MMSL
Military Medical
Science Letters

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2016, vol. 85(4), p. 139-146
ISSN 0372-7025
DOI: 10.31482/mmsl.2016.026

REVIEW ARTICLE

IMPACT OF EXTREME PHYSICAL EXERCISE ON HUMAN BODY

Martin Jakl [1,2] ✉, Pavel Skorepa [1,3], Jan M. Horacek [1,4]

[1] Department of Military Internal Medicine and Military Hygiene, Faculty of Military Health Sciences, University of Defence, Hradec Králové
[2] 1st Department of Internal Medicine - Cardioangiology, University Hospital Hradec Kralove, Czech Republic
[3] 3rd Department of Internal Medicine - Metabolic Care and Gerontology, University Hospital Hradec Kralove, Czech Republic
[4] 4th Department of Medicine and Haematology, University Hospital Hradec Kralove, Czech Republic

Received 29th August 2016.
Revised 12th December 2016.
Published 16th December 2016.

Summary

Extreme physical exercise is potentially harmful or even lethal activity. It is associated with several compensatory mechanisms focused on increasing functional capacity. Hormonal and metabolic pathways rearrange to maintain glucose supply in working tissue. Cardiovascular system substantially increases cardiac output and redistributes blood flow in working muscles. Respiratory system increases tidal volume and respiratory rate. Immune system and other systems are also affected.

If capacity of these mechanisms is exceeded, organism can be severely damaged. Frequently observed disturbances include hypoglycemia, mineral level disorders, bronchoconstriction, immune system impairment etc. More severe disturbances include arrhythmias, myocardial stunning, hypoxemia, rhabdomyolysis and many others.

Early diagnosis and treatment of these disturbances is essential for minimizing the health impairment. Unfortunately, in military settings are diagnostic and therapeutic options often limited. Moreover, physiological or benign processes can mimic life threatening conditions. Without complex understanding of participating pathophysiological mechanisms an interpretation of clinical findings might be confusing and treatment inefficient or even deleterious.

Key words: physical exercise; exhaustion; metabolism; cardiovasular system; respiratory system

✉ University of Defence, Faculty of Military Health Sciences, 1st Department of Military Internal Medicine and Military Hygiene, Třebešská 1575, 500 01 Hradec Králové, Czech Republic.
jaklm@seznam.cz
☎ +420 607 514 662
+420 495 832 006

INTRODUCTION

Physical exercise is unavoidable part of life. If adequate, it is generally considered beneficial, as it reduces burden of lifestyle disease [1-4], improves physical capacity and increases overall quality of life [5, 6]. On the other side, excessive physical exercise can be harmful and even lethal. The military personnel are

more often exposed to possibly harmful extreme physical exercise. Despite physical training and equipment, cases of physical overload are not rare. In military setting, diagnostic and therapeutic options are often limited. Without complex understanding of participating pathophysiological mechanisms an interpretation of clinical findings might be confusing and treatment inefficient or even deleterious. Unfortunately, evidence of pathophysiological mechanisms involved in harmful effects of exhaustion is scarce.

METABOLIC AND ENDOCRINE CHANGES

There are documented many metabolic, endocrine and immune changes during physical exercise [7, 8]. The spectrum of changes and the organism response depends both on individual training and type of physical stress [9, 10]. It is also know that there are gender differences. For example, there is a higher carbohydrate oxidation in men when compared to women [11]. The autonomic nervous system plays the main role in these adaptive changes by increasing the production of adrenaline, noradrenaline and cortisol. These hormones influence the metabolic changes leading to a boosting in energy supply, and are of extreme importance in maintaining an adequate glucose metabolism during strenuous exercise.

In healthy but poorly trained individuals, glucose reserves are rapidly consumed by above-mentioned contraregulatory hormones with subsequent hypoglycemia. For example, plasma level of adrenaline is higher in the hypoglycemic subjects during exhaustive exercise (probably as a stress response). However, even in well-trained individuals, the hypoglycemia is common [12]. Remarkably, hypoglycemia may persist several hours after exercise. Main reason for persistent hypoglycemia is depletion of glycogen stored in liver and muscles after prolonged exercise [13]. Moreover, prolonged exhaustive exercise with hypoglycemia elicits a decrease in brain glycogen due to an increase in brain monoamines (i.e. noradrenaline and 5-hydroxytryptamine), which contributes for the central nervous system fatigue [14]. Both mechanisms are expected to be important sources of fatigue during the exercise. Hypoglycemia is preventable by adequate pre-exercise feeding with carbohydrates, but it can be induced by a prior carbohydrate meal with high glycemic index. Intake of glucose (about 60 g per hour) during higher intensity training also prevents hypoglycemia, but seems did not alter perceived exertion or delay exhaustion [12, 15].

Muscular exercise is also associated with an intracellular accumulation of lactate, which may eventually result in acidification of the organism. Beneficial effect of acidosis is facilitated release of blood oxygen in tissues. Despite this mechanism can bridge the oxygen demand during exhaustive activity, it can also result in oxygen deficit [16]. Hypoxia is considered to be a contributor of fatigue in muscles.

A marked increase in the plasma fatty acid level, which may occur after liver glycogen depletion ("crisis of 30th kilometer") or during intermittent exercise when the rate of fatty acid oxidation do not match the mobilization of fatty acids, could be also indirectly involved in fatigue [17].

Exercise is associated with transmembrane movements of minerals, water and an accompanying cell swelling. The Na,K-ATPase is the major translator of metabolic energy in the form of ATP to electrical and chemical gradients for the two most common ions in the body [18]. The Na,K-ATPase catalyzes the efflux of three Na + and the influx of two K + ions per molecule of ATP hydrolyzed, thereby maintaining the steep transmembrane concentration gradients for Na + and K + that play a vital role in many biological processes.

Regulation of the Na,K- ATPase is therefore important for muscle functioning. It is generally accepted that the Na,K-ATPase is up regulated during muscle activity by a multifactorial process that includes sensitivity to hormones and elevated intracellular Na + concentrations [19]. It is well documented, that prolong exercise in athletes or military personnel often come into exertional hyponatremia [20]. Main source of hyponatremia is not only excessive sweating and salt-free fluid intake. It is complex, idiosyncratic, and unrelated to body weight measurement, thirst, and sodium consumed. Cerebral edema due to severe dilutional hyponatremia can cause rare sport-related death in young healthy athlete. Using emergent infusion of intravenous hypertonic saline to reverse cerebral edema is, on the basis of validated clinical paradigm, the only live saving option. Avoiding overhydration seems to be the most important means for preventing hyponatremia, otherwise sodium intake in supplements has minimal responsibility for this state [21]. There is no evidence

that drinking to stay ahead of thirst, as a popular mantra, during exercise produces a more beneficial outcome than using thirst to drive fluid intake. Proper hydration is important, but perpetuation of the myth that one needs to drink much more beyond the dictates of thirst can be deadly [22].

The rise of plasma K^+ concentration during high intensity exercise is due to an initially rapid loss of K+ from the exercising muscle to the circulation. The K+ loss is primarily governed by the balance between K^+ efflux rate from the muscle cells and the reuptake rate. Increase in plasma K+ level rise faster with increasing exercise. Moderate to severe hyperkalemia is detectable at peak exercise, but resolves after few minutes of rest [23]. The interstitial K + concentration is important for cell excitability and, thereby, for development of fatigue. It is also expected to play a role in regulation of muscle perfusion as well as cardiac and ventilator adjustments via muscle metaboreflexes [24]. It is suggested that prolong training is consistent with improved plasma and skeletal muscle K+ regulation [25]. As a vital factor for the prevention of dangerous fluctuations in homeostasis appears adequate nutrition before and during physical load [13].

CARDIOVASCULAR RESPONSE AND IMPAIRMENT

Intense exercise requires increased performance of cardiovascular system. Cardiac output increases four times in untrained and up to eight times in well-trained individuals [26]. This is due to both increased myocardial contractility and dilatation of muscular arteries. Exact mechanisms differ in static and dynamic exercise, as the vasodilation is more pronounced in dynamic exercise [27].

During exercise, low oxygen and high carbon dioxide tension are considered to be significant vasodilatory mechanisms [28]. Low oxygen tension in muscles also results in increased release of endogenous vasodilatory substances such as lactate, adenosine, phosphate, K^+ and H^+ ions [29-31], but of all these mechanisms seems to be of minor to moderate significance. However, endothelial nitric oxide and prostanoid production seem to be most potent local vasodilators in settings of physical exercise [32, 33]. Nitric oxide is also key mediator of hypoxia-induced vasodilation [34].

The local vasodilatation is counterweighted by systemic sympathetic activation resulting in profound vasoconstriction in less laden parts of body. This vasoconstriction is usually capable to maintain the blood pressure even in extensive muscular vasodilatation. However, in cases of concomitant systemic inflammatory reaction and subsequent excessive vasodilatation, the circulatory system becomes incapable to maintain blood pressure. Following tissue hypoperfusion results in excessive production of local vasoactive substances and finally distributive shock develops.

Another way of increasing of cardiac output is mediated by increase in cardiac inotropy and chronotropy. This is mediated mainly by endogenous adrenaline, noradrenaline and dopamine via β-1 adrenergic receptor activation. It is a G-protein coupled receptor associated with the Gs-heterotrimeric G-protein. Activation of β-1 adrenergic receptor renders adenylate cyclase activated, resulting in increase of cAMP and following excess in intra-cellular Ca^{2+} concentration. Myocardial inotropy is also augmented by cortisol. Glucocorticoids are traditionally considered to have catabolic effect. However, moderate and transient exposure also increases intracellular Ca^{2+} concentration and thus improves muscular performance [35].

Calcium ions enhance actin-myosin interaction and thus the intensity of myocyte contraction. However, high cytoplasmatic or sarcoplasmatic Ca^{2+} concentrations also enhance Na^+/ Ca^{2+}ion antiport. Resulting ion transport can activate Na^+ channels resulting in so called triggered myocardial activity [36]. Clinical presentation ranges from ventricular extrasystolia to polymorphic ventricular tachycardia, which may induce syncope or sudden death, even in otherwise healthy persons. In last years, several genetic mutations leading to catecholaminergic polymorphic ventricular tachycardia were recognized. Patients with this disease are highly prone to exercise-related death [37].

Influx of Ca^{2+} ions is also trigger of apoptosis [38]. During extreme exercise, high plasmatic levels of cardiac troponins suggest myocardial apoptosis or necrosis due to mechanic overload [39, 40]. This myocardial damage can be depicted using cardiac magnetic resonance by T2 weighted imaging and late gadolinium enhancement. These changes can be misinterpreted as first type myocardial infarction.

Excessive catecholamine activation in prone subjects can also lead in myocardial stunning [41]. As the density of myocardial β-1 adrenergic receptors rises from

cardiac basis towards apex, the stunning usually manifests as "apical ballooning" of Tako-tsubo cardiomyopathy and ECG changes similar to transmural myocardial infarction [42]. Despite its temporary nature, the stunning often results in acute heart failure or cardiogenic shock [43].

During intense exercise, thin-walled structures (eg. right ventricle and left atrium) have to withstand a disproportionate hemodynamic load [44] resulting in transient exercise-induced dysfunction and chronic remodeling with excessive fibrous tissue accumulation [45, 46]. That results in increased risk of both ventricular arrhythmia and atrial fibrillation [47, 48] and contribute to increased risk of sudden death in endurance athletes in comparison with low-intensity runners [49, 50]

RESPIRATORY SYSTEM DISORDERS

Contrary to other body systems, respiratory system has only very limited capacity to adapt to increased demands, as widely described in patients in chronic hypoxia or after lung resection [51, 52]. Disorders of respiratory system are often limiting, especially due to exercise-induced bronchoconstriction (EIB) that also occurs in 20-50 % of athletes [53-55]. Possible etiology of EIB is anticipated to be mechanic or cold irritation [56, 57], but usual triggers of bronchoconstriction, like allergens, infection etc. may also be responsible. Notably, increased ration of eosinophils in sputum is also detectable in athletes [55].

Diagnosis of EIB is usually based on clinical manifestation and spirometry findings. A fall in the FEV_1 of 10% from pre-exercise value confirms airway obstruction. The intensity of the bronchoconstriction typically reaches its peak at 5 to 10 minutes after an exhaustive exercise and usually ceases about 60 minutes thereafter [58]. A distinctive clinical element of EIB is the so-called refractory period, visible when exercise is repeated within 1 to 3 hours with less of an EIB response [59].

EIB usually responds well to β-2 agonists. Increasing of air humidity and temperature is also beneficial. Preventive administration of β-2 agonists is recommended, especially during exercise at low and subfreezing ambient temperatures [60]. Unfortunately, several lethal cases were recorded despite prevention and treatment [61].

Other cause of hypoxemia and respiratory distress involve upper airway obstruction [53], that is usually due to vocal cord dysfunction. Vocal cord dysfunction has been reported in 5-15 % of patients [62]. Hypoxemia also may be a result of exercise-induced recruitment of intrapulmonary arteriovenous shunt pathways [63, 64] or respiratory muscle exhaustion.

MUSCULOSKELETAL INJURY

During intense exercise, muscles are capable of outstanding metabolic and vascular adaptation, as described in previous chapters. However, extreme exercise can result in rhabdomyolysis. In both civic and military settings, exercise is a leading cause of rhabdomyolysis, especially if accompanied by hyperthermia or exhaustion. However, exertional rhabdomyolysis is associated with lower rates of complications than other causes of rhabdomyolysis [65].

Rhabdomyolysis is usually defined by serum creatine kinase of at least 10 times the upper limit of normal followed by a rapid decrease of the creatine kinase level to (near) normal values [66]. Clinical features are myalgia, weakness and pigmenturia. Acute renal failure due to acute tubular necrosis as a result of either direct toxicity and mechanical obstruction by myoglobin is the most common complication of rhabdomyolysis [67]. Risk of acute renal failure is imminent, if creatine kinase level reaches 250-330 μkat/l [68]. Predictive value of serum myoglobin is low, due to its unpredictable metabolism. Treatment of rhabdomyolysis requires intense hydration, treatment of possible hyperkalemia, hyperphosphatemia, hypocalcemia and urine alkalization to pH>6,5 [69]. In developed renal failure temporary hemodialysis should not be delayed. If rhabdomyolysis considered possible, nonsteroidal anti-inflammatory drugs should be avoided to minimize the risk of acute renal failure. In exertional rhabdomyolysis survivors the recurrence is low [65].

Vigorous exertion is also harmful for joints. While single episode of excessive exercise causes common injuries and soft tissue inflammation, repeated physical overload results in cumulative damage of cartilage [70]. Subsequent osteoarthrosis is one of main sources of professional disability in military personnel. Various forms of exercise seem to be diversely harmful. The risk of osteoarthrosis increases with intensity [71, 72] or duration of ex-

ercise [73, 74]. Exercise associated with repeated accelerations (soccer etc.) seems to be more harmful than sustained exercise or usual military training [70, 75].

INFLAMMATORY RESPONSE

Exercise induces changes in the immune system depend on type, intensity, and duration of the activity. In general, exercise alters the distribution, trafficking, and functional capabilities of different types of immune cell, as well as local and systemic levels of various soluble mediators (interleukine (IL)-2, IL-4, IL-6, CRP). For illus-tration prolonged strenuous exercise is followed by a temporary functional immune impairment. Low numbers of $CD4^+$T helper (Th) and $CD8^+$ T cytotoxic (Tc) cells are found in the circulation [76], while overall leucocyte count can be remarkably increased [77]. Also reactive oxygen species are generated in skeletal muscles during activity which may lead to chemical modification of muscle proteins of importance for muscle function [78]. Many factors (mainly hormonal, nutritional, and inflammatory interactions) are probably responsible in increase odds for infection episodes during or following heavy training [79]. However, in well trained individuals and later after activity, there are compensatory and beneficial effects in immunity response [80].

CONCLUSION

Vigorous and exhausting physical activity poses risk of severe health impairment. Even if such intense physical activity cannot be avoided, most of these health impairments can be prevented or minimized by simple medical interventions. Physical activity is also associated with distinctive physiological reaction, which can mimic various diseases. Distinguishing of physiological processes from pathological conditions is of paramount importance, as delayed treatment may result in life threatening complications.

ACKNOWLEDGEMENTS

Authors are grateful to prof. Luboš Sobotka for valuable comments. The work was supported by the Ministry of Defense of the Czech Republic through a Long-term organization development plan 1011 and by Specific research project FMHS 2015 – "Parenteral nutrition"

DECLARATION OF INTEREST

Authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. W. C. Knowler; E. Barrett-Connor; S. E. Fowler; R. F. Hamman; J. M. Lachin; E. A. Walker; D. M. Nathan. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. **2002**, 346, 393-403.
2. I. M. Vuori. Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Med Sci Sports Exerc*. **2001**, 33, S551-86; discussion 609-10.
3. K. E. Powell; P. D. Thompson; C. J. Caspersen; J. S. Kendrick. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health*. **1987**, 8, 253-87.
4. Y. M. Park; X. Sui; J. Liu; H. Zhou; P. F. Kokkinos; C. J. Lavie; J. W. Hardin; S. N. Blair. The effect of cardiorespiratory fitness on age-related lipids and lipoproteins. *J Am Coll Cardiol*. **2015**, 65, 2091-100.
5. D. Mereles; N. Ehlken; S. Kreuscher; S. Ghofrani; M. M. Hoeper; M. Halank; F. J. Meyer; G. Karger; J. Buss; J. Juenger; N. Holzapfel; C. Opitz; J. Winkler; F. F. Herth; H. Wilkens; H. A. Katus; H. Olschewski; E. Grunig. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. **2006**, 114, 1482-9.
6. K. J. Reid; K. G. Baron; B. Lu; E. Naylor; L. Wolfe; P. C. Zee. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Med*. **2010**, 11, 934-40.
7. D. A. Baur; C. W. Bach; W. J. Hyder; M. J. Ormsbee. Fluid retention, muscle damage, and altered body composition at the Ultraman triathlon. *Eur J Appl Physiol*. **2016**, 116, 447-58.
8. R. J. Simpson; J. A. Bosch. Special issue on exercise immunology: current perspectives on

aging, health and extreme performance. *Brain Behav Immun*. **2014**, 39, 1-7.
9. B. Mittendorfer; J. F. Horowitz; S. Klein. Effect of gender on lipid kinetics during endurance exercise of moderate intensity in untrained subjects. *Am J Physiol Endocrinol Metab*. **2002**, 283, E58-65.
10. M. S. Hedrington; S. N. Davis. Sexual Dimorphism in Glucose and Lipid Metabolism during Fasting, Hypoglycemia, and Exercise. *Front Endocrinol (Lausanne)*. **2015**, 6, 61.
11. S. N. Davis; P. Galassetti; D. H. Wasserman; D. Tate. Effects of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. *J Clin Endocrinol Metab*. **2000**, 85, 224-30.
12. P. Felig; A. Cherif; A. Minagawa; J. Wahren. Hypoglycemia during prolonged exercise in normal men. N Engl J Med. 1982, 306, 895-900.
13. K. L. Beck; J. S. Thomson; R. J. Swift; P. R. von Hurst. Role of nutrition in performance enhancement and postexercise recovery. *Open Access J Sports Med.* **2015**, 6, 259-67.
14. T. Matsui; S. Soya; M. Okamoto; Y. Ichitani; K. Kawanaka; H. Soya. Brain glycogen decreases during prolonged exercise. *J Physiol*. **2011,** 589, 3383-93.
15. J. F. Brun; M. Dumortier; C. Fedou; J. Mercier. Exercise hypoglycemia in nondiabetic subjects. *Diabetes Metab*. **2001**, 27, 92-106.
16. J. Bangsbo; P. D. Gollnick; T. E. Graham; C. Juel; B. Kiens; M. Mizuno; B. Saltin. Anaerobic energy production and O2 deficit-debt relationship during exhaustive exercise in humans. *J Physiol*. **1990**, 422, 539-59.
17. E. A. Newsholme; E. Blomstrand; B. Ekblom. Physical and mental fatigue: metabolic mechanisms and importance of plasma amino acids. *Br Med Bull*. **1992**, 48, 477-95.
18. T. Clausen. Quantification of Na+,K+ pumps and their transport rate in skeletal muscle: functional significance. *J Gen Physiol*. **2013**, 142, 327-45.
19. H. Walas; C. Juel. Purinergic activation of rat skeletal muscle membranes increases Vmax and Na+ affinity of the Na,K-ATPase and phosphorylates phospholemman and alpha1 subunits. *Pflugers Arch*. **2012**, 463, 319-26.
20. B. Armed Forces Health Surveillance; et al. Update: Exertional hyponatremia, active component, U.S. Army, Navy, Air Force, and Marine Corps, 2000-2015. *Msmr*. **2016**, 23, 25-8.
21. M. D. Hoffman; K. J. Stuempfle. Sodium Supplementation and Exercise-Associated Hyponatremia during Prolonged Exercise. *Med Sci Sports Exerc*. **2015**, 47, 1781-7.
22. B. Aughton. Is drinking to thirst a prudent guideline to avoid hyponatremia? *Wilderness Environ Med*. **2014**, 25, 492-3.
23. N. K. Vollestad; J. Hallen; O. M. Sejersted. Effect of exercise intensity on potassium balance in muscle and blood of man. *J Physiol*. **1994**, 475, 359-68.
24. C. Juel; H. Pilegaard; J. J. Nielsen; J. Bangsbo. Interstitial K(+) in human skeletal muscle during and after dynamic graded exercise determined by microdialysis. *Am J Physiol Regul Integr Comp Physiol*. **2000**, 278, R400-6.
25. M. J. McKenna; T. A. Schmidt; M. Hargreaves; L. Cameron; S. L. Skinner; K. Kjeldsen. Sprint training increases human skeletal muscle Na(+)-K(+)-ATPase concentration and improves K+ regulation. *J Appl Physiol* (1985). **1993**, 75, 173-80.
26. B. Ekblom; L. Hermansen. Cardiac output in athletes. J Appl Physiol (1985). 1968, 25, 619-25.
27. E. Asmussen. Similarities and dissimilarities between static and dynamic exercise. *Circ Res*. **1981**, 48, I3-10.
28. H. G. Welch; F. Bonde-Petersen; T. Graham; K. Klausen; N. Secher. Effects of hyperoxia on leg blood flow and metabolism during exercise. *J Appl Physiol Respir Environ Exerc Physiol.* **1977**, 42, 385-90.
29. B. Saltin. Metabolic fundamentals in exercise. *Med Sci Sports*. **1973**, 5, 137-46.
30. J. M. Marshall. The roles of adenosine and related substances in exercise hyperaemia. *J Physiol*. **2007**, 583, 835-45.
31. H. Barcroft; T. H. Foley; R. R. McSwiney. Experiments on the liberation of phosphate from the muscles of the human forearm during vigorous exercise and on the action of sodium phosphate on forearm muscle blood vessels. *J Physiol*. **1971**, 213, 411-20.
32. W. G. Schrage; M. J. Joyner; F. A. Dinenno. Local inhibition of nitric oxide and prostaglandins independently reduces forearm exercise hyperaemia in humans. *J Physiol.* **2004**, 557, 599-611.
33. W. G. Schrage; B. W. Wilkins; C. P. Johnson; J. H. Eisenach; J. K. Limberg; N. M. Dietz; T. B. Curry; M. J. Joyner. Roles of nitric oxide synthase and cyclooxygenase in leg vasodilation and oxygen consumption during prolonged low-intensity exercise in untrained humans. *J Appl Physiol* (1985). **2010**, 109, 768-77.

34. D. P. Casey; B. D. Madery; T. B. Curry; J. H. Eisenach; B. W. Wilkins; M. J. Joyner. Nitric oxide contributes to the augmented vasodilatation during hypoxic exercise. *J Physiol*. **2010**, 588, 373-85.
35. R. A. Casuso; L. Melskens; T. Bruhn; N. H. Secher; N. B. Nordsborg. Glucocorticoids improve high-intensity exercise performance in humans. *Eur J Appl Physiol*. **2014**, 114, 419-24.
36. C. H. Luo; Y. Rudy. A dynamic model of the cardiac ventricular action potential. II. Afterdepolarizations, triggered activity, and potentiation. *Circ Res*. **1994**, 74, 1097-113.
37. N. Sumitomo. Current topics in catecholaminergic polymorphic ventricular tachycardia. *J Arrhythm*. **2016**, 32, 344-351.
38. M. P. Mattson; S. L. Chan. Calcium orchestrates apoptosis. *Nat Cell Biol*. **2003**, 5, 1041-3.
39. L. J. Klinkenberg; P. Luyten; N. van der Linden; K. Urgel; D. P. Snijders; C. Knackstedt; R. Dennert; B. L. Kietselaer; A. M. Mingels; E. P. Cardinaels; F. E. Peeters; J. D. van Suijlen; J. Ten Kate; E. Marsch; T. L. Theelen; J. C. Sluimer; K. Wouters; O. Bekers; S. C. Bekkers; L. J. van Loon; M. P. van Dieijen-Visser; S. J. Meex. Cardiac Troponin T and I Release After a 30-km Run. *Am J Cardiol*. **2016**, 118, 281-7.
40. T. Savukoski; L. Mehtala; B. Lindahl; P. Venge; K. Pettersson. Elevation of cardiac troponins measured after recreational resistance training. *Clin Biochem*. **2015**, 48, 803-6.
41. I. S. Wittstein; D. R. Thiemann; J. A. Lima; K. L. Baughman; S. P. Schulman; G. Gerstenblith; K. C. Wu; J. J. Rade; T. J. Bivalacqua; H. C. Champion. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. **2005**, 352, 539-48.
42. A. R. Lyon; E. Bossone; B. Schneider; U. Sechtem; R. Citro; S. R. Underwood; M. N. Sheppard; G. A. Figtree; G. Parodi; Y. J. Akashi; F. Ruschitzka; G. Filippatos; A. Mebazaa; E. Omerovic. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. **2016**, 18, 8-27.
43. S. W. Sharkey; V. R. Pink; J. R. Lesser; R. F. Garberich; M. S. Maron; B. J. Maron. Clinical Profile of Patients With High-Risk Tako-Tsubo Cardiomyopathy. *Am J Cardiol*. **2015**, 116, 765-72.
44. A. La Gerche; H. Heidbuchel; A. T. Burns; D. J. Mooney; A. J. Taylor; H. B. Pfluger; W. J. Inder; A. I. Macisaac; D. L. Prior. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exerc*. **2011**, 43, 974-81.
45. G. Claessen; P. Claus; S. Ghysels; P. Vermeersch; S. Dymarkowski; L. A. G. A; H. Heidbuchel. Right ventricular fatigue developing during endurance exercise: an exercise cardiac magnetic resonance study. *Med Sci Sports Exerc*. **2014**, 46, 1717-26.
46. A. J. Teske; N. H. Prakken; B. W. De Boeck; B. K. Velthuis; E. P. Martens; P. A. Doevendans; M. J. Cramer. Echocardiographic tissue deformation imaging of right ventricular systolic function in endurance athletes. *Eur Heart J*. **2009**, 30, 969-77.
47. A. Aizer; J. M. Gaziano; N. R. Cook; J. E. Manson; J. E. Buring; C. M. Albert. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol*. **2009**, 103, 1572-7.
48. A. La Gerche; G. Claessen; S. Dymarkowski; J. U. Voigt; F. De Buck; L. Vanhees; W. Droogne; J. Van Cleemput; P. Claus; H. Heidbuchel. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. *Eur Heart J*. **2015**, 36, 1998-2010.
49. F. R. van de Schoor; V. L. Aengevaeren; M. T. Hopman; D. L. Oxborough; K. P. George; P. D. Thompson; T. M. Eijsvogels. Myocardial Fibrosis in Athletes. *Mayo Clin Proc*. **2016,**
50. D. C. Lee; R. R. Pate; C. J. Lavie; X. Sui; T. S. Church; S. N. Blair. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. **2014**, 64, 472-81.
51. J. B. West. High-altitude medicine. *Am J Respir Crit Care Med*. **2012**, 186, 1229-37.
52. P. D. Wagner. Why doesn't exercise grow the lungs when other factors do? *Exerc Sport Sci Rev*. **2005**, 33, 3-8.
53. K. W. Rundell; B. A. Spiering. Inspiratory stridor in elite athletes. *Chest*. **2003**, 123, 468-74.
54. J. M. Weiler; S. Bonini; R. Coifman; T. Craig; L. Delgado; M. Capao-Filipe; D. Passali; C. Randolph; W. Storms. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. *J Allergy Clin Immunol*. **2007**, 119, 1349-58.
55. I. J. Helenius; P. Rytila; T. Metso; T. Haahtela; P. Venge; H. O. Tikkanen. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy*. **1998**, 53, 346-52.
56. T. Stensrud; S. Berntsen; K. H. Carlsen. Exercise capacity and exercise-induced

bronchoconstriction (EIB) in a cold environment. *Respir Med.* **2007**, 101, 1529-36.
57. S. D. Anderson; P. Kippelen. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol.* **2008**, 122, 225-35; quiz 236-7.
58. K. Holzer; J. A. Douglass. Exercise induced bronchoconstriction in elite athletes: measuring the fall. *Thorax*. **2006**, 61, 94-6.
59. J. M. Weiler. Exercise-induced asthma: a practical guide to definitions, diagnosis, prevalence, and treatment. *Allergy Asthma Proc*. **1996**, 17, 315-25.
60. E. Millqvist; U. Bengtsson; O. Lowhagen. Combining a beta2-agonist with a face mask to prevent exercise-induced bronchoconstriction. *Allergy*. **2000**, 55, 672-5.
61. J. M. Becker; J. Rogers; G. Rossini; H. Mirchandani; G. E. D'Alonzo, Jr. Asthma deaths during sports: report of a 7-year experience. *J Allergy Clin Immunol*. **2004**, 113, 264-7.
62. E. W. Nielsen; J. H. Hull; V. Backer. High prevalence of exercise-induced laryngeal obstruction in athletes. *Med Sci Sports Exerc*. **2013**, 45, 2030-5.
63. M. W. Eldridge; J. A. Dempsey; H. C. Haverkamp; A. T. Lovering; J. S. Hokanson. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. *J Appl Physiol* (1985). **2004**, 97, 797-805.
64. M. K. Stickland; R. C. Welsh; M. J. Haykowsky; S. R. Petersen; W. D. Anderson; D. A. Taylor; M. Bouffard; R. L. Jones. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J Physiol*. **2004**, 561, 321-9.
65. J. P. Alpers; L. K. Jones, Jr. Natural history of exertional rhabdomyolysis: a population-based analysis. *Muscle Nerve*. **2010**, 42, 487-91.
66. R. Zutt; A. J. van der Kooi; G. E. Linthorst; R. J. Wanders; M. de Visser. Rhabdomyolysis: review of the literature. *Neuromuscul Disord*. **2014**, 24, 651-9.
67. S. Holt; K. Moore. Pathogenesis of renal failure in rhabdomyolysis: the role of myoglobin. *Exp Nephrol*. **2000**, 8, 72-6.
68. D. R. Patel; R. Gyamfi; A. Torres. Exertional rhabdomyolysis and acute kidney injury. *Phys Sportsmed*. **2009**, 37, 71-9.
69. J. M. Sauret; G. Marinides; G. K. Wang. Rhabdomyolysis. *Am Fam Physician*. **2002**, 65, 907-12.
70. G. Tran; T. O. Smith; A. Grice; S. R. Kingsbury; P. McCrory; P. G. Conaghan. Does sports participation (including level of performance and previous injury) increase risk of osteoarthritis? A systematic review and meta-analysis. *Br J Sports Med*. **2016**,
71. B. Marti; M. Knobloch; A. Tschopp; A. Jucker; H. Howald. Is excessive running predictive of degenerative hip disease? Controlled study of former elite athletes. *Bmj*. **1989**, 299, 91-3.
72. N. E. Lane; J. W. Oehlert; D. A. Bloch; J. F. Fries. The relationship of running to osteoarthritis of the knee and hip and bone mineral density of the lumbar spine: a 9 year longitudinal study. *J Rheumatol*. **1998**, 25, 334-41.
73. E. Vingard; L. Alfredsson; H. Malchau. Osteoarthrosis of the hip in women and its relationship to physical load from sports activities. *Am J Sports Med*. **1998**, 26, 78-82.
74. T. D. Spector; P. A. Harris; D. J. Hart; F. M. Cicuttini; D. Nandra; J. Etherington; R. L. Wolman; D. V. Doyle. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. *Arthritis Rheum*. **1996**, 39, 988-95.
75. O. Paxinos; A. Karavasili; G. Delimpasis; A. Stathi. Prevalence of Knee Osteoarthritis in 100 Athletically Active Veteran Soccer Players Compared With a Matched Group of 100 Military Personnel. *Am J Sports Med*. **2016**, 44, 1447-54.
76. A. Steensberg; A. D. Toft; H. Bruunsgaard; M. Sandmand; J. Halkjaer-Kristensen; B. K. Pedersen. Strenuous exercise decreases the percentage of type 1 T cells in the circulation. *J Appl Physiol* (1985). **2001**, 91, 1708-12.
77. R. Lechner; B. Tausch; U. Unkelbach; M. Tannheimer; C. Neitzel. Injuries, Medical Conditions, and Changes in Blood Levels in German Special Operations Forces Selection. *J Spec Oper Med*. **2015**, 15, 64-70.
78. L. Gliemann; M. Nyberg; Y. Hellsten. Nitric oxide and reactive oxygen species in limb vascular function: what is the effect of physical activity? *Free Radic Res*. **2014**, 48, 71-83.
79. D. C. Nieman; L. M. Johanssen; J. W. Lee; K. Arabatzis. Infectious episodes in runners before and after the Los Angeles Marathon. *J Sports Med Phys Fitness*. **1990**, 30, 316-28.
80. R. W. Braith; K. J. Stewart. Resistance exercise training: its role in the prevention of cardiovascular disease. *Circulation*. **2006**, 113, 2642-50.