Frey & Olson, 2003)(Finck & Kelly, 2007; McMullen et al., 2003)

The COMB group showed a distinct post-ischemic diastolic pressure profile. This finding should be interpreted cautiously and cannot be attributed specifically to nimesulide because a sedentary nimesulide-treated group was not included. COX-2 inhibition can influence prostaglandin and vascular signaling (Grosser et al., 2006; Ik Dahl et al., 2024), but prostacyclin, nitric oxide, COX-2 activity, inflammatory markers, and circulating drug concentrations were not measured in this study. Therefore, these pathways are discussed only as possible hypotheses for future investigation, not as demonstrated mechanisms. (Grosser et al., 2006; Ik Dahl et al., 2024)

Importantly, COMB retained an increased heart mass-to-body mass ratio relative to CTRL, while its morphometric response differed from TR. The appropriate interpretation is therefore that concomitant nimesulide administration was associated with a different magnitude of the cardiac mass-to-body mass response, rather than that nimesulide prevented or abolished cardiac hypertrophy. This distinction is especially important because the study lacked a sedentary nimesulide group and direct cellular measures of hypertrophy (Liang et al., 2024; Varas-Lorenzo et al., 2013). (Liang et al., 2024; Varas-Lorenzo et al., 2013)

The absence of reduced infarct size across groups can also be explained by the isolated-heart (Langendorff) model, which eliminates circulating humoral mediators such as myokines and hormones that contribute to

exercise-induced cardioprotection (Finck & Kelly, 2007). Consequently, while *in vivo* cardioprotection may rely on systemic crosstalk (e.g., IL-6, irisin, IGF-1), these effects are not preserved *ex vivo* unless intrinsic myocardial adaptations have been fully established.

Taken together, the findings show that RT increased load-carrying capacity and the heart mass-to-body mass ratio, whereas concomitant nimesulide administration did not alter the gain in load-carrying capacity and was associated with a distinct morphometric response. No protocol produced conclusive evidence of improved post-ischemic recovery. Mechanistic explanations involving COX-2, PGI₂, eNOS, antioxidant enzymes, or inflammatory signaling remain hypotheses that require direct measurement in future studies.

6. Conclusion

Resistance training increased load-carrying capacity and the heart mass-to-body mass ratio. Concomitant nimesulide administration did not alter the gain in load-carrying capacity, while the COMB group showed a morphometric response distinct from training alone. Neither protocol provided conclusive evidence of improved post-ischemic functional recovery or reduced infarct outcome. Because the study had a small and unequal sample and did not include a sedentary nimesulide-treated group, the observed differences cannot be causally attributed to the drug. The findings should therefore be regarded as exploratory and hypothesis-generating. A confirmatory study should use a factorial 2 × 2 design, prospectively defined sample size, randomization and blinding, and direct measures of cardiac structure, drug exposure, COX-2/prostanoid signaling, and myocardial injury.

Limitations

Several limitations materially constrain interpretation. First, the absence of a sedentary nimesulide-treated group prevents estimation of the main effect of nimesulide and formal separation of drug effects from drug × exercise interactions. Second, the sample was small and unequal across groups, so statistical inference is exploratory. Third, heart mass was obtained after prolonged *ex vivo* perfusion and ischemia-reperfusion; edema may therefore influence the heart mass-to-body mass ratio, and no cellular, histological, tibia-length, ventricular-mass, or echocardiographic measurements were available to establish physiological hypertrophy. Fourth, no pharmacokinetic or pharmacodynamic marker (e.g., circulating nimesulide, PGE₂/PGI₂, or COX-2 activity) was measured, so mechanistic interpretations remain speculative. Fifth, the infarct analysis and longitudinal Langendorff outcomes require more complete reporting of heart-level *n*, exclusions, repeated-measures analysis, and normalization to baseline. Finally, future work should include a factorial 2 × 2 design, prospective sample-size calculation, randomization, allocation concealment, blinded outcome analysis, standardized timing between the final training/drug exposure and heart isolation, and molecular, redox, inflammatory, renal, hepatic, histological, and echocardiographic endpoints. These limitations preclude causal claims that nimesulide prevents exercise-induced cardiac hypertrophy or independently impairs cardioprotection.

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Declaração Ética

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