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Review

Intense sport practices and cardiac biomarkers

C. Le Goff*, J. Farré Segura, P. Dufour, J.F. Kaux, E. Cavalier

Department of Clinical Chemistry, University Hospital of Liege, Belgium

ABSTRACT

Biomarkers are well established for the diagnosis of myocardial infarction, heart failure and cardiac fibrosis. Different papers on cardiac biomarker evolution during exercise have been published in the literature and generally show mild to moderate elevations. However, the mechanism responsible for these elevations, reflecting physiological or even pathophysiological changes, still has to be clearly elucidated. There are also indications of higher cardiac risk in poorly trained athletes than in well-trained athletes. Whether regular repetition of intensive exercise might lead, in the longer term, to fibrosis and heart failure remains to be determined. In this review, we summarized the main research about the effects of intense exercise (in particular, running) on cardiac biomarkers (including troponins, natriuretic peptides, etc.). We found that cardiac fibrosis biomarkers seemed to be the most informative regarding the biological impact of intense physical activity.

1. Introduction

Expert panels, composed of the Centers for Disease Control and Prevention (CDC), the American College of Sports Medicine (ACSM), and the American Heart Association (AHA), along with the 1996 US Surgeon General's Report on Physical Activity and Health, reinforced scientific evidence associating regular physical activity with various measures of cardiovascular health [1–3]. The evidence shows that more active and fit people are less susceptible to coronary heart diseases [2]. Even during midlife, lifestyle changes resulting in an increase in physical activity, such as a change in occupation or leisure activities, are also associated with a mortality decrease [4]. On the other hand, sports do not always seem to coincide with good health. Indeed, during the last decade, several cases of sudden death in young athletes have been brought to our attention by the mass media [5–8]. Additionally, in recent years, there has been an important increase in the popularity of long-distance, high-endurance activities such as marathons, triathlons, ultra-marathons and long-distance cycling races, especially in individuals aged 30+ [9]. The amount of physical activity in these strenuous exercises far exceeds the current recommended 150 min per week [10]. As a consequence, the subjects practising such exercises can develop cardiovascular adaptations as a consequence of athletic training, called "athletes' heart". The athletes' heart is a set of physiological adaptations due to exercise, which includes but is not limited to, cardiac chamber enlargement, increased ventricular wall thickness and increased resting vagal tone. These changes are associated with normal left ventricular (LV) function and probably have a benign prognosis. However, investigators recognize the possibility that LV hypertrophy (LVH) could provoke unfavourable alterations in LV function, which might be an important cause of sudden death among young athletes [5,11]. Vigorous-intensity exercise can also increase myocardial workload, as evidenced by heart rate, stroke volume, and systolic blood pressure during exercise [12].

In 1986, Paffenbarger et al. were the first to report a U-shaped association between leisure-time physical activity and mortality [4]. Shnorhr et al. also reported a U-shaped association between all-cause mortality and exercise dose and showed that the lowest mortality levels were found in those who jogged at a slow or average pace fewer than 3 times per week, accounting for a total of 2.5 h. On the other hand, those who jogged at a faster pace more than 3 times per week, accumulating more than 4 h of run time, demonstrated a loss of the longevity observed in the previous group [13].

Cardiac biomarkers are endogenous substances released in the circulation when the heart is damaged or stressed. A long race, such as a marathon or ultra-marathon, can lead to changes in biomarkers, electro- and echocardiography, indicating a pathological process potentially leading to physiopathological changes in the heart. These shifts are usually temporary, depending on the intensity and duration of the performance, and generally normalize after the race [14,15].

In clinical practice, higher biomarker values are generally associated with higher severity of a given condition or a disease, and increases in cardiac biomarkers after strenuous exercises deserve our attention. In the next sections, the potential interest of older and emerging new biomarkers in intensive sport practice will be reviewed. The Fig. 1 and the Table 1 summarize the potential mechanisms responsible of the release of the different markers and their characteristics, pre-analytical aspects and their role discussed in this paper.

* Corresponding author.
E-mail address: c.legoff@chuliege.be (C. Le Goff).

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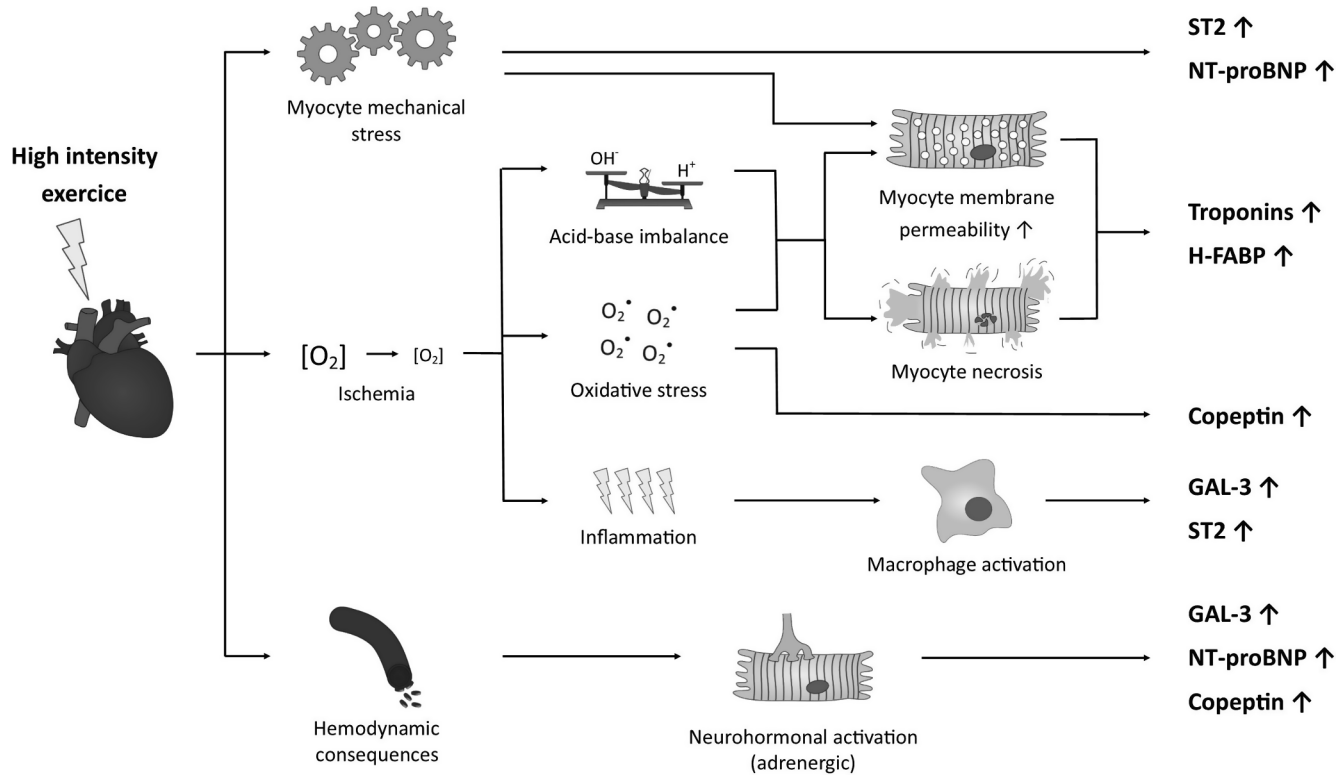

Fig. 1. Potential mechanisms involved in the release of the different cardiac biomarkers after an exercise.

2. Ischaemic biomarkers

2.1. Troponins

The first study where troponin was measured in subjects after exercise was published in 1987, and it was the beginning of a long debate not yet finished [16].

Many studies were not consistent regarding the sample size or the use of the first-generation assay of cardiac troponin T (cTnT) having known cross-reactivity with skeletal troponin. In addition, subjects were highly selected considering that only trained individuals are capable of performing strenuous exercise for several hours, all of which was limiting. After that (with the improvement of the troponin assay) and the ability to quantify very low concentrations of troponin plus the increase in the sample sizes and the fact that several types of populations were examined, it has become clear that exercise may lead to cardiac troponin elevation [17].

Numerous theories have been proposed to explain the exercise-induced elevation of troponin, but it is difficult to come to a general agreement about the clinical relevance of the cTn increase in athletes during and after a run. Nonetheless, some of the described mechanisms responsible for cTn increase during a run include a higher myocyte membrane permeability caused by an increased mechanical stress on the cardiomyocytes (bleb formation), an increased production of oxidative radicals or altered acid-base balance [18–24].

Normally, as the release of troponin in acute coronary syndrome occurs in two phases, we could imagine that the first amount of cTn release comes from the cytosol due to increased membrane permeability, while the subsequent rise is attributed to the release of bound cTns. Therefore, according to the magnitude of the observed increase, it could be released only from the cytosol or released from cytosol and bound cTn [9].

However, according to van Wijk et al., the release of cardiac troponin I (cTnI), in this case, could be the result of primarily complex cTn from myofibrillar origin in the absence of detectable tissue necrosis but not in the absence of cell death. This finding contrasts with the theory of Hickman et al., who hypothesized that cytosolic cTnI may be released in the absence of cell death [25].

Other observations have been made about troponin elevation after exercise: it has been observed that intensity is correlated with cTn release such that higher intensity but shorter duration leads to a greater release [26]. Additionally, milder levels of cTns have been observed in marathon runners who had trained longer distances, proposing a heart adaptation to intense exercise with a subsequent decrease in cardiac injury [27–29].

In the general population, an elevation in troponins above the 99th percentile of the reference population indicates a bad prognosis [30], but this level is exceeded in many studies after strenuous exercise [26,31–33].

The increase in troponin could be attributed to undetected small islands of necrosis, as suggested by some investigators [34,35]. Troponins are the cardiac biomarker that was probably the most widely studied in the context of intense physical activity. Many hypotheses have been proposed, but none have been clearly selected to explain the increase in troponins. However, the release seems to be more harmful, even if reversible, than beneficial [36]. Indeed, a study on older long-distance walkers of exercise-induced cardiac troponin I increase and incident mortality and cardiovascular events has been recently performed by Aengevaeren et al. and showed that the increase in troponin I above the 99th percentile after 30 to 55 km of walking is independently associated with a higher mortality and the onset of cardiovascular events [36,37]. Therefore, it is recommended that until the clinical impact of increased cTns after endurance exercise is clarified, affected athletes should undergo further cardiological investigation, including a stress test [5].

3. Neuro-endocrine peptides

3.1. Natriuretic peptides (NPs)

The synthesis of B-type natriuretic peptide is performed by cardiomyocytes [38,39]. Elevated levels in circulation indicate a large

Table 1
Characteristics, function, reference values, biological variation, pre-analytical consideration including matrix and stability, half-life of the cardiac biomarkers discussed.

Name	Abbreviations	Characteristic (MM)	Functions	Reference values/cutoff	Biological variation		Matrix	Stability	Half-life
					Within hours (%)	Within week (%)			
Troponins	*Myocyte injury*								
Troponin I	TnI	22 KDa	Ischemic necrosis/myocardial infarction diagnosis/ cardiac risk stratification	< 25 ng/L (women) < 32 ng/L (men)	54/-35	97/-49	Serum, EDTA or heparin plasma	8 h at RT 24 h between 2 and 8 °C 31 days at −10 °C 5 years at −70 °C	2 h
TroponinT	TnT	33 KDa	Ischemic necrosis/myocardial infarction diagnosis/ cardiac risk stratification	< 14 ng/L	26/-21	37/-27	Serum, EDTA or heparin plasma	7 days at 4 °C 1 year at −20 °C	2 h
B-type natriuretic peptides	*Myocyte stretch*								
B-type natriuretic peptide	BNP	3.5 KDa	Diagnosis, prognosis and monitoring of heart failure	< 35 pg/mL	34.1	66.2		24 h at RT 1 month at −20 °C (protease inhibitor aprotinin)	20 min
NH2-terminal pro B-type natriuretic peptide	NT-proBNP	8.4 KDa	Diagnosis, prognosis and monitoring of heart failure	< 125 pg/mL	16.1	49.2	Serum, EDTA or heparin plasma	72 h at RT or 4 °C, > 1 year at −80 °C	120 min
Galectin-3	Gal-3	30 KDa	Mediator of cardiac fibrosis and remodelling/ follow-up of heart failure	< 18.8 pg/mL	39	Not known	EDTA plasma	15 days at RT, 15 days at 4 °C, 6 months at −20 °C	Not known
Suppression tumorogenicity 2	ST2	63 KDa	Mediator of cardiac fibrosis and remodelling/ monitoring and prognosis of heart failure	7.1–33.5 (women) 8.5–49.3 (men)	30	Not known	Serum, EDTA or heparin plasma	48 h at 20 °C 7 days at 4 °C 18 months at −20° C to −80 °C	1–2 h
Others									
Heart-fatty acid binding protein	H-FABP	15 KDa	Myocardial damage	< 3,6 μg/L	14		EDTA plasma	24 h at RT or 4 °C	20 min
Copeptin	Copeptin	20 KDa	Surogate marker of arginine vasopressine/ diffentation of osmotic disorders and non-specific stress-related outcome marker in acute disease (AMI, dyspnoea, etc.)	1–12 pmol/L	Not known	Not known	EDTA, heparin or citrate plasma	14 days at RT (EDTA), 7 days at RT (citrate and heparin plasma)	> 100 min

afterload paretic tension in the myocardium as a result of myocyte elongation, derived from an increase in pressure, volume or neurohormonal activation in cases of heart dysfunction, failure, acute coronary syndromes, cardiomyopathies and other syndromes [40–42]. As an indicator for cardiac dysfunction, the determination of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) is essential for cardiovascular disease evaluation, optimal therapeutic management and risk stratification [43,44].

Indeed, circulating concentrations of NPs are directly related to the severity of ventricular dysfunction, and their powered negative prognostic values are used to exclude acute and chronic heart failure for concentrations below the decision cutoffs [41,45].

After heavy exercise, NT-proBNP increases have been shown in different studies [5,46–49]. Some authors have studied myocardial damage by echocardiography and magnetic resonance imaging to correlate the levels of cTn and NT-proBNP with the absence of the evidence of myocardial damage. The rise in NT-proBNP may reflect a physiological reaction without pathological harm in cardiomyocytes. The cardiovascular consequences of such physiological escalation, however, remain unknown [50]. A hypothesis is that it could indicate the activation of a counter-regulatory system (e.g., the adrenergic system). Therefore, during exercise, NT-proBNP may be considered an indicator of the neuroendocrine system rather than a marker of cardiac dysfunction [38]. It has been suggested that a close link exists between the plasma concentration of NP and cardiac morphology in different types of athletes. The increase observed after exercise indicates a transient production/secretion of NPs from the heart. These phenomena might be based on subclinical myocardial cell necrosis [5,51,52]. A possible mechanism inducing an increase in myocardial NP expression could be due to the increase in plasma catecholamines, increased mechanical stress on the ventricular wall, changes in energy dynamics and calcium homeostasis and oxygen-derived free radicals [5,49]. However, there is no doubt that NPs can reliably discriminate pathological from physiological cardiac hypertrophy. Therefore, persistently elevated plasma concentrations of NPs after effort warrant further cardiological evaluation [5].

Throughout strenuous exercise, occasional disruptions in local LV wall behaviour can occur. Many outcomes can result from subclinical myocardial damage throughout exercise, including reduced cardiac function and elevated mechanical myocardial pressure on the regional ventricular wall [52]. A time-dependent increase has also been observed. This observation is in accordance with the time-dependent increased expression of NPs in overstretched myocytes in vitro. Therefore, runners who run longer present the highest NP concentrations after exercise.

As demonstrated in a rat model, NPs could have cytoprotective effects by limiting the size of infarction effects via the elevation of cGMP by opening the adenosine triphosphate-sensitive potassium channels (K_{ATP}) of myocardial mitochondria via the natriuretic peptide receptor A signalling pathway [53]. Similarly, the increase in NPs observed during exercise could have a cytoprotective effect on the heart and not a deleterious effect.

However, a pitfall in all mentioned studies is that the intensity of the effort and mechanical stress are two factors that are difficult to measure.

Elevation in NPs can be seen in many apparently healthy athletes following intense exercise. The production of NPs both during and after exercise, even when medical cut-off values are reached, may not result in myocardial injury but may have an active role in cytoprotection or growth regulation [54]. Therefore, as for troponins, the mechanism underlying NP release is not yet elucidated and has to be studied but seems to be more physiological than pathological and could even have a cytoprotective effect.

3.2. Copeptin

Copeptin is the C-terminal fragment of the vasopressin prohormone. In this way, some authors suggested that the measurement of this peptide may serve as a surrogate marker of arginine vasopressin secretion. However, copeptin reflects haemodynamic and endocrine stress levels in several conditions, including acute myocardial infarction (MI), and has been shown to increase 30 min following induced MI. In addition to troponin, copeptin has been proposed as an additional biomarker of non-ST-segment elevation myocardial infarction-acute coronary syndrome in the 2015 European Society of Cardiology guidelines [55]. Very few studies have assessed the variation in copeptin during either long-distance endurance exercise or short-term exercise. Copeptin was independently associated with the maximal work rate [56]. Copeptin was evaluated in the exploration of exercise-associated hyponatraemia [57]. Copeptin levels increased significantly throughout and at the end of extreme distance runs [55,58]. An increase in copeptin was described by the clear association between exercise intensity and plasma volume reduction and the subsequent increase in blood sodium levels already recorded during brief exercise [56].

Copeptin was measured in the participants of a 100 km ultra-marathon and in those of a 60 km ultra-marathon. An increase in copeptin was observed at the end of the races with a magnitude of 12.4 and 6 times between prerun and postrun sampling, respectively, despite decreases in plasma sodium, suggesting the existence of nonosmotic vasopressin stimulation during this strenuous exercise activity [56,57]. To summarize, and according to the study of Aakre et al, copeptin response after exercise did not seem to predict ischaemia [55].

4. Cardiac fibrosis – emerging biomarkers

The literature is poor about emerging cardiac fibrosis biomarkers during exercise. As shown above, the increased concentrations of troponins and NPs are not clearly understood. A recent systematic review highlights an increased prevalence of clinical myocardial fibrosis in endurance athletes [59].

Hence, fibrosis cardiac biomarkers could help elucidate the long-term effects of vigorous exercise on the individual.

Galectin-3 (Gal-3) and suppression of tumorigenicity 2 (ST2) are assessed in cardiac fibrosis exploration. These proteins participate in heart failure pathophysiology, and each of their concentrations is increased in patients who exhibit cardiac remodelling and fibrosis, making them useful in the monitoring of disease progression [60,61].

4.1. Galectin-3

Gal-3 is involved in numerous physiological and pathophysiological mechanisms, such as immune and inflammatory reactions. In the general population, high levels of Gal-3 are an indicator of poor prognosis and mortality [62–64]. In the cardiovascular field, Gal-3 is secreted by cardiac macrophages, which are activated during the inflammatory process [62,65]. As a biomarker, Gal-3 complements NT-proBNP; it provides upstream information about the progression of cardiomyopathy (an indicator of fibrosis and remodelling), while NT-proBNP is a downstream indicator of raised blood pressure in the cardiac wall (the result of fibrosis and remodelling). Determining the levels of Gal-3 as a means of cardiac prognosis was approved in early 2013 by the American College of Cardiology (ACC) and the American Heart Association (AHA) [66]. A high level of Gal-3 indicates an increased risk of mortality or re-hospitalization for patients with heart failure [65,66]. Furthermore, the doubling of Gal-3 levels over six months, independent of the initial concentration, is also a sign of an adverse evolution [67].

Some studies have shown that participating in intense and sustained exercise leads, in the long term, to the formation of cardiac fibroid deposits, which may be involved in cardiac arrhythmias [68,69]. Gal-3 thus appears to be an interesting cardiac biomarker for cardiovascular screening in athletes [70]. Few studies have been conducted on the relationship between Gal-3 and sports. A significant increase in Gal-3 levels has been observed after running 30 km [69] or after a marathon

[71] or a 60 km ultra-marathon [72]. These increases did not correlate with an increase in cardiac markers such as troponins (cTn) and NT-proBNP. Gal-3 expression also seems to be higher in athletes than in sedentary subjects, and this difference has been tentatively attributed to insufficient rest periods between training sessions. The increase in Gal-3 appears to be inversely proportional to the runners' habitual training intensity, as does the increase in IL-6 and white blood cells, both known as markers of inflammation. Muscle adaptation with training reduces the inflammatory response, accounting for these inversely proportional relationships [69]. Whether the increase in Gal-3 is of skeletal muscle origin [45,69] or reflects structural cardiac anomalies caused by intense exercise remains unknown [45]. Gal-3 levels recovered relatively quickly after exercise, showing that strenuous effort-induced cardiac stretch and inflammatory processes may not be able to cause shorter-term heart remodelling and fibrosis. The possible adverse impact of long-term cardiovascular effects for repetitive vigorous sporting activities must still be shown.

To summarize, Gal-3 release seems to be due to an inflammatory response, and it is clear that inflammatory processes occur during vigorous exercise. Therefore, with the relatively few studies already performed, it is difficult to conclude whether Gal-3 release is a harmful effect of the physical activity or only a physiological process.

4.2. Suppression of tumorogenicity-2

ST2, also known as soluble interleukin-1 receptor-like 1, has a prominent role in cardiovascular disease as a marker of inflammation, tissue fibrosis, matrix remodelling, and myocyte strain [73].

The novel cardiomyocyte stress and fibrosis biomarker offers value in addition to that of NPs for risk evaluation of patients with a wide range of cardiovascular diseases (CVDs). Blood levels of ST2 rise in various diseases, such as inflammatory diseases and heart disease, and in both cases are deemed a reliable prognostic indicator. Currently, the major source of ST2 circulating in healthy individuals and patients with distinct disorders remains incompletely resolved [74].

On the basis of all available data, the 2013 AACC and AHA guidelines now recommend the measurement of ST2 for additive risk stratification in patients with acute or chronic ambulatory heart failure and for heart failure prognostication [73–75].

A recent study positions vascular endothelial cells as the main source of ST2, rather than the myocardium, in human CVD [76]. ST2 was seen in patients with stable chronic coronary artery disease as a good independent indicator for the prediction of long term all-cause and cardiovascular mortality [77]. Interestingly, the Framingham study highlighted that ST2 offered prognostic data in a low-risk community-based population [78].

ST2 measurement also provides a strong serological overview of the cumulative myocardial fibrotic process [75].

ST2 was not studied in exercise before the recent contribution of Aengevaeren et al. in 2018 [12]. The effect of repeated exercise may increase the ST2 concentration in blood due to an acute rise in cardiac load. According to the systematic review of van de Schoor et al., the prevalence of myocardial fibrosis was strongly associated with the cumulative lifelong exercise dose [79].

According to our recent study, ST2 was higher at baseline, probably due to the accumulation of exercises, and could be considered a good predictor of cardiac fibrosis development. ST2 levels were higher in the highest length race (64 km) group, especially at the end of the race, than in the marathon group [70]. Contrary to the Gal-3 increase, which seemed to be correlated with the intensity of exercise, the ST2 increase seemed to be more correlated with the duration of exercise than with the intensity. It thus seems that more exercise correlates with a higher ST2 concentration [70]. As data from Bayes-Genis et al. indicate that for every 10 ng/ml increase in ST2, there is an approximately 20% increase in event risk [75], these populations could be more at risk.

ST2 appears to be an interesting biomarker according to the few observations done in the field of physical activity, but as all the studies performed to date were carried out with the same kit (Presage, Critical Care Diagnostic, USA), we have to remain cautious concerning the interpretations. However, five kits are available on the market and have been analytically evaluated by Mueller and Dieplinger [80]. The Presage assay is the most commonly used kit in different studies, and it is considered a highly sensitive assay compared to the other kits.

Further studies are needed because, as for Gal-3, ST2 is also described as a marker of inflammation in CVD. The large difference from the other biomarkers studied is related to a longer period of high ST2 concentration, even after the recovery time, and could possibly reflect the accumulation of strenuous exercise on the heart [70].

5. Other markers referenced to detect or exclude early-stage myocardial ischaemia

5.1. Heart fatty acid binding protein (H-FABP)

H-FABP is a low-molecular-mass protein involved in the intracellular uptake and buffering of long-chain fatty acids in the myocardium [81,82]. H-FABP is considered a sensitive and early marker of myocardial damage [83,84] but is not widely used because of the sensitivity of troponin to myocardial damage.

In the field of sports, H-FABP has been very rarely studied, and its concentration was found to be increased in all cyclists involved in the 4800 km Race Across America [85].

Another work studied the immediate impact on H-FABP and cardiovascular function of ultra-endurance activity. H-FABP was assessed at five stages during a 24-h ultra-marathon (i.e., prerace; sprint, 12-h run, 24-h run, and 48-h postrace) in 14 male ultra-marathoners (age 40 ± 12 years) [86]. In this study, significantly higher H-FABP levels were observed at the post-12-h- and post-24-h-run time points than at the postmarathon distance. As expected, a significant correlation was found between post-24-h-run H-FABP levels and CKMB activity as well as running distance. One important observation made in this study was that H-FABP has been found to have different release times of reaching maximal concentrations during the 24-h ultra-marathon from other markers of myocardial injury [86].

It was reported that H-FABP levels started increasing 1 h following myocardial cell damage with peak levels between the 6th and 8th hours and that H-FABP may be more effective for detecting postexercise cardiac injury. It has been suggested that the lower molecular mass of H-FABP (15 kDa) might especially lead to its higher membrane permeability than CKMB and cTnT (86 kDa and 33 kDa, respectively). The correlations between running length and serum H-FABP concentrations suggest that exercise span was accountable for its increase. [86]. In conclusion, there seems to be a correlation between running length and serum H-FABP concentration.

6. Prospective biomarkers

6.1. MicroRNAs (miRNAs)

miRNAs are small non-coding RNAs that target mRNAs and are consequently involved in transcriptional regulation of gene expression. Some miRNAs are expressed only in some specific tissues, whereas others are constantly present [87]. Therefore, the measurement of miRNA in serum may provide information on the tissue or cell of origin. Because they are involved in the regulation of gene expression, they can participate in the adaptation of muscle to exercise and training. Some miRNAs, such as miR-1, miR-133a, miR-208a (only heart), miR-208b, miR486, miR-499a and miR-499b, have been shown to have muscle (heart and skeletal) specificity [88]. The effects of exercise affect plasma levels of miR-1, miR-133a and miR-133b, with peak values observed 6 h after exercise ($p < 0.0001$), showing that they are up-regulated in the early recovery period [89]. Therefore, the exploration

of miRNAs appears to be a new perspective in the evaluation of the cardiac impact of exercise.

7. Conclusion

Healthy individuals and particularly athletes often have variations in a number of cardiovascular biomarkers in response to physical practice. A precise evaluation of augmented cardiac biomarkers is therefore mandatory after vigorous exercise. Biomarkers such as troponins, natriuretic peptides, and creatine kinase have been widely studied, but only hypotheses have been proposed to explain the observed increase during and after strenuous exercise. Prospective studies about the impact of exercise-induced cardiac troponin are lacking. However, in 2019, research on older long-distance walkers showed that these phenomena may not be a benign physiological response to exercise but instead an early marker of future risk of cardiovascular events or mortality even in runners without established cardiovascular risk[36]. Biomarkers to detect or exclude early-stage myocardial ischaemia, such as H-FABP, did not show added value in comparison with the first markers studied. On the other hand, as an increased prevalence of clinical myocardial fibrosis has been demonstrated in athletes, the measurement of cardiac fibrosis biomarkers such as ST2 or Gal-3 could be helpful in attempts to prevent the onset of cardiac injury. As new biomarkers, miRNAs could provide valuable information to exclude pathological myocardial injury before and after resistance exercise.

References

[1] A. Winterfeld, Physical activity guidelines, NCSL Legisbrief. 17 (2009) 1–2.
[2] M.E. Nelson, W.J. Rejeski, S.N. Blair, P.W. Duncan, J.O. Judge, A.C. King, C.a. Macera, C. Castaneda-Sceppa, Physical activity and public health in older adults, Med. Sci. Sport. Exerc. 39 (2007) 1435–1445, https://doi.org/10.1249/mss.0b013e3180616aa2.
[3] J. Myers, Cardiology patient pages. Exercise and cardiovascular health, Circulation 107 (2003) e2–e5.
[4] R.S. Paffenbarger, R. Hyde, A.L. Wing, C. Hsieh, Physical activity, all-cause mortality, and longevity of college alumni, N. Engl. J. Med. 314 (1986) 605–613, https://doi.org/10.1056/NEJM198603063141003.
[5] E. Faviou, A. Zachari, C. Nounopoulos, E. Agrafiotis, G. Vourli, A. Dionyssiou-Asteriou, Elevation of serum N-terminal pro-brain natriuretic peptide after exercise is an index of myocardial damage or a cytoprotective reflection? J. Sports Med. Phys. Fitness 48 (2008) 90–96.
[6] N. Chandra, R. Bastiaenen, M. Papadakis, S. Sharma, Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas, J. Am. Coll. Cardiol. 61 (2013) 1027–1040, https://doi.org/10.1016/j.jacc.2012.08.1032.
[7] J. Sweeting, C. Semsarian, Sudden cardiac death in athletes, Hear Lung Circ. 27 (2018), https://doi.org/10.1016/j.hlc.2018.03.026.
[8] K.G. Harmon, J.A. Drezner, M.G. Wilson, S. Sharma, Incidence of sudden cardiac death in athletes: a state-of-the-art review, Br. J. Sports Med. 48 (2014) 1185–1192, https://doi.org/10.1136/bjsports-2014-093872.
[9] E. Donnellan, D. Phelan, Biomarkers of cardiac stress and injury in athletes: what do they mean? Curr. Heart Fail. Rep. 15 (2018) 116–122, https://doi.org/10.1007/s11897-018-0385-9.
[10] M.F.H. Maessen, M.T.E. Hopman, A.L.M. Verbeek, T.M.H. Eijsvogels, Dose of jogging: mortality versus longevity, J. Am. Coll. Cardiol. 65 (2015) 2672–2673, https://doi.org/10.1016/j.jacc.2015.02.080.
[11] S.M. Stevens, K. Reinier, S.S. Chugh, Increased left ventricular mass as a predictor of sudden cardiac death: is it time to put it to the test? Circ. Arrhythm. Electrophysiol. 6 (2013) 212–217, https://doi.org/10.1161/CIRCEP.112.974931.
[12] V.L. Aengevaeren, R.R.J. Van Kimmenade, M.T.E. Hopman, N. VAN Royen, J.V. Snider, J.L. Januzzi, K.P. George, T.M.H. Eijsvogels, Exercise-induced changes in Soluble ST2 concentrations in marathon runners, Med. Sci. Sport. Exerc. 1 (2018), https://doi.org/10.1249/MSS.0000000000001806.
[13] P. Schnohr, J.H. O'Keefe, J.L. Marott, P. Lange, G.B. Jensen, Dose of jogging and long-term mortality: the Copenhagen City heart study, J. Am. Coll. Cardiol. 65 (2015) 411–419, https://doi.org/10.1016/j.jacc.2014.11.023.
[14] P. Nikolaidis, B. Knechtle, Age of peak performance in 50-km ultramarathoners – is it older than in marathoners? Open Access J. Sport. Med. 9 (2018) 37–45, https://doi.org/10.2147/oajsm.s154816.
[15] B. Knechtle, P.T. Nikolaidis, Physiology and pathophysiology in ultra-marathon running, Front. Physiol. 9 (2018), https://doi.org/10.3389/fphys.2018.00634.
[16] P. Cummins, A. Young, M.L. Auckland, C.A. Michie, P.C.W. Stone, B.J. Shepstone, Comparison of serum cardiac specific troponin-I with creatine kinase, creatine kinase-MB isoenzyme, tropomyosin, myoglobin and C-reactive protein release in marathon runners: cardiac or skeletal muscle trauma? Eur. J. Clin. Invest. 17 (1987) 317–324, https://doi.org/10.1111/j.1365-2362.1987.tb02194.x.
[17] T. Gresslien, S. Agewall, Troponin and exercise, Int. J. Cardiol. 221 (2016) 609–621, https://doi.org/10.1016/j.ijcard.2016.06.243.
[18] D.L. Christensen, D. Espino, R. Infante-Ramírez, M.S. Cervantes-Borunda, R.P. Hernández-Torres, A.E. Rivera-Cisneros, D. Castillo, K. Westgate, D. Terzic, S. Brage, C. Hassager, J.P. Goetze, J. Kjaergaard, Transient cardiac dysfunction but elevated cardiac and kidney biomarkers 24 h following an ultra-distance running event in Mexican Tarahumara, Extrem. Physiol. Med. 6 (2017) 1–10, https://doi.org/10.1186/s13728-017-0057-5.
[19] A. Goette, A. Bukowska, D. Dobrev, J. Pfeiffenberger, H. Morawietz, D. Strugala, I. Wiswedel, F.W. Röhl, C. Wolke, S. Bergmann, P. Bramlage, U. Ravens, U. Lendeckel, Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles, Eur. Heart J. 30 (2009) 1411–1420, https://doi.org/10.1093/eurheartj/ehp046.
[20] R. Shave, A. Baggish, K. George, M. Wood, J. Scharhag, G. Whyte, D. Gaze, P.D. Thompson, Exercise-induced cardiac troponin elevation, J. Am. Coll. Cardiol. 56 (2010) 169–176, https://doi.org/10.1016/j.jacc.2010.03.037.
[21] P.L. McNeil, R. Khakee, Disruptions of muscle fiber plasma membranes. Role in exercise-induced damage, Am. J. Pathol. 140 (1992) 1097–1109.
[22] E. Hultman, K. Sahlin, Acid-base balance during exercise, Exerc. Sport Sci. Rev. 8 (1980) 41–128.
[23] J. Mair, B. Lindahl, O. Hammarsten, C. Müller, E. Giannitsis, K. Huber, M. Möckel, M. Plebani, K. Thygesen, A.S. Jaffe, How is cardiac troponin released from injured myocardium? Eur. Hear. J. Acute Cardiovasc. Care 7 (2018) 553–560, https://doi.org/10.1177/2048872617748553.
[24] O. Hammarsten, J. Mair, M. Möckel, B. Lindahl, A.S. Jaffe, Possible mechanisms behind cardiac troponin elevations, Biomarkers 23 (2018) 725–734, https://doi.org/10.1080/1354750X.2018.1490969.
[25] X.M.R. van Wijk, S. Claassen, N.S. Enea, P. Li, S. Yang, M.A. Brouwer, G.E. Cramer, R. Zuk, K.L. Lynch, A.H.B. Wu, Cardiac troponin I is present in plasma of type 1 myocardial infarction patients and patients with troponin I elevations due to other etiologies as complex with little free I, Clin. Biochem. 73 (2019) 35–43, https://doi.org/10.1016/j.clinbiochem.2019.06.012.
[26] T. Danielsson, J. Carlsson, H. Schreyer, J. Ahnesjo, L. Ten Siethoff, T. Ragnarsson, Å. Tugetam, P. Bergman, Blood biomarkers in male and female participants after an Ironman-distance triathlon, PLoS One 12 (2017) 1–9, https://doi.org/10.1371/journal.pone.0179324.
[27] T. Eijsvogels, K. George, R. Shave, D. Gaze, B.D. Levine, M.T.E. Hopman, D.H.J. Thijssen, Effect of prolonged walking on cardiac troponin levels, AJC 105 (2010) 267–272, https://doi.org/10.1016/j.amjcard.2009.08.679.
[28] R. Shave, A. Baggish, K. George, M. Wood, J. Scharhag, G. Whyte, D. Gaze, P.D. Thompson, Exercise-induced cardiac troponin elevation: Evidence, mechanisms, and implications, J. Am. Coll. Cardiol. 56 (2010) 169–176, https://doi.org/10.1016/j.jacc.2010.03.037.
[29] R.E. Shave, G.P. Whyte, K. George, D.C. Gaze, P.O. Collinson, Prolonged exercise should be considered alongside typical symptoms of acute myocardial infarction when evaluating increases in cardiac troponin T, Heart 91 (2005) 1219–1220, https://doi.org/10.1136/hrt.2004.046052.
[30] T.W. Wallace, S.M. Abdullah, M.H. Drazner, S.R. Das, A. Khera, D.K. McGuire, F. Wians, M.S. Sabatine, D.A. Morrow, J.A. De Lemos, Prevalence and determinants of troponin T elevation in the general population, Circulation 113 (2006) 1958–1965, https://doi.org/10.1161/CIRCULATIONAHA.105.609974.
[31] D.S. Jassal, D. Moffat, J. Krahn, R. Ahmadie, T. Fang, G. Eschun, S. Sharma, Cardiac injury markers in non-elite marathon runners, Int. J. Sports Med. 30 (2009) 75–79, https://doi.org/10.1055/s-0028-1104572.
[32] N. Middleton, K. George, G. Whyte, D. Gaze, P. Collinson, R. Shave, Cardiac troponin T release is stimulated by endurance exercise in healthy humans, J. Am. Coll. Cardiol. 52 (2008) 1813–1814, https://doi.org/10.1016/j.jacc.2008.03.069.
[33] F. Fu, J. Nie, T.K. Tong, Serum cardiac troponin T in adolescent runners: effects of exercise intensity and duration, Int. J. Sports Med. 30 (2009) 168–172, https://doi.org/10.1055/s-0028-1104586.
[34] A. Urhausen, J. Scharhag, M. Herrmann, W. Kindermann, Clinical significance of increased cardiac troponins T and I in participants of ultra-endurance events, Am. J. Cardiol. 94 (2004) 696–698, https://doi.org/10.1016/j.amjcard.2004.05.050.
[35] Y. Chen, R.C. Serfass, S.M. Mackey-Bojack, K.L. Kelly, J.L. Titus, F.S. Apple, Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise, J. Appl. Physiol. 88 (2017) 1749–1755, https://doi.org/10.1152/jappl.2000.88.5.1749.
[36] V.L. Aengevaeren, M.T.E. Hopman, P.D. Thompson, E.A. Bakker, K.P. George, D.H.J. Thijssen, T.M.H. Eijsvogels, Exercise-induced cardiac troponin I increase and incident mortality and cardiovascular events, Circulation 140 (2019) 804–814, https://doi.org/10.1161/CIRCULATIONAHA.119.041627.
[37] T. Omland, K.M. Aakre, Cardiac troponin increase after endurance exercise, Circulation 140 (2019) 815–818, https://doi.org/10.1161/CIRCULATIONAHA.119.042131.
[38] A. Clerico, F.A. Recchia, C. Passino, M. Emdin, Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications, Am. J. Physiol. Circ. Physiol. 290 (2005) H17–H29, https://doi.org/10.1152/ajpheart.00684.2005.
[39] S. Wiese, T. Breyer, A. Dragu, R. Wakili, T. Burkard, S. Schmidt-Schweda, E.-M. Füchtbauer, U. Dohrmann, F. Beyersdorf, D. Radicke, C.J.F. Holubarsch, Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium, Circulation 102 (2012) 3074–3079, https://doi.org/10.1161/01.cir.102.25.3074.
[40] E.M. Dixon, M.V. Kamath, N. McCartney, E.L. Fallen, Neural regulation of heart rate

variability in endurance athletes and sedentary controls, Cardiovasc. Res. 26 (1992) 713–719, https://doi.org/10.1093/cvr/26.7.713.
[41] C. Le Goff, T. Laurent, J.-F. Kaux, J.-P. Chapelle, Intense physical exercise related to the emergent generation of cardio-vascular risk markers: a review, Biol. Sport. 29 (2012) 11–16, https://doi.org/10.5604/20831862.979290.
[42] C. Le Goff, J.-F. Kaux, S.B. Goffaux, E. Cavalier, Cardiac biomarkers and cycling race, J. Sport. Sci. Med. 14 (2015).
[43] Y.T. Huang, Y.T. Tseng, T.W. Chu, J. Chen, M.Y. Lai, W.R. Tang, C.C. Shiao, Corrigendum: N-terminal pro b-type natriuretic peptide (NT-pro-BNP)-based score can predict in-hospital mortality in patients with heart failure, Sci. Rep. 7 (2017) 46866, https://doi.org/10.1038/srep46866.
[44] J.A. de Lemos, D.A. Morrow, Combining natriuretic peptides and necrosis markers in the assessment of acute coronary syndromes, Rev. Cardiovasc. Med. 4 (Suppl. 4) (2003) S37–S46.
[45] G.L. Salvagno, F. Schena, M. Gelati, E. Danese, G. Cervellin, G.C. Guidi, G. Lippi, The concentration of high-sensitivity troponin I, galectin-3 and NT-proBNP substantially increase after a 60-km ultramarathon, Clin. Chem. Lab. Med. 52 (2014) 267–272, https://doi.org/10.1515/cclm-2013-0601.
[46] A.J. Siegel, J. Januzzi, P. Sluss, E. Lee-Lewandrowski, M. Wood, T. Shirey, K.B. Lewandrowski, Cardiac biomarkers, electrolytes, and other analytes in collapsed marathon runners, Am. J. Clin. Pathol. 129 (2008) 948–951, https://doi.org/10.1309/4L0M60MGAQBCHMV7.
[47] G. Neumayr, R. Pfister, G. Mitterbauer, G. Eibl, H. Hoertnagl, Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists, Am. J. Cardiol. 96 (2005) 732–735, https://doi.org/10.1016/j.amjcard.2005.04.054.
[48] C.A. Dorrian, B.J. Toole, S. Alvarez-Madrazo, A. Kelly, J.M. Connell, A.M. Wallace, A screening procedure for primary aldosteronism based on the Diasorin Laision automated chemiluminiscent immunoassay for direct renin, Ann. Clin. Biochem. 47 (2010) 195–200.
[49] J. Scharhag, M. Herrmann, A. Urhausen, M. Haschke, W. Herrmann, W. Kindermann, Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise, Am. Heart J. 150 (2005) 1128–1134, https://doi.org/10.1016/j.ahj.2005.01.051.
[50] H. Hamasaki, The effects of exercise on natriuretic peptides in individuals without heart failure, Sports 4 (2016) 32, https://doi.org/10.3390/sports4020032.
[51] N. Rifai, P.S. Douglas, M. O'Toole, E. Rimm, G.S. Ginsburg, Cardiac troponin T and I, electrocardiographic wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman Triathlon, Am. J. Cardiol. 83 (1999) 1085–1089, https://doi.org/10.1016/S0002-9149(99)00020-X.
[52] H. Ohba, H. Takada, H. Musha, J. Nagashima, N. Mori, T. Awaya, K. Omiya, M. Murayama, Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men, Am. Heart J. 141 (2001) 751–758, https://doi.org/10.1067/mhj.2001.114371.
[53] S.P. D'Souza, D.M. Yellon, C. Martin, R. Schulz, G. Heusch, A. Onody, P. Ferdinandy, G.F. Baxter, B-type natriuretic peptide limits infarct size in rat isolated hearts via K ATP channel opening, Am. J. Physiol. Circ. Physiol. 284 (2015) H1592–H1600, https://doi.org/10.1152/ajpheart.00902.2002.
[54] J. Scharhag, A. Urhausen, G. Schneider, M. Herrmann, K. Schumacher, M. Haschke, A. Krieg, T. Meyer, W. Herrmann, W. Kindermann, Reproducibility and clinical significance of exercise-induced increases in cardiac troponins and N-terminal pro brain natriuretic peptide in endurance athletes, Eur. J. Cardiovasc. Prev. Rehabil. 13 (2006) 388–397, https://doi.org/10.1097/01.hjr.0000219117.33038.90.
[55] K.M. Aakre, Ø. Kleiven, Ø. Skadberg, M.F. Bjørkavoll-Bergseth, T. Melberg, H. Strand, T.A. Hagve, S. Ørn, The copeptin response after physical activity is not associated with cardiac biomarkers or asymptomatic coronary artery disease: the North Sea Race Endurance Exercise Study (NEEDED), Clin. Biochem. 52 (2018) (2013) 8–12, https://doi.org/10.1016/j.clinbiochem.2017.10.007.
[56] G. Lippi, F. Schena, G.L. Salvagno, F. Sanchis-Gomar, G.C. Guidi, Serum Copeptin and Midregion Proadrenomedullin (MR-proADM) after an Ultramarathon, J. Clin. Lab. Anal. 29 (2015) 15–20, https://doi.org/10.1002/jcla.21720.
[57] J. Burge, B. Knechtle, P. Gnadinger, C.A. Rüst, T. Rosemann, Maintained serum sodium in male ultra-marathoners – the role of fluid intake, vasopressin and aldosterone in fluid and electrolyte regulation, Zurich Open Repos. Arch. 43 (2011) 646–652.
[58] T. Hew-Butler, M.D. Hoffman, K.J. Stuempfle, I.R. Rogers, N.G. Morgenthaler, J.G. Verbalis, Changes in copeptin and bioactive vasopressin in runners with and without hyponatremia, Clin. J. Sport Med. 21 (2011) 211–217, https://doi.org/10.1097/JSM.0b013e31821a62c2.
[59] 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. 36 (2015) 1998–2010, https://doi.org/10.1093/eurheartj/ehv202.
[60] W.C. Meijers, A.R. van der Velde, R.A. de Boer, ST2 and galectin-3: ready for prime time? Ejifcc 27 (2016) 238–252.
[61] A.H.B. Wu, F. Wians, A. Jaffe, Biological variation of galectin-3 and soluble ST2 for chronic heart failure: implication on interpretation of test results, Am. Heart J. 165 (2013) 995–999, https://doi.org/10.1016/j.ahj.2013.02.029.
[62] D. Gruson, G. Ko, Galectins testing: new promises for the diagnosis and risk stratification of chronic diseases? Clin. Biochem. 45 (2012) 719–726, https://doi.org/10.1016/j.clinbiochem.2012.04.009.
[63] J. Dumic, S. Dabelic, M. Flögel, Galectin-3: an open-ended story, Biochim. Biophys. Acta 1760 (2006) 616–635, https://doi.org/10.1016/j.bbagen.2005.12.020.
[64] R.A. de Boer, D.J. van Veldhuisen, R.T. Gansevoort, A.C. Muller Kobold, W.H. van Gilst, H.L. Hillege, S.J.L. Bakker, P. van der Harst, The fibrosis marker galectin-3 and outcome in the general population, J. Intern. Med. 272 (2012) 55–64, https://doi.org/10.1111/j.1365-2796.2011.02476.x.
[65] N. Hrynchyshyn, P. Jourdain, M. Desnos, B. Diebold, F. Funck, Galectin-3: a new biomarker for the diagnosis, analysis and prognosis of acute and chronic heart failure, Arch. Cardiovasc. Dis. 106 (2013) 541–546, https://doi.org/10.1016/j.acvd.2013.06.054.
[66] A. Gupta, G. Ghimire, F.G. Hage, Guidelines in review: 2013 ACCF/AHA guideline for the management of heart failure, J. Nucl. Cardiol. 21 (2014) (2013) 397–399, https://doi.org/10.1007/s12350-013-9832-x.
[67] P.A. Mccullough, A. Olobatoke, T.E. Vanhecke, Galectin-3: a novel blood test for the evaluation and heart failure, Rev. Cardiovasc. Med. 12 (2011) 200–210, https://doi.org/10.3909/ricm0624.
[68] J.E. Trivax, P.A. McCullough, Phidippides cardiomyopathy: a review and case illustration, Clin. Cardiol. 35 (2012) 69–73, https://doi.org/10.1002/clc.20994.
[69] R. Hättasch, S. Spethmann, R.A. de Boer, W.P.T. Ruifrok, S. Schattke, M. Wagner, S. Schroeckh, T. Durmus, I. Schimke, W. Sanad, G. Baumann, A.C. Borges, F. Knebel, Galectin-3 increase in endurance athletes, Eur. J. Prev. Cardiol. 21 (2014) 1192–1199, https://doi.org/10.1177/2047487313492069.
[70] C. Le Goff, J.F. Kaux, J.F. Segura, V. Stojkovic, A. Ancion, L. Seidel, P. Lancellotti, E. Cavalier, Evolution of the slopes of ST2 and galectin-3 during marathon and ultratrail running compared to a control group, Clin. Chem. Lab. Med. (2019), https://doi.org/10.1515/cclm-2019-0555.
[71] C. Le Goff, L. Lennartz, L. Vranken, J.-F. Kaux, E. Cavalier, Comparison of cardiac biomarker dynamics in marathon, semi-marathon and untrained runners: what is the impact on results interpretation? J. Lab. Precis. Med. 4 (2019), https://doi.org/10.21037/jlpm.2019.01.04.
[72] G. Lippi, F. Schena, G.L. Salvagno, R. Aloe, G. Banfi, G.C. Guidi, Foot-strike haemolysis after a 60-km ultramarathon, Blood Transfus. 10 (2012) 377–383, https://doi.org/10.2450/2012.0167-11.
[73] G. Miñana, J. Núñez, A. Bayés-Genís, E. Revuelta-López, C. Ríos-Navarro, E. Núñez, F.J. Chorro, M.P. López-Lereu, J.V. Monmeneu, J. Lupón, V. Bodí, ST2 and left ventricular remodeling after ST-segment elevation myocardial infarction: a cardiac magnetic resonance study, Int. J. Cardiol. 270 (2018) 336–342, https://doi.org/10.1016/j.ijcard.2018.06.073.
[74] A. Bayes-Genis, Y. Zhang, B. Ky, ST2 and patient prognosis in chronic heart failure, Am. J. Cardiol. 115 (2015) 64B–69B, https://doi.org/10.1016/j.amjcard.2015.01.043.
[75] J. Peñafiel, J. Lupón, E. Zamora, A. Urrutia, J. Vila, M. de Antonio, J. Barallat, A. Galán, A. Bayes-Genis, Head-to-head comparison of 2 myocardial fibrosis biomarkers for long-term heart failure risk stratification, J. Am. Coll. Cardiol. 63 (2013) 158–166, https://doi.org/10.1016/j.jacc.2013.07.087.
[76] T.M. Benjamin Dieplinger, Soluble ST2 in heart failure, Heart Fail. Clin. 14 (2018) 41–48, https://doi.org/10.1016/j.hfc.2017.08.005.
[77] B. Dieplinger, M. Egger, M. Haltmayer, M.E. Kleber, H. Scharnagl, G. Silbernagel, R.A. de Boer, W. Maerz, T. Mueller, Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study, Clin. Chem. 60 (2014) 530–540, https://doi.org/10.1373/clinchem.2013.209858.
[78] T.J. Wang, K.C. Wollert, M.G. Larson, E. Coglianese, E.L. McCabe, S. Cheng, J.E. Ho, M.G. Fradley, A. Ghorbani, V. Xanthakis, T. Kempf, E.J. Benjamin, D. Levy, R.S. Vasan, J.L. Januzzi, Prognostic utility of novel biomarkers of cardiovascular stress, Circulation 126 (2012) 1596–1604, https://doi.org/10.1161/CIRCULATIONAHA.112.129437.
[79] F.R. van de Schoor, V.L. Aengevaeren, M.T.E. Hopman, D.L. Oxborough, K.P. George, P.D. Thompson, T.M.H. Eijsvogels, Myocardial fibrosis in athletes, Mayo Clin. Proc. 91 (2016) 1617–1631, https://doi.org/10.1016/j.mayocp.2016.07.012.
[80] T. Mueller, B. Dieplinger, Soluble ST2 and galectin-3: what we know and don't know analytically, Ejifcc 27 (2016) 224–237.
[81] U. Cavus, F. Coskun, B. Yavuz, O. Ciftci, L. Sahiner, H. Aksoy, A. Deniz, E. Ozakin, K. Aytemir, L. Tokgozoglu, G. Kabakci, Heart-type, fatty-acid binding protein can be a diagnostic marker in acute coronary syndromes, J. Natl. Med. Assoc. 98 (2006) 1067–1070.
[82] S. Da Molin, F. Cappellini, R. Falbo, S. Signorini, P. Brambilla, Verification of an immunoturbidimetric assay for heart-type fatty acid-binding protein (H-FABP) on a clinical chemistry platform and establishment of the upper reference limit, Clin. Biochem. 47 (2014) 247–249, https://doi.org/10.1016/j.clinbiochem.2014.07.011.
[83] T. Nakata, A. Hashimoto, M. Hase, K. Tsuchihashi, K. Shimamoto, Human heart-type fatty acid-binding protein as an early diagnostic and prognostic marker in acute coronary syndrome, Cardiology 99 (2003) 96–104, https://doi.org/10.1159/000069726.
[84] J.M. Young, J.W. Pickering, P.M. George, S.J. Aldous, J. Wallace, C.M. Frampton, R.W. Troughton, M.A. Richards, J.H. Greenslade, L. Cullen, M.P. Than, Heart fatty acid binding protein and cardiac troponin: development of an optimal rule-out strategy for acute myocardial infarction, BMC Emerg. Med. 16 (2016) 1–10, https://doi.org/10.1186/s12873-016-0089-y.
[85] K. Williams, K. George, A. Hulton, R. Godfrey, I. Lahart, M.G. Wilson, S. Charlesworth, D. Warburton, D. Gaze, G. Whyte, A unique case series of novel biomarkers of cardiac damage in cyclists completing the 4800 km Race Across America (RAAM), Curr. Med. Chem. 18 (2011) 3446–3451.
[86] A. Żebrowska, Z. Waśkiewicz, P.T. Nikolaidis, R. Mikołajczyk, D. Kawecki, T. Rosemann, B. Knechtle, Acute responses of novel cardiac biomarkers to a 24-h ultra-marathon, J. Clin. Med. 8 (2019) 57, https://doi.org/10.3390/jcm8010057.
[87] D. Domańska-Senderowska, M.J.N. Laguette, A. Jegier, P. Cieszczyk, A.V. September, E. Brzeziańska-Lasota, MicroRNA profile and adaptive response to exercise training: a review, Int. J. Sports Med. 40 (2019) 227–235, https://doi.org/

10.1055/a-0824-4813.
[88] J. Siracusa, N. Koulmann, S. Banzet, Circulating myomiRs: a new class of biomarkers to monitor skeletal muscle in physiology and medicine, J. Cachexia. Sarcopenia Muscle 9 (2018) 20–27, https://doi.org/10.1002/jcsm.12227.
[89] S. Banzet, M. Chennaoui, O. Girard, S. Racinais, C. Drogou, H. Chalabi, N. Koulmann, Changes in circulating microRNAs levels with exercise modality, J. Appl. Physiol. 115 (2013) 1237–1244, https://doi.org/10.1152/japplphysiol.00075.2013.