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Swimming exercise demonstrates advantages over running exercise in reducing proteinuria and glomerulosclerosis in spontaneously hypertensive rats

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Experimental studies in animal models have described the benefits of physical exercise (PE) to kidney diseases associated with hypertension. Land- and water-based exercises induce different responses in renal function. Our aim was to evaluate the renal alterations induced by different environments of PE in spontaneously hypertensive rats (SHRs). The SHRs were divided into sedentary (S), swimming exercise (SE), and running exercise (RE) groups, and were trained for 8 weeks under similar intensities (60 min/day). Arterial pressure (AP) and heart rate (HR) were recorded. The renal function was evaluated through urinary volume at each week of training; sodium and potassium excretions, plasma and urinary osmolarities, glomerular filtration rate (GFR), levels of proteinuria, and renal damage were determined. SE and RE rats presented reduced mean AP, systolic blood pressure, and HR in comparison with S group. SE and RE rats showed higher urine osmolarity compared with S. SE rats showed higher free water clearance ($P < 0.01$), lower urinary density ($P < 0.0001$), and increased weekly urine volume ($P < 0.05$) in comparison with RE and S groups. GFR was increased in both SE and RE rats. The proteinuria of SE (7.0 ± 0.8 mg/24 h) rats was decreased at the 8th week of the PE in comparison with RE (9.6 ± 0.8 mg/24 h) and S (9.8 ± 0.5 mg/24 h) groups. The glomerulosclerosis was reduced in SE rats ($P < 0.02$). SE produced different response in renal function in comparison with RE, in which only swimming-trained rats had better profile for proteinuria and glomerulosclerosis.

Keywords: swimming exercise, running exercise, renal function, spontaneously hypertensive rats, glomeruloesclerosis, physical training

Introduction

Hypertension is widely related to diseases of the cardiovascular and urinary systems (25). High blood pressure (BP) is one of the main risk factors for the progression of chronic kidney diseases (18, 42). In the evolution of kidney diseases, changes due to the direct or indirect influence of increased BP, such as vascular lesions, mesangial lesions, glomerulonephritis, and glomerulosclerosis, lead to changes in filtration capacity, elevations in the proteinuria level, and decline in the glomerular filtration rate (GFR) (34, 36).

Experimental studies in animal models have described the benefits of physical exercise (PE) to kidney diseases associated with hypertension (45). Studies in humans with hypertension (7) have also shown the benefits of exercise. In addition, it is also known that the reduction of PE in hypertensive persons with kidney disease is associated with lower survival (27).

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Alterations in renal function, both short term and long term, caused by PE depend on the environment in which the exercise was performed (12, 19, 39). PE that is performed in a land environment produces increased sympathetic activity and cardiac output, and decreased blood flow from some organs, especially to the kidneys (13). On the other hand, PE that is performed in aquatic environments induces translocation of peripheral flow to the central part of the body, which stimulates the secretion of atrial natriuretic peptide (ANP) (2); increases urinary volume; causes loss of sodium and potassium; and suppresses vasopressin, renin, and plasma aldosterone (9, 30).

Few studies have compared the different modalities of PE and their effects on the renal system, especially in hypertensive conditions. Totou et al. (39) demonstrated that, in spontaneously hypertensive rats (SHRs), PE that is performed in an aquatic environment (swimming) improved the sensitivity of the cardiopulmonary reflex and led to an early decrease in systolic BP compared with exercise performed on land (treadmill) of the same duration and intensity. Gomes et al. (19) showed in humans with hypertension that an exercise performed in a land environment increased the diastolic BP (DBP), whereas the same exercise performed in an aquatic environment reduced the DBP.

Given that there are important physiological differences between running and swimming, the purpose of this study was to evaluate the renal function alterations induced in different environments of PE in SHR.

Methods

Ethical care

The procedures performed in the study were approved by the Animal Research Ethics Committee of the Federal University of Ouro Preto (CEUA no. 02/2013).

Rats

Male SHRs of the SHR line, with body mass varying between 350 and 400 g, obtained from the Laboratory of Hypertension of the Federal University of Minas Gerais, were used. The rats were divided into three experimental groups, such as running exercise (RE), swimming exercise (SE), and sedentary (S), and were housed in plastic boxes, provided with water, and fed *ad libitum*, with controlled temperature of 27 ± 1 °C and 12-h light–dark cycle.

Training protocols

RE training. The rats underwent a 5-day period of adaptation to training consisting of a daily running session on a treadmill with a speed of 18 m/min. Each day, the exercise duration was increased by 10 min. The training was conducted for 8 weeks in 60-min daily races. The speed of the race was maintained at 18 m/min in the first 3 weeks, and then increased to 20 m/min in the 4th week, 22 m/min in the 5th and 6th weeks, and 24 m/min in the 7th and 8th weeks (1, 35).

SE training. All adaptation and swimming training procedures were carried out in a tank adapted for rats. Water depth was 50 cm and temperature was set to 30–32 °C. The training consisted of 60-min swimming sessions 5 days/week for 8 weeks. The swimming time on the 1st day was 10 min, which was increased daily by 10 min until it reached 60 min on the 5th day. The training was conducted for 8 weeks with 60-min daily sessions. During the first 3 weeks, swimming sessions were performed without load. At week 4, a weight equivalent of a body mass overload of 2% was attached to the rats' tails. In the 5th and 6th weeks, the overload was increased to 4% and then to 6% in the 7th and 8th weeks. PE under load is necessary once the rats adapt to exercise intensity during the protocol; in addition, our goal was to set exercise intensity close to submaximal. Data in the literature noted that S rats are able to maintain a stable lactate/removal at a work load 20 m/min for treadmill and 5.5% of body weight for swimming (6) and other works show that 25 m/min for treadmill and 6% of body weight for swimming were maximal lactate steady states (3).

Evaluation of cardiovascular parameters

After 8 weeks of physical training, the rats were anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg). Polyethylene cannulas filled with a solution of heparin in isotonic saline were implanted in the femoral artery to record BP and heart rate (HR). The BP records were made 24 h after surgery. Before beginning the records, the rats remained in the recording room for at least 1 h to adapt to the environmental conditions. Immediately before beginning the records, a solution of heparin in isotonic saline was injected into the femoral artery to prevent clot formation at the vascular end. The arterial cannula was connected to a pressure transducer linked to a PowerLab 400 digital biological signal acquisition system (ADInstruments, Sydney, Australia). The Chart 4.0 for Windows software was used to record the BP and HR. The baseline levels of BP and HR were evaluated for a 40-min period in each group.

Evaluation of renal function

Every week during the experimental protocol, the rats were individually housed with free access to water and food in metabolic cages (Beira Mar LTDA, São Paulo, Brazil) for a 24-h period for urine collection. The metabolic cages offer 99% separation efficiency of urine and feces. Assuring maximum purity of samples, the feeder is isolated from the collection compartments of feces and urine, which excludes contamination with feed. Water consumption was controlled at standard volume (200 ml). Urine produced in 24 h was gravimetrically measured, and samples were immediately frozen at −20 °C for further analysis. Urinary volume was obtained at the end of first 7 weeks of physical training. Urinary sodium and potassium concentrations were measured in a flame photometer (CELM FC-180, Belo Horizonte/MG, Brazil) and urinary sodium and potassium excretions were calculated. Plasma and urinary osmolarities were evaluated with an osmometer (Osmomette 5004; Tech Circle, Natick, MA, USA). Blood and urine creatinine concentrations were determined by colorimetric kinetic using a kit (Bioclin, Belo Horizonte, Brazil) based on the Jaffé reaction, and used to estimate the GFR by calculating creatinine clearance. The levels of proteinuria were determined using a Lab Test kit (Lab Test, Minas Gerais, Brazil) in spectrophotometric assay following the manufacturer's instructions. For determining urinary density, a refractometer device (RTP-20 ATC, Instrutherm, São Paulo, Brazil) was used. For evaluating the free water clearance (CH_2O), the osmolar clearance was calculated with the following equation: Cosm = (urine osmolarity × total urine volume)/plasma osmolarity. CH_2O was calculated using the following equation: CH_2O = total urine volume–Cosm.

Histological evaluations

During euthanasia of the rats, the kidneys were removed and fixed in buffered formalin solution for a minimum of 72 h and embedded in paraffin. The tissues were processed through routine histological techniques to obtain 4-μm-thick paraffin sections that were then mounted on glass slides. Histological sections were stained with hematoxylin and eosin to evaluate tissue inflammatory infiltration and sclerosis of the vascular network in the glomeruli. For determining the inflammatory pattern, we used 20 random images of each rat in a 440-fold increase (total area: 1.49×10^6 μm^2), obtained with the Leica BM5000 microscope, with a digital camera (Leica DFC 300 FX, Leica Microsystems, Wetzlar, Germany) coupled with RGB module activated and associated with the Leica Application Suite image capture software. The total cells were quantified using the Leica Q-Win Plus software by automatic counting of the total cell nuclei present in each image. The differences in inflammatory processes were assessed by differences between the total number of cells in the same total area of renal tissue. Glomerulosclerosis was determined by counting the sclerotic glomeruli, using 20 random images of each rat in a 110-fold increase (total area: 5.96×10^6 μm^2) obtained as described above. The glomerulosis index was calculated using the ratio of the numbers of sclerotic glomeruli to the total glomeruli (3).

Statistical analyses

Data were tested for normality using the Kolmogorov–Smirnov test. Data that presented a normal distribution were inferred using an analysis of variance table, analyzed with Tukey's *post-hoc* test, and expressed as mean ± standard error. For the other (non-normal) data, the Kruskal–Wallis test was used followed by Dunn's *post-hoc* test. Non-normal data are expressed as median and 5% and 95% percentiles. Analyses were performed with GraphPad Prism software (version 6.0; GraphPad, San Diego, CA, USA). Differences were considered significant when P values were <0.05.

Results

BP and HR

SE and RE rats presented reduced mean arterial pressure (AP) (mmHg) and systolic AP (mmHg) compared with S rats. Similarly, PE that is performed in aquatic and land environments decreased the resting HR in SE and RE rats compared with S rats (Table I).

Evaluation of renal function

Rats that did not perform PE and those that performed PE in aquatic or land environments presented similar patterns of water intake and sodium and potassium excretions (Table I). However, both SE and RE rats showed higher urine osmolarity. The SE rats showed higher free water clearance and lower urinary density compared with S and RE rats (Table I). Moreover, SE rats presented increased weekly urine volume for 7 weeks compared with S rats. The urine volume of SE rats was also increased in relation to that of RE rats in the 1st, 5th, and 7th weeks of the experiment (Fig. 1). GFR was increased in both SE and RE rats when compared with S rats (Fig. 2a). In another measurement, the proteinuria of SE rats was decreased compared with the other groups at the 8th week of the exercise training (Fig. 2b).

Renal morphology

No cellular degenerative processes, necrotic lesions, and reparative lesions were found in any rats. Moreover, the glomerulosis index and glomerulosclerosis were reduced in SE rats when compared with the S rats (Fig. 3). In addition, no differences were found in the total number of cells between rats that performed PE and those that did not (Table I).

Table I. Cardiovascular and renal function parameters pressure in sedentary (S), running (RE), and swimming exercise (SE)-trained spontaneously hypertensive rats

	S	RE	SE
Heart rate (beats/min)	398 ± 8	312 ± 13*	307 ± 13*
Systolic arterial pressure (mmHg)	183 ± 4	145 ± 3*	145 ± 2*
Mean arterial pressure (mmHg)	155 ± 3	139 ± 3*	134 ± 3*
Body weight (g)	381 ± 5	315 ± 10	321 ± 8.5
Water intake (ml)	42.3 ± 1.5	44.7 ± 1.0	44.1 ± 3.4
Urinary sodium excretion (mEq)	56 ± 6	66 ± 6	91 ± 13
Urinary potassium excretion (mEq)	21.5 ± 2	28 ± 3	32 ± 5
Osmolarity urinary (mOsmol)	669 ± 61	1,366 ± 205*	1,630 ± 87*
Osmolarity plasma (mOsmol)	326.4 ± 30	312 ± 38	278 ± 38
Free water clearance (ml)	−85.2 ± 26	−302 ± 81	−396 ± 71*
Urinary density (g/ml)	36.4 ± 2.7	36.8 ± 2.8	13.8 ± 1.5#
Glomerulosclerosis (total number)	54.7 ± 7	39.7 ± 7.4	23.8 ± 7.7*
Glomerulosis index	0.6 ± 0.06	0.5 ± 0.08	0.2 ± 0.07*
Number of inflammatory cells	389 ± 23.8	420 ± 28.3	407 ± 10.8

Values are expressed as mean ± SEM. Statistically significant differences in one-way ANOVA.
*$P < 0.05$ vs. group S and $^{\#}P < 0.0001$ vs. groups RE and S

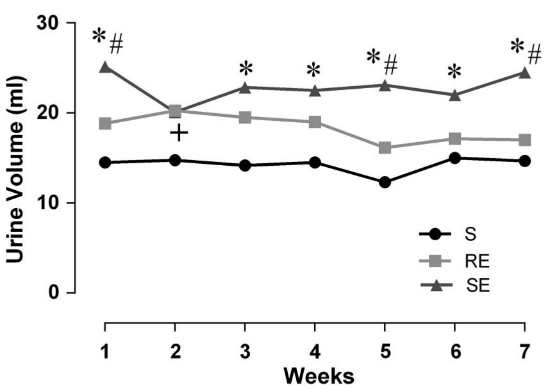

Fig. 1. Urine volume (ml) for 7 weeks of sedentary (S), running (RE), and swimming exercise (SE)-trained spontaneously hypertensive rats. *$P < 0.001$ in comparison with S group; $^{\#}P < 0.01$ in comparison with RE group; $^{+}P < 0.01$ in comparison with S group

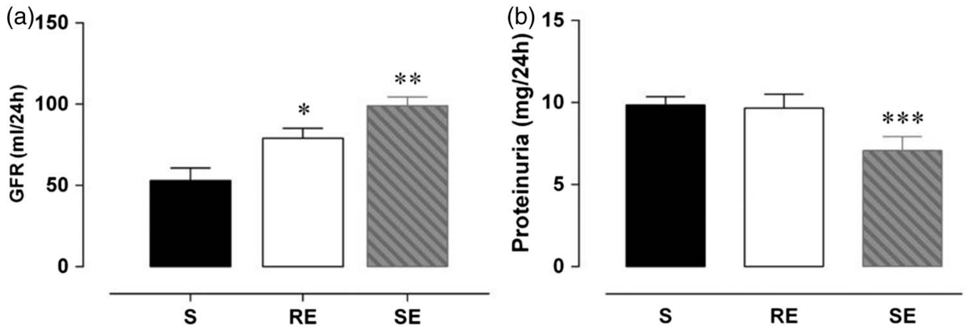

Fig. 2. (a) Glomerular filtration rate (GFR) and (b) levels of proteinuria (mg/24 h) after training in running (RE), swimming exercise (SE), and group sedentary (S) of SHR. Data are mean ± SEM. *$P < 0.01$ in comparison with S group; **$P < 0.001$ in comparison with RE group; ***$P < 0.04$ in comparison with RE and S groups

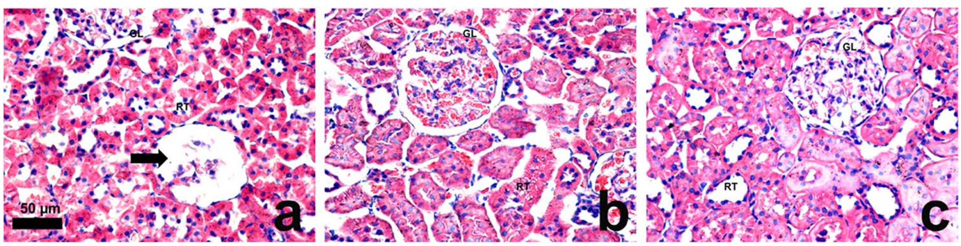

Fig. 3. Representative photomicrography's of kidney of sedentary (S), running (RE), and swimming exercise (SE)-trained spontaneously hypertensive rats. (a) Group S. Note the presence of sclerotic glomeruli (arrow) and normal tubules. (b) Groups RE and (c) SE. Note the normal histopathological picture of hematoxylin and eosin staining. GL: glomeruli; RT: renal tubule. Barr = 50 μm

Discussion

Aerobic exercises, such as swimming, running, and walking, are used as non-pharmacological therapy in the treatment of hypertension (5, 14, 37). However, the effects of aquatic exercise are still not well understood. Our data show that SHRs trained in the aquatic environment produced more urine with higher free water clearance and lower urinary density. This is the first study to show that PE performed in water induces the lowest level of proteinuria and glomerulosis compared with training carried out in land.

Resting HR is considered to be an excellent marker of physical training in both humans and rats. This study demonstrated a decrease in HR and resting BP for both rats trained in water and for those trained on land. This result indicates that both physical training protocols used in the study were effective in causing changes in the cardiovascular system. Endlich et al. (8) trained SHRs in both aquatic and land environments. Training in both environments was efficient in reducing HR and BP.

In classic studies, it has been shown that immersion induces increased free water clearance (8, 11) probably owing to the inhibition of vasopressin release (15, 31), and that the primary mechanism of vasopressin release control is the mechanoreceptors (arterial baroreceptors and cardiac receptors) (15, 31). Totou et al. (39) showed that exercise performed in an aquatic environment induces a greater sensitivity of the cardiopulmonary reflex; therefore, rats trained in water had greater activation of the cardiorenal axis, inducing greater diuresis. Endlich et al. (8) compared the effect of the two training media on the ANP production of SHRs, and found higher levels of ANP in the group that performed aquatic exercise. In this study, no differences in urine sodium levels were observed; however, urine osmolarity was higher for the trained groups, indicating a better capacity for solute elimination. A study conducted by Ito et al. (21) showed that PE increased the expression of nitric oxide (NO) in the renal medulla of SHRs, which contributed to the inhibition of solute absorption and increase of water permeability of the collecting tubes (14, 16, 29). In this study, the group trained in the aquatic environment produced more urine during the training weeks, which may indicate that the training medium may lead to different alterations in the control of renal tubular reabsorption.

Classic studies indicate that, in arterial hypertension, renal ischemia secondary to functional vasoconstriction of afferent arterioles (initiated by an increase in renal vascular resistance), decreased renal blood flow, and increased filtration fraction, generates progressive damage to glomerular tuft capillaries, leading to collapse of the blood filtration network and consequently the sclerosis of these glomeruli. One of the first signs of glomerulosclerosis is elevated proteinuria. The evolution of glomerulosclerosis then leads to nephrotic syndrome with impairment of all renal functions (40).

In animal models with chronic renal failure, diabetic nephropathy (22, 24, 40), and also in SHR and fructose-fed rats (40, 43), PE produces renal-protective effects, decreasing plasma creatinine and proteinuria and improving glomerulosclerosis. In this study, we found that PE, regardless of the medium, improves the GFR. Interestingly, the proteinuria and glomerulosis levels were lower only in the group trained in aquatic environment. Barbosa Neto et al. (3) showed attenuation of glomerulosis in SHR trained in an aquatic environment, and attributed this improvement to the decrease of renal sympathetic activity in the trained rats.

Possibly, the aquatic environment contributes more than the land environment to the decrease of sympathetic activity, owing to the chronic stimulation of cardiopulmonary receptors. Studies in the literature have shown that chronic loading of cardiopulmonary receptors due to volume expansion or increasing extracellular volume modulates sympathetic and baroreflex activities (17, 38). The limitation of this study is that we did not measure renal sympathetic activity, future studies will be necessary to elucidate the possible sympathetic renal differences in training types. Data in the literature (28) have shown that renal denervation in dogs completely abolished diuretic and natriuretic responses to water immersion, whereas hemodynamic responses in these animals remained equal to those in intact dogs. It is therefore likely that renal sympathetic nerve activity (RSNA) plays a major role in determining natriuresis during water immersion. This conclusion supports the hypothesis that a reflex reduction of RSNA originating in the cardiopulmonary mechanoreceptors (cardiac–renal neural reflex) may be responsible, at least in part, for the diuresis and natriuresis that occur during water training (20).

During exercise, the cardiopulmonary reflex activation also contributes to the modulation of the sympathetic activity. When exercising on a cycle ergometer, the sympathetic nervous activity of the skeletal muscles is decreased when the cardiopulmonary reflex is activated through the increase of the rotations per minute (23). The changes produced by PE in central blood volume stimulate the cardiopulmonary reflex, which modulates the BP response during exercise, as well as the operating range of the baroreflex (32–34, 41).

The better responses observed in swim exercise may be related to the immersion effects, such as suppression of aldosterone secretion, alterations in intrarenal blood flow distribution, decrease in sympathetic nervous system activity, and alterations in the endogenous release of renal prostaglandins (10). We believe that long-term exercise in water can induce the responses citied above, and it may contribute more to reducing renal ischemia induced secondarily by hypertension than RE.

Data suggest that the upregulation of renal NO by exercise may contribute, at least in part, to the antihypertensive and renal-protective effects in SHR (21). Previous studies have shown positive correlation between water exercise and increase in cerebral flow, these studies illustrate the potential for enhanced shear-stress-mediated vascular adaptation by exercising in water, so it is possible that aquatic exercise induces higher NO production in different tissues (4).

The mechanism by which exercise training alters reflex renal sympathoinhibition, diuresis, and natriuresis in response to acute volume expansion is not fully understood. It has been reported that acute volume expansion produces an increase in NO in micro-dialysate from the paraventricular nucleus (26). Furthermore, inhibition of NO synthase within the paraventricular nucleus causes a blunting of renal sympathoinhibitory as well as renal excretory responses to acute volume expansion (26). Zheng et al. (44) showed that exercise improves endogenous NO mechanisms within the paraventricular nucleus.

Both types of exercise training maintained the GFR, but only swim exercise was able to moderate glomerulosclerosis and proteinuria. The evolution of the renal insufficiency begins with a decrease in the total number of functional nephrons and an increase in protein load (35). Analyzing the evolution of the disease, the RE was able to maintain the GFR, which is the final step in the progression of renal failure, so the swimming training is more effective in preventing renal dysfunction.

We conclude that physical training alters the renal tubular reabsorption and improves the GFR in SHR; however, only swimming training leads to better profile of the proteinuria and glomerulosclerosis.

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REFERENCES

1. Almeida JA, Petriz Bde A, da Costa Gomes CP, Pereira RW, Franco OL: Assessment of maximal lactate steady state during treadmill exercise in SHR. BMC Res. Notes 30, 661 (2012)
2. Arborelius M Jr, Ballidin UI, Lilja B, Lundgren CE: Hemodynamic changes in man during immersion with the head above water. Aerosp. Med. 43, 592–598 (1972)
3. Barbosa Neto O, Abate DT, Marocolo Junior M, Mota GR, Orsatti FL, Rossi e Silva RC, Reis MA, da Silva VJ: Exercise training improves cardiovascular autonomic activity and attenuates renal damage in spontaneously hypertensive rats. J. Sports Sci. Med. 12, 52–59 (2013)
4. Carter HH, Spence AL, Pugh CJ, Ainslie P, Naylor LH, Green DJ: Cardiovascular responses to water immersion in humans: impact on cerebral perfusion. Am. J. Physiol. Regul. Integr. Comp. Physiol. 306, 636–640 (2014)
5. Cider A, Svealv BG, Tang MS, Schaufelberger M, Andersson B: Immersion in warm water induces improvement in cardiac function in patients with chronic heart failure. Eur. J. Heart Fail. 8, 308–313 (2006)

6. Contarteze RV, Manchado Fde B, Gobatto CA, De Mello MA: Stress biomarkers in rats submitted to swimming and treadmill running exercises. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 151(3), 415–422 (2008)
7. Cornelissen VA, Fagard RH: Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension 46, 667–675 (2005)
8. Endlich PW, Firmes LB, Goncalves WL, Gouvea SA, Moyses MR, Bissoli NS, Reis AM, Abreu GR: Involvement of the atrial natriuretic peptide in the reduction of arterial pressure induced by swimming but not by running training in hypertensive rats. Peptides 32, 1706–1712 (2011)
9. Epstein M: Cardiovascular and renal effects of head-out water immersion in man: application of the model in the assessment of volume homeostasis. Circ. Res. 39, 619–628 (1976)
10. Epstein M: Renal effects of head-out water immersion in man: implications for an understanding of volume homeostasis. Physiol. Rev. 58, 529–581 (1978)
11. Epstein M: Renal effects of head-out water immersion in humans: a 15-year update. Physiol. Rev. 72, 563–621 (1992)
12. Fabri T, Machado K, Rezende R, Merces L, Vieira M, Campagnole-Santos M, Rocha-Vieira E, Becker LK: Aquatic and land exercise training affects renal function in rats under isosmotic volume expansion. J. Exerc. Physiol. Online 13, 42–51 (2010)
13. Flaim SF, Minteer WJ, Clark DP, Zelis R: Cardiovascular response to acute aquatic and treadmill exercise in the untrained rat. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 46, 302–308 (1979)
14. Floras JS, Notarius CF, Harvey PJ: Exercise training – not a class effect: blood pressure more buoyant after swimming than walking. J. Hypertens. 24, 269–272 (2006)
15. Gabrielsen A, Warberg J, Christensen NJ, Bie P, Stadeager C, Pump B, Norsk P: Arterial pulse pressure and vasopressin release during graded water immersion in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278, R1583–R1588 (2000)
16. Garvin JL, Herrera M, Ortiz PA: Regulation of renal NaCl transport by nitric oxide, endothelin, and ATP: clinical implications. Annu. Rev. Physiol. 73, 359–376 (2011)
17. Gauer OH, Henry JP: Neurohormonal control of plasma volume. Int. Rev. Physiol. 9, 145–190 (1976)
18. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N. Engl. J. Med. 351, 1296–1305 (2004)
19. Gomes SG, Silva LG, Santos TM, Totou NL, Souza PM, Pinto KMC, Coelho DB, Becker LK: Elderly hypertensive subjects have a better profile of cardiovascular and renal responses during water-based exercise. J. Exerc. Physiol. Online 19, 21–31 (2016)
20. Hajduczok G, Miki K, Hong SK, Claybaugh JR, Krasney JA: Role of cardiac nerves in response to head-out water immersion in conscious dogs. Am. J. Physiol. 253, 242–253 (1987)
21. Ito D, Ito O, Cao P, Mori N, Suda C, Muroya Y, Takashima K, Ito S, Kohzuki M: Effects of exercise training on nitric oxide synthase in the kidney of spontaneously hypertensive rats. Clin. Exp. Pharmacol. Physiol. 40, 74–82 (2013)
22. Kanazawa M, Kawamura T, Li L, Sasaki Y, Matsumoto K, Kataoka H, Ito O, Minami N, Sato T, Ootaka T, Kohzuki M: Combination of exercise and enalapril enhances renoprotective and peripheral effects in rats with renal ablation. Am. J. Hypertens. 19, 80–86 (2006)
23. Katayama K, Ishida K, Saito M, Koike T, Hirasawa A, Ogoh S: Enhanced muscle pump during mild dynamic leg exercise inhibits sympathetic vasomotor outflow. Physiol. Rep. 2, e12070 (2014)
24. Kohzuki M, Kamimoto M, Wu XM, Xu HL, Kawamura T, Mori N, Nagasaka M, Kurosawa H, Minami N, Kanazawa M, Saito T, Yoshida K: Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. J. Hypertens. 19, 1877–1882 (2001)
25. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am. J. Kidney Dis. 32, 853–906 (1998)
26. Li YF, Mayhan WG, Patel KP: Role of the paraventricular nucleus in renal excretory responses to acute volume expansion: role of nitric oxide. Am. J. Physiol. Heart Circ. Physiol. 285, H1738–H1746 (2003)
27. McCullough PA, Franklin BA, Leifer E, Fonarow GC: Impact of reduced kidney function on cardiopulmonary fitness in patients with systolic heart failure. Am. J. Nephrol. 32, 226–233 (2010)
28. Miki K, Hayashida Y, Shiraki K: Role of cardiac-renal neural reflex in regulating sodium excretion during water immersion in conscious dogs. J. Physiol. 545, 305–312 (2002)

29. Mount PF, Power DA: Nitric oxide in the kidney: functions and regulation of synthesis. Acta Physiol. (Oxf.) 187, 433–446 (2006)
30. Norsk P, Bonde-Petersen F, Christensen NJ: Catecholamines, circulation, and the kidney during water immersion in humans. J. Appl. Physiol. 69, 479–484 (1990)
31. Norsk P, Epstein M: Effects of water immersion on arginine vasopressin release in humans. J. Appl. Physiol. (1985) 64, 1–10 (1988)
32. Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S, O-Yurvati A, Raven PB: Effects of changes in central blood volume on carotid-vasomotor baroreflex sensitivity at rest and during exercise. J. Appl. Physiol. (1985) 101, 68–75 (2006)
33. Ogoh S, Fisher JP, Fadel PJ, Raven PB: Increases in central blood volume modulate carotid baroreflex resetting during dynamic exercise in humans. J. Physiol. 581, 405–418 (2007)
34. Ono H, Ono Y, Takanohashi A, Matsuoka H, Frohlich ED: Apoptosis and glomerular injury after prolonged nitric oxide synthase inhibition in spontaneously hypertensive rats. Hypertension 38, 1300–1306 (2001)
35. Pilis W, Zarzeczny R, Langfort J, Kaciuba-Uscilko H, Nazar K, Wojtyna J: Anaerobic threshold in rats. Comp. Biochem. Physiol. Comp. Physiol. 106, 285–289 (1993)
36. Ruggenenti P, Schieppati A, Remuzzi G: Progression, remission, regression of chronic renal diseases. Lancet 357, 1601–1608 (2001)
37. Tanaka H, Bassett DR Jr, Howley ET, Thompson DL, Ashraf M, Rawson FL: Swimming training lowers the resting blood pressure in individuals with hypertension. J. Hypertens. 15, 651–657 (1997)
38. Thorén P: Role of cardiac vagal C-fibers in cardiovascular control. Rev. Physiol. Biochem. Pharmacol. 86, 1–94 (1979)
39. Totou NL, Sá RWM, Alzamora AC, Cardoso LM, Becker LK: Cardiopulmonary reflex and blood pressure response after swimming and treadmill exercise in hypertensive rats. J. Exerc. Physiol. Online 18, 86–95 (2015)
40. Tufescu A, Kanazawa M, Ishida A, Lu H, Sasaki Y, Ootaka T, Sato T, Kohzuki M: Combination of exercise and losartan enhances renoprotective and peripheral effects in spontaneously type 2 diabetes mellitus rats with nephropathy. J. Hypertens. 26, 312–321 (2008)
41. Volianitis S, Yoshiga CC, Vogelsang T, Secher NH: Arterial blood pressure and carotid baroreflex function during arm and combined arm and leg exercise in humans. Acta Physiol. Scand. 181, 289–295 (2004)
42. Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS: Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003-2004. Arch. Intern. Med. 167, 2431–2436 (2007)
43. Yoshida K, Kawamura T, Xu HL, Ji L, Mori N, Kohzuki M: Effects of exercise training on glomerular structure in fructose-fed spontaneously hypertensive rats. Hypertens. Res. 26, 907–914 (2003)
44. Zheng H, Li YF, Cornish KG, Zucker IH, Patel KP: Exercise training improves endogenous nitric oxide mechanisms within the paraventricular nucleus in rats with heart failure. Am. J. Physiol. Heart Circ. Physiol. 288, 2332–2341 (2005)
45. Zucker IH, Patel KP, Schultz HD, Li YF, Wang W, Pliquett RU: Exercise training and sympathetic regulation in experimental heart failure. Exerc. Sport Sci. Rev. 32, 107–111 (2004)