Exercise-related major adverse cardiovascular events in asymptomatic recreational master athletes: a case series

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Background

In master athletes, atherosclerotic coronary artery disease (CAD) is the primary condition leading to major adverse cardiovascular events during sports. We report two cases of asymptomatic recreational athletes who suffered from an exercise-induced cardiovascular event.

Case summary

The first athlete is a 70-year-old male speed skater without known history of cardiovascular disease. He has no typical risk factors for CAD and denied preceding symptoms. During training at the speed skating rink, he suddenly experienced severe chest pain. Electrocardiogram (ECG) showed ST-segment elevation in the precordial leads. In the ambulance, an episode of ventricular fibrillation was converted to atrial fibrillation. Coronary angiography showed a thrombus in the left anterior descending (LAD) coronary artery, treated with a glycoprotein IIb/IIIa inhibitor intravenously.

The second athlete is a 59-year-old male endurance athlete who presented with chest pain during cycling. He had a history of cavotricuspid isthmus ablation and pulmonary vein isolation for paroxysmal atrial fibrillation and flutter but experienced no symptoms in the weeks prior to the event. He also had no risk factors for CAD. ECG showed ST-segment elevation in the inferior leads and reciprocal depression in V2–V4. Successful primary percutaneous intervention of the circumflex artery was performed.

Discussion

Limited data are available to guide recommendations for cardiovascular screening in master athletes. Since master athletes with CAD are often asymptomatic, more knowledge on the optimal pre-participation screening algorithm for identifying individuals at risk of adverse cardiac events is required.

Keywords

Sports cardiology • Coronary artery disease • Master athletes • Case series

ESC curriculum

3.1 Coronary artery disease • 8.1 Sports cardiology • 8.5 Primary prevention

Learning points

• In adult and senior athletes, atherosclerotic coronary artery disease (CAD) is the primary condition leading to exercise-induced major adverse cardiovascular events.

• Pre-participation screening (PPS) in master athletes should target detection of asymptomatic atherosclerotic CAD to identify individuals at risk for adverse cardiac events.

• More knowledge on the optimal PPS algorithm for identifying individuals at risk of adverse cardiac events during exercise is required.

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Introduction

The majority of sports-related deaths occur among athletes older than 35 years of age.1 Sudden cardiac events in young athletes are mainly caused by congenital, structural, and electrical disorders of the heart. In master athletes (> 35-years-old), however, atherosclerotic coronary artery disease (CAD) is the leading cause for the occurrence of major adverse cardiovascular events (MACEs).2

Timeline

| Age | CAD history | CVD risk | Sports | Clinical manifestation | Management | Follow-up |
|-----|-------------|----------|--------|-----------------------|------------|-----------|
|Case 1 | 70 | No | High cardiovascular risk (5–9%). Risk factor: age of 70 years. | Speed skating, cycling | Chest pain during speed skating with ST-segment elevation on rest ECG, episode of ventricular fibrillation | Defibrillation in ambulance, treatment with antiplatelet medication | Cardiac rehabilitation programme and return to previous sports activities. Remained symptom-free during a follow-up period of 2 years |
|Case 2 | 59 | No | Low cardiovascular risk (<5%). No CVD risk factors. | Cycling, running, swimming | Chest pain during cycling, ECG showed an inferior posterior myocardial infarction | Percutaneous coronary intervention of the coronary occlusion | Anti-arrhythmic drug therapy for paroxysmal atrial fibrillation. Return to previous sports activities. |

Exercise-induced MACE includes a variety of diagnoses, including sudden cardiac arrest, sudden cardiac death, acute coronary syndromes, transient ischaemic attacks, cerebrovascular accidents and (supra-)ventricular tachyarrhythmia’s.2 Exercise-induced MACE typically occurs during or within 24 h post-exercise. Especially, sports-related sudden cardiac arrest in middle-aged athletes is associated with CAD in more than 80%.4,5

The risk of adverse cardiovascular events during exercise increases with age due to a higher prevalence of atherosclerotic disease in those older than 35 years of age. In fact, the incidence is almost 10-fold higher in individuals >35 years old when compared with those below the age 35 years (2.1 per 100 000 person-years vs. 0.3, respectively).6 Another factor associated with an increased risk of MACE is exercise intensity. The proportion of acute myocardial infarction associated with exertion ranges from 4.4 to 13.6%.5,6 Vigorous exercise is associated with an even higher risk of acute myocardial infarction due to plaque rupture or demand ischaemia (a mismatch between myocardial oxygen supply and demand), which both could serve as a trigger for the occurrence of (fatal) ventricular arrhythmias.6,8

Pre-participation screening (PPS) has been advocated as a strategy to identify athletes with an increased risk of exercise-induced MACE. Currently, an unknown number of master athletes undergo PPS at the hospital or at sports medicine centers. For some competitions, a PPS is even mandatory to obtain eligibility. Other athletes undergo voluntary screening to evaluate their exercise capacity and to set their (heart rate) training zones and thresholds. The evidence for cardiovascular (CV) screening in master athletes is limited and concrete recommendations for asymptomatic master athletes engaged in vigorous exercise are lacking. One of the major problems associated with PPS is that it is not clear which athletes should be referred. The MASS study reported that 73% of master athletes diagnosed with CAD were asymptomatic.9 In addition, low-risk male master athletes had a higher prevalence of atherosclerotic plaques compared with sedentary men, albeit with a more benign morphology.10 However, currently screening is only recommended for symptomatic athletes or individuals with a high risk for adverse events,3 while a substantial subset of master athletes with underlying CAD does not fit these criteria. Therefore, more research is needed to determine if other subgroups could also benefit from screening.

Another problem associated with implementation of PPS is that there is insufficient research on which protocol should be used for master athletes. There is only limited data available regarding the predictive value of electrocardiogram (ECG) during PPS in master athletes, as the international criteria for ECG interpretation in athletes are solely based on studies in athletes aged 12–35 years.11,12 Routine screening for ischaemia with exercise testing in asymptomatic low-risk athletes has a low positive predictive value for detection of obstructive CAD and is associated with a high number of false-positive tests.3,13,14 However, recent studies show that a subset of the athletes with abnormal results during exercise testing does have a higher risk for MACE when compared with athletes with a normal test result.15 Therefore, it remains to be established whom and how we should screen to identify the athletes who are at risk. To illustrate this dilemma, we report two cases of recreational master athletes without typical risk factors who suffered an exercise-induced adverse event and discuss whether or not they should have been screened.

Case presentations

Case 1

A 70-year-old male athlete suddenly experienced a sudden onset of chest pain during the first part of a speed skating training. The athlete is a former soccer player and has been skating and cycling for many years for about 150 min a week, corresponding to 22.5 metabolic equivalent task (MET) hours. He had no background nor family history of cardiovascular diseases and denied having pre-existing symptoms. He is a non-smoker with a normal systolic blood pressure and a total cholesterol <6.0 mmol/L. He denied the use of any medication. Based on his age and according to the SCORE risk chart, the baseline 10-year risk of a fatal CVD event was estimated of >5%. The ECG showed marked ST-segment elevation in leads V1–V4 and aVL, and reciprocal depression in leads II, III, and aVF (Figure 1), indicating an ST-elevation myocardial infarction (STEMI) of the anterolateral wall. In the ambulance, the athlete had one episode of ventricular fibrillation, successfully treated with short-duration of cardiopulmonary resuscitation and electrical defibrillation. Upon arrival at the coronary care unit, the chest pain was already decreasing and there was resolution of the ST-segment deviation. Physical examination demonstrated a regular hearth rhythm of 78 beats per minute with a blood pressure of 117/70 mmHg, saturation of 100% with oxygen supplementation and respiratory rate of 19 per minute. On auscultation, he had normal heart sounds with no additional murmurs, and there were no abnormal lung sounds. Emergency coronary...
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**Figure 1** Case 1: Twelve-lead ambulance ECG demonstrating ST-segment elevation myocardial infarction of the anterior wall.

**Figure 2** Case 1: Coronary angiogram in right anterior oblique cranial view of the LCA. A thrombus is seen in the proximal part of the LAD (red circle).

**Figure 3** Case 2: Twelve-lead resting electrocardiogram 6 months before the exercise-related adverse event.
angiogram demonstrated a left-dominant coronary circulation with a thrombus in the left anterior descending (LAD) coronary artery (Figure 2, Supplementary material online, Video S1). Treatment with tirofiban intravenously, a glycoprotein IIb/IIIa antagonist (platelet aggregation inhibitor), was initiated for twelve hours. The interventional cardiologist decided to not place a stent during the procedure. Although this decision can be debated, it is beyond the scope of these cases’ presentation. No residual coronary stenosis were seen on a secondary angiogram. Echocardiogram showed a preserved left ventricular systolic function (LVEF >55%) with asynergy in the LAD territory. There was no significant valvular heart disease. In addition, mild bi-atrial enlargement was observed, which was considered to be a manifestation of sports adaptation. No previous ECG or echocardiogram was available. During admission, there was one episode of atrial fibrillation with spontaneous conversion to sinus rhythm. After discharge, the athlete participated in a 12-week cardiac rehabilitation programme as part of standard care. After completion of his cardiac rehabilitation programme, he started skating and cycling again and remained free of symptoms during a follow-up period of 2 years.

Case 2
A 59-year-old recreational male athlete presented with an STEMI during cycling. He exercises several times a week for a total of 1200 min, including running, cycling and swimming (160 MET hours). The athlete has a low cardiovascular risk (<5% according to the SCORE risk chart) based on his age, normal systolic blood pressure, total cholesterol of 5.55 mmol/L and the fact that he is a non-smoker. Six months earlier, his ECG demonstrated sinus rhythm, ventricular rate 48 b.p.m., with a normal heart axis, normal conduction intervals, no repolarization abnormalities, and no pathological Q waves (Figure 3), which is considered normal for an athlete according to current international expert consensus.11 His medical history revealed paroxysmal atrial fibrillation and flutter for which a combined pulmonary vein isolation and cavotricuspid isthmus ablation successfully was performed five years before his cardiovascular event. Prior cardiac evaluation, including ECG and echocardiography, demonstrated no cardiac abnormalities. After he experienced persistent chest pain while exercising for about ten minutes, the ECG in the ambulance (Figure 4) showed normal sinus rhythm with ST-segment elevation in lead II, III, aVF, reciprocal depression in V2–V4 and T-wave inversion in aVL. Physical assessment was unremarkable and vital signs in the emergency department were: heart rate 52 beats per minute, blood pressure 153/90 mmHg, oxygen saturation of 99% in ambient air and temperature 36.9°C Celsius. Coronary angiography demonstrated a distal occlusion of the circumflex artery (Cx) and a stenosis in the mid segment of the LAD (Figure 5, Supplementary material...
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Successful percutaneous coronary intervention (PCI) of the Cx was performed to treat the acute inferior posterior myocardial infarction (Figure 6, Supplementary material online, Video S3). A second coronary angiography was performed for PCI of the residual lesion in the LAD. The echocardiogram showed a preserved left ventricular systolic function (LVEF 60%) without any wall motion abnormalities. Atrial and ventricular dimensions were normal. Submaximal exercise testing four weeks after the myocardial infarction did not show ischaemia. During follow-up and after starting flecainide (Class IC anti-arrhythmic) for paroxysmal atrial fibrillation, a cardiopulmonary exercise test was performed nine months after the cardiac event, demonstrating a high maximum oxygen uptake (43.2 mL/min/kg, 121% of predicted). Resting and exercise ECG showed no ischaemia nor arrhythmias. During follow-up, the athlete complained of repeated symptoms suggestive of paroxysmal atrial fibrillation, similar to the symptoms he also had regularly before. Several anti-arrhythmic drugs failed to maintain sinus rhythm or caused side effects. Although there is an increased risk with the use of flecainide in patients with ischaemic

Figure 6 Case 2: Coronary angiogram in right anterior oblique caudal view of the LCA. Restoration of flow after stenting the occlusion of the distal part of the RCx.

Figure 7 Proposed ESC algorithm for cardiovascular assessment in asymptomatic individuals aged >35-years-old with risk factors for cardiovascular disease and possible subclinical chronic coronary syndrome before engaging in sports. *Consider functional test or CCTA if exercise stress test is equivocal or the ECG is uninterpretable. CVD = cardiovascular disease; ECG = electrocardiogram; SCORE = Systematic Coronary Risk Evaluation.
heart disease according to current guidelines and previous trials, it was presumed to be save to start given the time frame after revascularisation, a normal left ventricular function on recent echocardiography and no other therapeutic options. After shared decision making and given previous good results, there was chosen to restart flecainide under closed supervision.

**Discussion**

This report describes the cases of two recreational master athletes who suffered from a myocardial infarction during exercise. Both athletes had no history of CAD and denied having pre-existing symptoms suggestive for cardiac disease. An imminent question is whether PPS potentially could have prevented these cardiovascular events.

In line with the current guideline, the athlete from Case 2 had a low cardiovascular risk (<5%) and was not selected for PPS (Figure 7). The athlete from Case 1 should have been screened based on a high risk (5–9%) according to the SCORE chart, mainly driven by his age, and the proposed algorithm for cardiovascular assessment in asymptomatic individuals aged 35-years-old.

The most recent ESC guideline ‘Sports cardiology and exercise in patients with cardiovascular disease’ published in 2020 states that data are insufficient to provide specific recommendations for screening in master athletes. In both cases, the cardiac event was the first manifestation of CAD without any prior symptoms. This is in line with the Master Athlete Screening Study, where symptoms were reported in only 27% of the participants diagnosed with obstructive CAD. An explanation for this finding may be that athletes have an altered pain perception and modulation when compared with non-athletes. For instance, endurance-based sport is associated with improved pain inhibition. This might play a role in the clinical presentation of these athletes and raises the question whether this should be taken into account in establishing screening criteria for master athletes. In addition, this warrants a thorough evaluation of other signs than traditional symptoms that may indicate (subclinical) CAD. As such, a case-control study in Dutch athletes showed that a recent episode of fatigue or flu-like symptoms was associated with an increased risk of MACE, indicating that a focus on (slight) changes in exercise capacity could be more predictive than the traditional symptoms only. To our knowledge, this has not yet been sufficiently investigated, and new methods should need to be developed to investigate this.

For PPS strategies to be effective, it is crucial that only athletes are selected with the highest risk at MACE. Selection criteria, as mentioned previously, now only include symptoms or a risk evaluation for possible subclinical chronic coronary syndrome by the SCORE chart. An important limitation of this strategy is that it does not identify individuals with, for instance, mild to moderate atherosclerotic plaques. It is shown that these individuals also have a higher risk of myocardial infarction during exercise. This can be explained by the fact that oxygen demand by the contracting myocardium substantially increases during heavy physical exercise, causing an imbalance between oxygen demand and supply, leading to myocardial ischaemia and, subsequently, to cardiac arrest or sudden cardiac death. When looking at the mechanism of oxygen demand during vigorous exercise, exercise intensity, and environmental factors are important determinants. Therefore, we postulate that exercise intensity, the total training volume and type of training and sport are important aspects to consider when deciding whether a master athlete should be screened. The RACER study group showed that the incidence of cardiac arrest during running was significantly higher during marathons than during half-marathons. Most events occurred during the last quartile of the race. In addition, exercising circumstances should be taken into account. Exertion at altitude and in abnormal/extreme weather conditions can put more strain on the cardiovascular system. The aforementioned factors are currently not considered in the selection of athletes.

Another question is whether the use of the ESC SCORE system adequately identifies the athletes with a substantial increased risk for MACE. The widely used SCORE risk assessment predicts fatal atherosclerotic cardiovascular disease (CVD) events over a 10-year period. This chart is based on the risk factors age, gender, smoking, systolic blood pressure and total cholesterol. Individuals with a risk of more than 5% at a fatal CVD during the next 10 years are identified as high-risk subjects. According to this model, athletes below the age of 50 years hardly can be classified as high-risk. However, the MASS study showed that 50% of athletes with significant CAD were not classified as high-risk. This clearly demonstrates that efforts should be made to develop more sophisticated models to predict the risk at MACE specifically in master athletes. For instance, every athlete >35 years is considered to be a master athlete. However, it is known that with increasing age, the risk of any MACE is substantially increased in normal individuals. Therefore, dividing master athletes in age groups (35–50 and 50–75 years of age for instance) could be of help to distinguish which cause for MACE is most imminent.

Besides establishing appropriate selection criteria, the contents of PPS screening programmes is an important determinant of the success. The current guideline recommends a physical examination, 12-lead ECG and exercise stress test for sedentary individuals and/or those at high or very high-risk planning to undertake high-intensity exercise, as well as selected individuals planning to undertake moderate-intensity exercise. It is well known that a standardized exercise test is not the right screening modality to detect CAD in low-risk and asymptomatic athletes. There are other diagnostic methods to screen for subclinical CAD, such as computed tomography (CT) with or without contrast or myocardial perfusion scintigraphy (MPS). However, it would not be cost effective to screen every master athlete with these invasive tests. The development of new non-invasive and non-radiation methods and screening algorithms would help to improve PPS in master athletes. There could be a role for more continuous monitoring, preferably in the home-setting, with wearable sensors. Currently, no validated techniques for long-term mobile ischaemia detection are yet available, but this could be of potential added value. Particularly in athletes, monitoring of cardiac performance during activities in free-living conditions could lead to a higher diagnostic yield as exercise intensity and duration and environmental factors are also taken into account.

This case series of two asymptomatic athletes demonstrates the importance of increasing knowledge about the optimal criteria and methods for PPS to identify master athletes at risk of MACEs. As more and more master athletes are participating in endurance and competitive sports, the incidence of exercise-related myocardial infarction, sudden cardiac arrest and sudden cardiac death is expected to increase.

**Lead author biography**

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**Supplementary material**

Supplementary material is available at European Heart Journal – Case Reports online.
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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for the submission and publication of this case series including images and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: None declared.

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References

1. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. J Am Coll Cardiol 1986;7:204–214.
2. Eckart RE, Shry EA, Burke AP, McNear JA, Appel DA, Castillo-Rojas LM, Avedissian L, Pease LA, Potter RN, Tremaine L, Gentleski PJ, Huffer L, Reich SS, Stevenson WG. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol 2011;58:1254–1261.
3. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Peters RJG. ECG Criteria for the detection of high-risk cardiovascular conditions in master athletes. Eur J Prev Cardiol 2020;27:1529–1538.
4. Marijon E, Uy-Evanado A, Reinier K, Teodorescu C, Narayanan K, Jouven X, Gunson K, Jui J, Chugh SS. Sudden cardiac arrest during sports activity in middle age. Circulation 2015;131:1384–1391.
5. Bendicková J, de Beus MF, Blom M, Bardai A, Bots ML, Doevendans PA, Groobbee DE, Tan HL, Tijssen JGP, Koster RW, Mosterd A, Exercise-related out-of-hospital cardiac arrest in the general population: incidence and prognosis. Eur Heart J 2021;42:17–96.
6. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. J Am Coll Cardiol 1986;7:204–214.
7. Smyth A, O’Donnell M, Lamelas P, Teo K, Rangarajan S, Yusuf S. Physical activity and anger or emotional upset as triggers of acute myocardial infarction: the INTERHEART study. Circulation 2016;134:1059–1067.
8. Ruscioni F. Triggering of sudden death from cardiac causes by vigorous exertion. Ital Heart J Suppl 2001;2:324–326.
9. Morrison BN, McKinney J, Iserow S, Lethwick D, Taunton J, Nazari D, De Souza AM, Heilbron B, Cater C, MacDonald M, Hiles BA, Warburton DER. Assessment of cardiovascular risk and preparticipation screening protocols in masters athletes: the masters athlete screening study (MASS): a cross-sectional study. BMJ Open Sport Exerc Med 2018;4:e000370.
10. Merghani A, Maestrini V, Rosmini S, Cox AT, Dhuita H, Bastaenaa R, David S, Yeo T, Narain R, Malhotra A, Papadakis M, Wilson MG, Tome M, AliFakhk M, Moon JC, Sharma S. Prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile. Circulation 2017;136:126–137.
11. Drezner JA, Sharma S, Bagghish A, Papadakis M, Wilson MG, Prutkin JM, Gerche A, Ackerman MJ, Börjesson M, Salsano JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Sarael S, Schmied CM, Shippin DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International criteria for electrocardiographic interpretation in athletes: consensus statement. Br J Sports Med 2017;51:704–731.
12. Panhuysen-Goedkoop NM, Wellens HJ, Verbeek ALM, Jørstad HT, Smeets JRLM, Peters RJG. ECG Criteria for the detection of high-risk cardiovascular conditions in master athletes. Eur J Prev Cardiol 2020;27:1529–1538.
13. Mont L, Pelliccia A, Sharma S, Abar B, Börjesson M, Brugada Terradellas J, Carré F, Guasch E, Heidbuchel H, La Gerche A, Lampert R, McKenna W, Papadakis M, Priori SG, Scamavacca M, Thompson P, Stichler C, Viskin S, Wilson M, Corrado D; Reviewers Lip GY, Gorenek B, Bloemström Lundqvist C, Merkely B, Hindricks G, Hernández-Madrid A, Lane D, Boriani G, Narasimhan C, Marquez MF, Haines D, Mackall J, Manuel Marques-Vidal P, Corra U, Halle M, Tiberi M, Niebauer J, Piepoli M. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by AFHRS, HRS, and SOLAECE. Eur J Prev Cardiol 2017;24:41–69.
14. Parry-Williams G, Gati S, Sharma S. The heart of the ageing endurance athlete: the role of chronic coronary stress. Eur Heart J 2021;42:2737–2744.
15. van de Sande DAP, Barneveld PC, Hoogsteen J, Doevendans PA, Kens MHC. Coronary microvascular function in athletes with abnormal exercise test results. Neth Heart J 2019;27:621–628.
16. Tesarz J, Schuster AK, Hartmann M, Gerhardt A, Eich W. Pain perception in athletes compared to normally active controls: a systematic review with meta-analysis. Pain 2012;153:1253–1262.
17. Assa T, Geva N, Zarikh Y, Defrin R. The type of sport matters: pain perception of endurance athletes versus strength athletes. Eur J Pain 2019;23:686–696.
18. van Teeffelen WM, de Beus MF, Mosterd A, Bots ML, Mosterd WL, Pool J, Doevendans PA, Groobbee DE. Risk factors for exercise-related acute cardiac events. A case-control study. Br J Sports Med 2009;43:722–725.
19. Lippi G, Favaloro EJ, Sanchis-Gomar F. Sudden cardiac and noncardiac death in sports: epidemiology, causes, pathogenesis, and prevention. Semin Thromb Hemost 2018;44:780–786.
20. Kim JH, Malhotra R, Chiampas G, d’Hemecourt P, Troyanos C, Gianja J, Smith RN, Wang T, Roberts WO, Thompson PD, Bagghish AL. Cardiac arrest during long-distance running races. N Engl J Med 2012;366:130–140.
21. Bartsch P, Gibbs JSR. Effect of altitude on the heart and the lungs. Circulation 2007;116:2191–2202.
22. González-Alonso J, Crandall CG, Johnson JM. The cardiovascular challenge of exercising in the heat. J Physiol 2008;586:45–53.
23. Ikäheimo TM. Cardiovascular diseases, cold exposure and exercise. Temperature 2018;5:123–146.