Review Article



# Cardiovascular biomarkers modified by exercise

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**Abstract:** When managing patients with cardiovascular disease (CVD), clinical assessment has its limitations and clinicians usually need additional tools to help with the diagnosis. Cardiovascular biomarkers are one such tool to diagnose the condition promptly and accurately, and guide the therapeutic approach. While physical exercise is recommended for the prevention and therapy of several disorders including CVD, exercise can modify blood concentrations of several laboratory variables. In effect, the finding of abnormal levels of cardiac biomarkers after an acute bout of strenuous exercise has been a cause of concern. However, it is now starting to emerge that levels of some biomarkers outside the normal range in healthy physically active subjects, rather than reflecting an underlying disease, may indicate an adaptive response to exercise. This means that laboratory results in these individuals need to really be interpreted with caution.

**Keywords:** Sport; physical activity; myocardial infarction; neutrophil gelatinase-associated lipocalin (NGAL); troponin; creatine kinase

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## Introduction

Cardiovascular disease (CVD) is the term used to describe any condition that affects the blood vessels and/or heart such as high blood pressure, subclinical atherosclerosis, coronary heart disease (CHD), acute coronary syndrome, acute myocardial infarction (AMI), stroke (cerebrovascular disease), congenital cardiovascular defects, cardiomyopathy, chronic heart failure (CHF), and other less prevalent conditions. CVD is one of the main causes of morbidity and mortality worldwide and thus its prevention is a public health priority. According to the Non-communicable Diseases Country Profiles 2014 of the World Health Organization (WHO), mortality rates for chronic diseases in the United States have been estimated at 31% for CVD, 23% for cancer and 46% for other chronic diseases (1).

Although clinical assessment is the basis for CVD patient management, this assessment has several limitations because of the heterogeneity and complexity of associated conditions. Hence, clinicians use additional tools to help identify the CVD in question. Cardiovascular biomarkers have been successfully used to promptly and accurately diagnose CVD and guide therapeutic approaches (2).

Physical exercise induces physiological and metabolic adaptations for health, including cardiovascular health (3). However, intense continuous exercise, training, and competitions can induce changes in blood concentrations of numerous laboratory variables (4). For example, exercise can cause transient ischemia, myocardial stress, and left diastolic ventricular dysfunction, sometimes leading to increased levels of biomarkers (5,6). Cardiac biomarkers are released during exercise, especially endurance training. However, abnormal biomarker concentrations should not be interpreted as a sign of cardiac damage or wall stress but rather as a sign of myocardial adaptation (4,5). This review describes the behavior of the main CVD-related laboratory variables that are often modified during and after exercise training. Understanding

these exercise induced responses will help exercise physiologists interpret cardiovascular data in athletes.

## Cardiovascular biomarkers

The definition of biomarker was standardized in 2001 as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (7). Thus, a biomarker may be measured in a biological sample (urine, blood, or biopsy), may be a recording obtained (e.g., blood pressure, electrocardiogram, or Holter), or may be an imaging test (echocardiogram or computed tomography scan) (2). Several different types of biomarker exist based on their characteristics and uses. The overall expectation of a CVD biomarker is that should help the clinician to optimally manage the patient (2). A new biomarker will be of clinical value only if it is accurate, can be reproducibly obtained in a standardized fashion, is acceptable to the patient, is easy to interpret by clinicians, has a high sensitivity and specificity for the outcome it is expected to identify, consistently explains a reasonable proportion of the outcome independently of established predictors in multiple studies, and there are data to suggest that knowledge of the given biomarker will modify the management strategy (8).

Although the best diagnostic approach to acute coronary syndrome and other cardiovascular disorder is still puzzling (9,10), numerous classifications exist to classify CVD biomarkers (11). Commonly, they are classified according to disease specificity such as biomarkers of heart failure [e.g., brain natriuretic peptide (BNP), N-terminal prohormone of BNP (NT-proBNP), atrial natriuretic peptide (ANP), soluble suppression of tumorigenicity (ST-2), etc.], or atherosclerotic coronary disease [e.g., troponin T or I, creatine kinase [CK], CK-myoglobin binding (CK-MB), etc.]. They can also be grouped according to the pathologic process they reflect such as inflammation (e.g., C-reactive protein, interleukin 6, fibrinogen, monocyte chemotactic protein-1, tumor necrosis factor alpha, etc.), oxidative stress (e.g., isoprostanes) or a metabolic pathway [e.g., lipoprotein (a), low-density lipoproteins, high-density lipoprotein, ApoB100, lipoprotein-associated phospholipase A2, homocysteine, vitamin D, fibroblast growth factor 23, adiponectin, glycated hemoglobin, haptoglobin, etc.]. *Table 1* shows the main biomarkers currently used in the management of CVD patients.

Until other biomarkers became available, total CK was the most widely used biomarker for a diagnosis of myocardial and musculoskeletal disorders (13). This biomarker is still used for the follow-up of subacute stage myocardial infarction, although it is not a cardiospecific molecule and its reference range varies with age, race and physical activity (14). Much more cardiospecific is its isoenzyme CK-MB (13). However, CK-MB is also found in small proportion in skeletal muscle and may be elevated during physical exercise or in certain pathological conditions such as genetic myopathy (15,16). Thus, the possible presence of background plasma circulating CK-MB activity in individuals without CVD limits its value as an indicator of myocardial necrosis.

Blood cardiac troponins (cTns T and I) are sensitive and specific markers of myocardial damage and are the 'gold standard' for the diagnosis and management of individuals who present chest pain, and/or a suspected myocardial infarction (9). The mechanism of detecting myocardial ischemia is their release in response to cardiomyocyte necrosis (11). However, elevated blood levels of both troponin T and I also occur in patients with advanced heart failure and have been used to predict heart failure or determine the prognosis of CHF (11). Levels of troponins become elevated in blood 4–12 h after the onset of chest pain (17). This may be too late for an early diagnosis of myocardial ischemia, affecting its prognosis, such that earlier markers are also needed for rapid patient assessment (9).

Myoglobin is one such marker quickly released into the blood when there is heart or skeletal muscle damage due to its low molecular weight (13). Thus, serum myoglobin concentrations rise 1–2 h after the onset of chest pain or AMI, peaking 6 and 12 h later and vanishing from the circulation from 12 to 24 h due to its rapid renal clearance. However, the limited cardiospecificity of myoglobin limits its diagnostic sensitivity (13). In contrast, proBNP is produced in response to myocardial stretching and later broken down into BNP and NT-proBNP (inactive form). Elevated blood BNP concentrations in an emergency room setting increase the likelihood of a diagnosis of heart failure, and the more stable form of BNP, NT-proBNP, is also predictive of a diagnosis of heart failure (11). A higher BNP concentration on hospital admission has also been linked to higher in-hospital mortality (11). Another biomarker, circulating ANP, is more unstable than BNP or NT-proBNP. However, MR-proANP a prohormone isolated from the mid region of the ANP molecule has shown promise as a prognostic marker of heart failure

 

**Table 1** Main cardiovascular disease biomarkers according to the pathophysiologic processes they reflect

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|---|
| Cardiomyocyte stretch |
| Brain natriuretic peptide B (BNP) |
| N-terminal prohormone of BNP (NT-proBNP) |
| Mid-regional pro-atrial natriuretic peptide (MR-proANP) |
| Growth-differentiation factor-15 (GDF-15) |
| Inflammation |
| C-reactive protein (CRP) |
| Tumor necrosis factor α (TNF-α) |
| Growth-differentiation factor-15 (GDF-15) |
| FAS (APO-1, apoptosis antigen 1) |
| Lipoprotein associated phospholipase A2 (LP-A2) |
| CHI3L1, chitinase-3-like protein 1 (YKL-40) |
| Interleukin 1 (IL-1) |
| Osteoprotegerin |
| Pentraxin |
| Procalcitonin |
| Cytokines |
| Serine protease PR3 |
| Soluble endoglin |
| Adiponectin |
| Neutrophil gelatinase-associated lipocalin (NGAL) |
| Soluble urokinase-type plasminogen activator receptor (suPAR) |
| Oxidative stress |
| Oxidized low density lipoprotein (LDL) |
| Myeloperoxidase-oxidized (MPO) |
| Urinary biopyrrins |
| Urinary and plasma isoprostanes |
| Urinary 8-hydroxyl-2'-deoxygunosine |
| Plasma malondialdehyde |
| Neurohormonal |
| Norepinephrine |
| Renin |
| Angiotensin II |
| Aldosterone |
| Arginine vasopressin (ADH) |
| Copeptin |
| Endothelin-1 |
| Urocortin |
| Chromogranin A and B |
| Mid-regional pro-adrenomedullin (MR-proADM) |
| Myocardial injury |
| Troponin T and I |
| Myosin light-chain kinase I |
| Heart-type fatty acid binding protein (H-FABP) |
| Creatine kinase-MB (CK-MB) |
| Saturated fatty acids (sFAS) |
| Heat shock protein 60 (HSP60) |
| Tumor necrosis factor-related apoptosis-inducing ligand (sTRAIL) |
| Extracellular matrix remodeling |
| Metalloproteases that degrade collagen (MMP) -2, -3, -9 |
| Metalloprotease inhibitors (TIMP1) |
| Interleukin 6 (IL-6) |
| Collagen propeptides |
| N-terminal collagen type III peptide |
| Myostatin |
| Sydecan-4 |
| Galectin-3 |

Adapted from References (11,12).

(11,18). Finally, copeptin is a stable peptide of the arginine vasopressin precursor whose elevated levels have been related to the immediate post-ischemic period and also correlated with an increased risk of death and new-onset heart failure (11).

Other biomarkers also being assessed as indicators of heart failure include osteoprotegerin (19), osteopontin (20), neutrophil gelatinase-associated lipocalin (NGAL) (21), galectin-3 (22), ST-2 and soluble ST2 (sST2) (23), adiponectin (24), neopterin (25), cardiotrophin-1 (26), glycoprotein 130 (27), mid-regional pro-adrenomedullin (MR-proADM) (28,29), growth differentiation factor 15 (GDF15) (30), and red cell width (RDW) (31).

## Cardiovascular biomarkers modified by exercise

During exercise training, the use of progressive workloads involves an increasing contribution of oxygen to skeletal muscle activity and to the activity of other systems in play during the exercise. Adaptive responses consist of modifications at the central (cardiac adaptations) and peripheral (muscular and vascular adaptations) levels, which are related to previous training, the specific conditions in which the exercise is performed, age, sex, type of exercise, fitness and the presence or absence of organic heart disease.

During a maximal exercise involving large muscle groups, energy requirements at rest may increase by more than 20-fold and cardiac output about 6-fold. This balance between cardiac output and increasing oxygen demands reaches its limit at the point of exhaustion.

Physical exercise, even exhaustive exercise (32), is recommended for the primary and secondary prevention and therapy of numerous clinical disorders including metabolic disorders, hypertension, CVD, muscle atrophy, osteoporosis, depression, Alzheimer's disease, and colon and breast cancer, among others (3,33,34). The benefits of exercise translate to metabolic adaptations that, in turn, may modify serum concentrations of several laboratory variables (5).

Laboratory abnormalities produced in response to endurance exercise (marathon runners) were first reported by Blake and Larrabee in 1903 (35). Levels of biochemical variables outside the normal range, may easily prompt further tests or even discourage further training or competition. Also, when athletes show abnormal laboratory results they will likely be warned about the dangers associated with physical activity, thus questioning the benefits of exercise (5). Abnormal levels of hematological and cardiac biomarkers found in athletes at baseline or after an acute bout of strenuous exercise are a cause of both concern and discrepancy (16,36,37). For example, some authors have reported a reduced hematocrit after a marathon (38), while others have detected no such reduction (39) or an increased hematocrit (40). Some of these discrepancies have been attributed to differences in the sampling time, participant fitness, and/or environmental conditions (41).

Kratz *et al.* [2002] published an interesting table showing the percentage of marathon runners (N=37) returning laboratory results outside the normal reference ranges quoted by the instrument manufacturers. At baseline, 11% and 89% of runners had CK-MB and myoglobin levels outside the normality range, respectively, while 4 h after the marathon, levels outside the normal range were recorded in 95% for CK-MB, 3% for troponin I and 100% for myoglobin (42).

### *Creatine kinase and CK-MB isoenzyme*

Though, as mentioned earlier, the classic cardiac biomarker CK is losing popularity because of its low specificity and variation with age, sex, race and physical activity, an increase in CK after an exercise effort has been directly related to exercise duration and intensity, and inversely related to training level (14). As its isoenzyme CK-MB occurs in small proportion in skeletal muscle, this biomarker can also increase under conditions of intense physical exercise (e.g., in marathon runners) or disease conditions such as in some genetic alterations or myopathies (15,16).

In the last stages of intense physical exercise, such as in the final kilometers of a marathon, a decline is produced in physical capacity due to energy, metabolic and psychological factors. In parallel with this decline, the activities of muscle enzymes increase due to modifications in the permeability and destruction of myofibrils (43). Increased CK levels are considered a qualitative marker of skeletal muscle microtrauma resulting from strenuous exercise, mostly after endurance events or eccentric exercise efforts (42,44). In vigorous intensity exercises, the catalytic activity of CK-MB increases in skeletal muscle, with similar effects to those produced in the myocardium. Thus, microtrauma to the myofibrils induces an increase in the catalytic activity of CK-MB in plasma or its proportion on the catalytic activity of CK as observed in the acute phase of myocardial infarction (45). When resting or after prolonged exertion, athletes show elevated CK-MB plasma concentrations, as observed in individuals suffering AMI. However, in 94% of athletes, the ratio of CK-MB concentration to total catalytic activity of CK (mg/L) is similar to that observed in non-physically active individuals, while this ratio is elevated in 100% of patients experiencing an AMI enabling distinction between the two types of situation (45).

Mean CK and CK-MB levels in physically active subjects are higher (nearly double) than those detected in sedentary individuals matched for age and sex (5,6,9,42). In four running workouts differing in terms of distance (300 *vs.* 400 m) and execution mode (continuous/single *vs.* intermittent), Saraslanidis *et al.* noted that the increase in CK produced during training was related to the work intensity and not the execution mode (46). Kratz *et al.* also reported that marathon runners had baseline CK-MB outside conventional normality values. These authors also noted increases in CK and CK-MB activity after the marathon that were unrelated to age or to the presence of cardiovascular risk factors (42).

Some of these elevated cardiovascular biomarker levels are in line with the criteria defined for CVD such as AMI. Thus, analytical results in physically active individuals need to be interpreted with caution as they may reflect an adaptation to regular training rather than an underlining disease.

 

### *NT-proBNP*

BNP is produced by cardiomyocytes in the ventricles and released into the blood in response to ventricle wall stretching. The cleaved form of the BNP precursor is NT-proBNP, which can also be measured in blood as a marker of events in which there is myocardial wall stress such as in heart failure (5). Myocardial wall stress provoked by strenuous exercise may be offset by this hormone promoting natriuresis, vasodilatation and sympathetic response inhibition.

Several studies have shown a rise in NT-proBNP levels after strenuous exercise, mostly in endurance efforts but also in short strenuous modalities (47), and this increase has been proportionally correlated with time (48-52). Banfi *et al.* detected lower NT-proBNP concentrations in mountain marathoners than in controls at rest and these lower levels were similar to those observed in professional soccer and rugby players. After the race, NT-proBNP concentrations significantly increased to levels still within the physiological range (53). Scharhag *et al.* compared baseline levels of NT-proBNP between endurance athletes and healthy untrained controls and found no differences in this cardiac biomarker (54). Lippi *et al.* detected lower NT-proBNP levels in professional cyclists than physically inactive individuals (55). Such lower levels of NT-proBNP in trained subjects can be interpreted as a physiological and potentially beneficial adaptation of the myocardium to regular physical exercise.

In ultraendurance sports modalities, increased NT-proBNP concentrations as a consequence of ventricular wall stress has been linked to concomitant elevations in GDF 15 and endoglin, both related to an oxidative endothelial response correlated with inflammation. These elevated biomarkers protect the heart, blood vessels and other tissues as they reflect a transient adaptation to strenuous exercise (56).

### *Troponins*

cTns are present in high concentrations in myocytes. The presence or elevation of these cardiac biomarkers after physical exercise does not normally indicate clinically threatening myocardial injury such as myocardial infarction. In the absence of clinical symptoms of myocardial disease, these biomarkers could rather be linked to increased cellular permeability and early troponin release as a transient and acute response to intense physical exercise (57). Their presence or elevation has also been related to a response to myocardial ischemia and development of blebs from the plasma membrane in cardiac myocytes when reoxygenation is not recovered (58,59).

In recent studies examining high sensitive (Hs) cTn, the number of individuals over-reaching the thresholds of a normal healthy population following strenuous exercise is magnified (60). Strenuous exercise such as running a marathon may induce transient elevation of cTn concentrations (61,62). Scharhag *et al.* showed that endurance athletes showed increased concentrations of both cTnI and cTnT after exercise (74% and 47%, respectively) (49). After a kettlebell class, Savukoski *et al.* noted that cTn concentrations were significantly higher than pre-exercise values and that levels returned to baseline during the three days of follow up (63). The results of a meta-analysis with 939 participants showed that only six runners had elevated prerace cTns (0.6%) while 579 runners had elevated postrace cTns (62%) (62). In a study conducted in middle-aged healthy individuals, close to 50% showed a rise in cTn levels following a bicycle maximal stress test (64). In several subjects, the cTn increase exceeded the 99th percentile of the upper reference limit thus complying with criteria for AMI (4). In a report by O'Hanlon *et al.*, elevated cTns after exercise could not be linked to alterations in cardiac function or any detectable myocardial damage, as measured by cardiovascular magnetic resonance. These authors proposed that the rise in cTns could reflect reversible cardiomyocyte membrane damage indicating a remodeling process (65). It should also be noted that normal physical activity can also provoke a cTn rise in healthy individuals as observed in response to basketball training (66,67).

### *Neutrophil gelatinase associated lipocalin (NGAL)*

NGAL, a low molecular weight protein produced by injured nephron epithelia, is a new indicator of active kidney damage and other conditions such as atherosclerosis and myocardial infarction (68,69). Lippi *et al.* examined 16 trained individuals after a 60 km ultramarathon and detected 1.6- and 7.7-fold increases in serum and urine NGAL concentrations, respectively (70). In a study by Junglee *et al.*, urine NGAL levels rose in response to exercise-induced muscle damage (crossover trial involving a 60-min downhill muscle-damaging run) after a run in the heat, compared to an exercise intensity-matched non-muscle-damaging flat run; while plasma NGAL levels were correlated with plasma interleukin-6 levels (71). The same

 

authors showed that 64% of participants (N=100) had urine NGAL concentrations above the normal range and reduced plasma NGAL concentrations 25 minutes after a high-intensity exercise (72). However, other authors detected no such difference in urine and plasma NGAL levels after a graded treadmill exercise test (73) or after high endurance physical exercise in the *Giro D'Italia* and *Tour de France* (74).

## Concluding remarks

In response to physical exercise, healthy individuals and especially athletes often show alterations in several cardiovascular biomarkers. In some subjects, biomarker levels may be as high or low as to indicate a pathological condition. We recommend that physicians should consider whether their patients were physically active around the time of a test or undergo regular physical exercise before interpreting an anomalous biomarker result.

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