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Benda, NM, Hopman, MT, van Dijk, AP, Oxborough, D, George, KP, Thijssen, DHJ and Eijsvogels, TM (2016) Impact of prolonged walking exercise on cardiac structure and function in cardiac patients versus healthy controls. EUROPEAN JOURNAL OF PREVENTIVE CARDIOLOGY. ISSN 2047-4873

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**IMPACT OF PROLONGED WALKING EXERCISE ON CARDIAC STRUCTURE
AND FUNCTION IN CARDIAC PATIENTS *VERSUS* HEALTHY CONTROLS**

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Short title: Post-exercise cardiac function in cardiac patients

WORD COUNT: 3322

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ABSTRACT

Background and design. Previous studies have demonstrated that endurance exercise can cause an acute transient decrease in cardiac function in healthy subjects. Whether this also occurs in cardiac patients is unknown. We investigated the impact of prolonged single day and 3-day walking exercise on cardiac function and cardiac biomarkers between cardiac patients and healthy controls in an observational study.

Methods. We recruited 10 cardiac patients (9 males, 1 female, 68 ± 5 yrs) and 10 age- and sex-matched healthy control subjects (9 males, 1 female, 68 ± 4 yrs) to perform 30 or 40 km of walking exercise per day for 3 subsequent days. Cardiac function was examined using echocardiography and cardiac biomarkers (cardiac troponin and B-type natriuretic peptide) with blood samples. Data was collected before walking and directly after walking on day 1 and 3.

Results. Post-exercise early systolic tissue contraction velocity of the left ventricle (LV) ($P=0.005$) and global longitudinal LV strain ($P=0.026$) were increased in both groups compared to baseline. Post-exercise right ventricle peak early diastolic tissue filling velocity and systolic blood pressure/LV end-systolic volume ratio decreased in both groups ($P=0.043$ and $P=0.028$), respectively). Post-exercise cardiac troponin levels increased ($P=0.045$) but did not differ across groups ($P=0.60$), whereas B-type natriuretic peptide levels did not change ($P=0.43$).

Conclusion. This study suggests that stable cardiac patients are capable of performing 3 days of prolonged walking exercise without clinically significant acute overall deterioration in cardiac function or more pronounced increase in cardiac biomarkers compared to healthy controls.

ABSTRACT WORD COUNT: 243

KEY-WORDS: endurance exercise, heart failure, echocardiography, cardiovascular disease

ABBREVIATIONS

LV	left ventricle
RV	right ventricle
SBP	systolic blood pressure
DBP	diastolic blood pressure
BSA	body surface area
LVEF	left ventricular ejection fraction
LVEDV	left ventricular end-diastolic volume
LVIDd	end-diastolic left ventricular diastolic internal diameter
LVESV	left ventricular end-systolic volume
SBP/ESV	ratio of systolic blood pressure to left ventricular end-systolic volume
E	peak flow velocity of the early rapid filling wave at the mitral leaflet tips
A	peak flow velocity of the late filling wave at the mitral leaflet tips
Em	peak annular tissue velocity during early filling
Am	peak annular tissue velocity during late diastolic atrial contraction
Sm	peak annular tissue velocity during systole
TDI	tissue Doppler imaging
cTnI	cardiac troponin I
BNP	B-type natriuretic peptide

INTRODUCTION

Cardiovascular diseases are a major health problem, associated with a large disease burden and high mortality rates [1]. Exercise is an important component in the prevention and treatment of cardiac diseases [2, 3]. More specifically, regular exercise is recommended in the current guidelines for the rehabilitation of cardiac patients [4, 5, 6]. Improvements in physical fitness are associated with reduced risks for future cardiac events and mortality in these patients [7, 8].

Despite the long-term clinical benefits of an active lifestyle,[2, 3] multiple studies have described an acute transient decline in cardiac function after bouts of prolonged exercise in healthy subjects [9, 10, 11, 12]. This response has been reported for indices of systolic and diastolic function, in both the left ventricle (LV) and right ventricle (RV), with a recent suggestion that alterations in RV function may precede changes in LV function [12]. In addition, elevated cardiac troponin (cTn) and B-type natriuretic peptide (BNP) levels, biomarkers of cardiac cell injury and cardiac stretch respectively [13, 14], are also reported after prolonged exercise [15, 16]. To date, studies of these phenomena have typically focused on athletes and healthy subjects. Whether bouts of endurance exercise result in acute changes in cardiac function or biomarkers of cardiac damage/stretch in subjects with an *a priori* impaired cardiac function is currently unknown.

The aim of this study was to compare the impact of single or multiple days of prolonged (>6-h) walking exercise on cardiac function and cardiac biomarkers between cardiac patients diagnosed with an impaired left ventricular function and healthy age- and sex-matched controls. We hypothesised that exercise leads to a greater acute decline in cardiac function and larger elevation of cardiac biomarkers in cardiac patients compared to healthy controls, and that these changes are more pronounced after 3 days of prolonged walking.

METHODS

Subjects

All subjects participated in an annual walking event (Nijmegen Four Day Marches) in which participants walk 30 or 40 km per day on 4 consecutive days. Ten cardiac patients with left ventricular systolic dysfunction were recruited through an electronic questionnaire among participants of the Nijmegen Four Day Marches. The inclusion criteria were a clinical history of cardiac disease including a history of an impaired left ventricular ejection fraction (LVEF <55%) measured during echocardiography. After inclusion of 10 cardiac patients, we recruited 10 healthy age- and sex-matched controls. Subjects in the healthy control group were free from (a history of) cardiovascular and cerebrovascular diseases and did not use cardiovascular medication. Ethical approval for this study was obtained from the Independent Review Board Nijmegen. This study conforms with the principles outlined in the declaration of Helsinki. All subjects provided written informed consent prior to participation.

Experimental protocol

Prior to participation, medical records were obtained for the cardiac patients from their cardiologists. Data was collected at baseline (1 day before the start of the walking event), and directly after walking day 1 and 3 of the event. At baseline, we examined cardiac function using echocardiography, a blood sample for assessment of cardiac biomarkers, and anthropometric and blood pressure data. After finishing the walking exercise on day 1 and day 3, we repeated cardiac ultrasound measurements within 30-minutes post-exercise. Furthermore, post-exercise blood samples were collected. During exercise, we continuously measured heart rate and the metabolic equivalents of task in all subjects.

Measurements

At baseline, height and weight were measured to calculate body mass index (BMI) and body surface area (BSA) [17]. A 4-point skin fold measurement (biceps, triceps, sub-scapular, supra-iliac) was done to estimate body fat percentage [18]. Finally, waist circumference was measured midway between the lower rib margin and iliac crest, and hip circumference was measured at the level of widest circumference over the greater trochanters, to determine waist-to-hip ratio.

Exercise characteristics

Heart rate was monitored continuously during walking with a heart rate monitor (Polar Electro Oy, Kempele, Finland), wore around the chest. Mean heart rate during exercise was expressed as a percentage of the maximal predicted heart rate [19] to indicate exercise intensity. Walking speed was calculated from walking duration and walking distance. An activity monitor (SenseWear Pro3 Armband, SWA, Body Media) was used to assess the metabolic equivalents of task (METs) during the walking march.

Echocardiographic measurements

A comprehensive transthoracic echocardiographic examination was performed by 3 experienced sonographers. All participants were examined by the same sonographer on the different test days to minimize inter-operator variability. Echocardiography was performed with a 1.6 to 4 MHz multi-frequency phased array probe on a portable ultrasound system (Vivid Q, General Electric (GE) Medical, Horten, Norway). Images of 3-5 cardiac cycles during end-expiration with breath-holding (avoiding Valsalva maneuver) were recorded digitally on a disc and analysed post-hoc with EchoPAC software (version 113, GE Medical, Horten, Norway). Measurements were performed according to current guidelines of the American Society of Echocardiography [20]. All parameters relating to cardiac structure are

also expressed relative to BSA. Prior to the cardiac ultrasound, subjects were given a 10-minute supine rest after which blood pressure and heart rate were measured.

Estimates of preload. Left ventricular end-diastolic volume (LVEDV) was determined from the 2-dimensional echocardiograms in the apical 4- and 2-chamber views using the biplane Simpson's method. End-diastolic left ventricular diastolic internal diameter (LVIDd) was measured in the parasternal long axis. We determined the ratio of the peak mitral flow velocity during early filling (E) and peak mitral septal and lateral annular tissue velocity during early filling (Em), as a surrogate parameter of left atrial pressure. An average of both sites is presented (E/Em).

LV systolic function. We estimated LV ejection fraction from LVEDV and LV end-systolic volume (LVESV) using biplane data by $((LVEDV-LVESV)/LVEDV)*100\%$. The ratio of systolic blood pressure to ESV was determined (SBP/ESV). We obtained pulsed-wave tissue Doppler imaging (TDI) measurements of peak systolic annular tissue velocities at the septal and lateral mitral annulus from apical 4 chamber images. An average of both sites is presented (SmLV).

LV strain. Two-dimensional images of the apical LV 4 chamber and 3 chamber view were obtained. Images were optimised for speckle tracking by keeping the frame-rate between 60-90 Hz, adjusting imaging dept and focal zone for optimal images. Images of the apical 4 chamber view was post-processed by a single experienced reader (AvD) using EchoPAC software (version 113). Aortic valve closure was marked, relative to the QR beginning of the QRS-complex, using pulsed-wave Doppler from apical 3 chamber view. By manual end-systolic endocardial border tracing, the region of interest was determined and adjusted to include the LV wall. The software calculated the average global longitudinal strain from all myocardial segments. Segments judged to be of poor tracking quality, also after readjustment of the region of interest, were excluded.

LV diastolic function. To examine diastolic function we measured standard LV inflow pulsed-wave Doppler at the mitral leaflet tips. These measurements included peak flow velocity of the early rapid filling wave (E) and peak flow velocity of the late filling wave due to atrial contraction (A). From these parameters we calculated the E/A ratio. From TDI measurements, we obtained peak early diastolic mitral annular tissue velocity (EmLV), and peak late diastolic mitral annular tissue velocity during atrial contraction (AmLV), for the septal and lateral annulus. An average of both sites is presented.

RV systolic function. Peak systolic tricuspid lateral annular tissue velocity was measured by placing the pulsed-wave sample in the lateral aspect of the tricuspid annulus. Care was taken to ensure longitudinal movement was in line with the ultrasound beam.

RV diastolic function. Using the same approach, peak tricuspid lateral annular tissue velocities during early diastole (EmRV) and during atrial contraction (AmRV) were recorded as indices of RV diastolic function.

Cardiac biomarkers

Cardiac troponin I (cTnI) levels and BNP levels were assessed from repetitive venous blood samples. The samples were analysed using high-sensitive cTnI-assays (ADVIA Centaur TnI-ultra, Siemens Healthcare diagnostics, The Hague, the Netherlands) and BNP-assays (ADVIA Centaur, Siemens Healthcare diagnostics, The Hague, the Netherlands). The detection limit of the cTnI-assay was 6 ng/L, and the coefficient of variation was 5.3% at 80 ng/L. The detection limit of the BNP-assay was 2 pg/mL, and the coefficient of variation was 4.7% at 29.4 pg/mL.

Statistical analysis

No previous study examined the impact of prolonged exercise on cardiac function in cardiac patients. Therefore, no data was available to perform a sample size calculation. Hence, we decided to include 10 cardiac patients and 10 age- and sex-matched controls in this explorative, observational study. Statistical analysis was done using IBM SPSS Statistics 20.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). Parameters were checked for normality using a Kolmogorov-Smirnov test. When parameters were not normally distributed, a non-parametric alternative was used. Baseline characteristics of both groups were compared with an independent-samples *t*-test. Echocardiographic variables and cardiac biomarkers were analyzed with a 2-way linear mixed model analysis, with 'time' (baseline, day 1, day 3) and 'group' (cardiac patients, controls) as factors in the model. Troponin and BNP data underwent natural logarithmic transformation before analysis. Due to the presence of values of zero, to which natural logarithmic transformation cannot be applied, all troponin and BNP data were increased with the value 1 before natural logarithmic transformation was performed. Continuous variables are presented as mean \pm standard deviation (SD), unless stated otherwise. Significance level was set at $P < 0.05$.

RESULTS

Subject characteristics

Age, sex, body characteristics, baseline blood pressure and resting heart rate were not different between groups (Table 1). Medication use of the cardiac patients included: beta-blockers (9/10), diuretics (6/10), statins (5/10), angiotensin converting enzyme inhibitors (6/10), antiplatelet drugs (4/10), angiotensin II receptor antagonists (3/10), coumarin derivatives (4/10), and anti-arrhythmic drugs (1/10). Three of the 6 patients that used diuretics did not use this medication during the days of exercise. Control subjects did not use medication. Aetiology of the cardiac disease was ischaemic heart disease (5/10, myocardial

infarction (n=3) or coronary artery disease (n=2)), idiopathic dilated cardiomyopathy (3/10) and severe mitral valve insufficiency (1/10), and multi-factorial (1/10, ischemic heart disease and mitral valve insufficiency). Some patients reported an intra-cardiac device (6/10). Six patients were classified by their cardiologist with heart failure. Cardiac patients walked 5±5 hours a week, performed 12±17 hours per week of household activities and exercised for 4±4 hours a week. Control subjects walked 5±6 hours per week, performed household activities for 18±15 hours a week and exercised for 4±3 hours a week. All habitual physical activity parameters did not differ between groups ($p>0.05$).

Exercise characteristics

All subjects completed the walking event. In both groups, 8 subjects walked 30 km/day and 2 subjects walked 40 km/day. Controls reported a higher absolute and relative heart rate during exercise, whilst walking duration, walking speed and METs were comparable between groups (Table 2).

Cardiac function All subjects were in normal sinus rhythm as determined by the monitoring ECG inherent to the ultrasound machine. Post-exercise heart rate was higher compared to baseline in both groups ($P=0.001$, Table 3). Both groups demonstrated a significantly lower systolic (SBP) and diastolic blood pressure (DBP) after exercise compared to baseline (SBP: $P<0.001$; DBP: $P=0.001$; Table 3). SmLV increased post-exercise to the same extent in both groups ($P=0.005$, Table 3). We observed a significant improvement in global longitudinal LV strain after day 1, but not after day 3, in both patients and controls ($P=0.026$, Table 3). After repeated exercise, SBP/ESV ratio decreased in both groups ($P=0.028$, Table 3). Exercise resulted in a decrease in EmRV after walking day 3 for both groups ($P=0.043$, Table 3).

Cardiac biomarkers

Cardiac patients reported higher cTnI and BNP levels compared to controls at baseline and post-exercise on day 1, 2 and 3. Prolonged walking resulted in a significant increase in cTnI levels in both groups ($P=0.045$, Figure 1A). Prolonged walking did not change BNP levels in both groups (Figure 1B).

DISCUSSION

To our knowledge, this is the first study to investigate the effects of single and/or repeated exercise on cardiac function in cardiac patients compared to healthy age- and sex-matched controls. We report a number of novel observations. First, we demonstrate that single or repeated walking exercise does not impair LVEF or LV strain, whilst a small decrease in SBP/ESV ratio and RV diastolic filling is observed after 3 days of walking. Secondly, exercise induced a significant increase in cTnI, but not BNP, after walking. Most importantly, we found that cardiac patients and healthy controls demonstrate comparable exercise-induced changes when exploring the acute impact of prolonged walking exercise on cardiac function and cardiac biomarkers. These data emphasise that cardiac patients are well capable of performing strenuous, prolonged walking exercise, even when performed repeatedly (i.e. 3 consecutive days), without evidence for a larger impact on cardiac function or cardiac biomarkers compared to their healthy peers.

A post-exercise decrease in LV function in healthy volunteers after prolonged, strenuous exercise is reported in previous studies [9, 10, 11]. Moreover, Middleton *et al.* demonstrated a cumulative decrement in LV systolic function after repeated running exercise [21]. Although the post-exercise decrease in SBP/ESV ratio suggests a decrease in contractility, we found no

decrease in LVEF after 1 day or 3 days of walking 30-40 km. Moreover, we demonstrated a small increase in other parameters of LV systolic function (i.e. LV strain and SmLV) as previously described [22]. Therefore, we found no evidence of an overall decline in LV function after exercise. Heart rate was higher after exercise compared to baseline levels, which may have influenced cardiac function parameters. However, a previous animal study demonstrated that a higher heart rate does not lead to an increase in longitudinal strain [23], accordingly, we believe that the increased heart rate after exercise in our study does not importantly influence our outcome measures. The absence of an exercise-induced decrease in overall LV function might relate to the relatively low intensity of walking exercise (54-68% of maximal estimated heart rate), as most previous studies included exercise with higher intensity such as long-distance running (84% of maximal heart rate [21]) or cycling (71-76% of maximal heart rate [24]).

The absence of a change in LV function in our study was seen in controls as well as cardiac patients. This indicates that an *a priori* impairment in LV function does not necessarily relate to an exercise-induced change in LV function. An explanation for the comparable exercise-induced changes in cardiac patients and controls may relate to the comparable training status (control: 575±711 *versus* cardiac patients: 699±687 walking kilometers in the previous year, P=0.57) and similar exercise duration of the two groups (control: 7±2h *versus* cardiac patients: 8±1h, P=0.60). These factors, training status and exercise duration, have previously been associated with a decrease in LV systolic function after exercise [11]. Taken together, we reject our hypothesis as data from this study show that an *a priori* impaired LV function is not associated with a (larger) decrease in LV function after prolonged walking exercise.

Due to a relatively large increase in RV afterload during exercise, the hemodynamic demand placed on the RV is larger than the demand placed on the LV [12]. Indeed, some studies indicate that the RV function is more prone to (early) exercise-induced changes, and these RV-changes may precede changes in LV function [25, 26]. Whilst we demonstrated a small decrease in RV diastolic function, similar to previous literature [27], it was only observed after 3 days of prolonged walking exercise. This suggests the presence of a small but statistically significant cumulative effect of exercise on RV diastolic function. However, not all RV indices were diminished, as we did not find a decrease in RV systolic function. These findings can be related to the relatively low exercise intensity and corresponding smaller increase in heart rate and blood pressure during walking exercise compared to running or cycling activities like performed in previous work [25, 26]. Our study thus confirms earlier reports in healthy volunteers of a small decrease in RV diastolic function after prolonged exercise [27], whilst RV systolic function remains unaffected.

An increase in cTnI after prolonged walking exercise was seen in both of our groups. The exercise-induced increase in cTnI in our study was not accompanied by an increase in BNP. Previously, it has been suggested that patients with cardiovascular diseases or associated risk factors are more likely to demonstrate an increase in cTnI in response to prolonged exercise [28, 29]. Although baseline cTnI and BNP levels were higher in cardiac patients, the relative change after exercise was not different between our patients and controls. A factor contributing to this finding might be the similar exercise intensity (measured in METs and walking speed) and exercise duration in cardiac patients and controls, considering that these are important parameters in exercise-induced biomarker release [30, 31]. Since the exercise-induced increase in cTnI is not accompanied by significant changes in cardiac function, we suggest that the changes in cTnI most likely does not reflect considerable cardiac damage,

which is also in line with the current theory on exercise-induced increase in troponin levels [32].

Clinical relevance. Absence of impairment in cardiac function in cardiac patients after exercise is clinically relevant as lifelong, regular (3-5 times a week) physical activity, in various forms, represents a cornerstone of contemporary cardiac rehabilitation [4, 5, 33]. Moreover, regular exercise at moderate-intensity, such as walking, is recommended in recent guidelines for cardiac patients [5, 33]. Since exercise is recommended for cardiac patients, it is not uncommon for these patients to participate in exercise events such as walking marches. Characteristic in these marches is that exercise is performed for several hours and, often, on consecutive days. Our observations suggest that walking exercise represents a safe type of exercise, even when performed for multiple hours and on consecutive days, and is not related to a significant impairment in cardiac function or excessive biomarker response.

Limitations. The number of participants in this study was small and heterogeneous in etiology of heart disease. This may increase the chance for statistical errors and influences the generalizability of the results of this study. Moreover, due to the lack of previous data on cardiac function after endurance exercise in cardiac patients, a sound sample size calculation could not be performed. Therefore, this study should be considered as a pilot-study that may be a base for future studies. Participants of this study were recruited through self-administered questionnaires. Whilst in the patient group the medical history was confirmed through records of their cardiologists, we did not exclude the presence of cardiovascular disease in control subjects. Therefore, it is possible that the controls had some degree of (latent or silent) cardiovascular disease. Moreover, cardiac patients included in this study do not represent the general cardiac patient population as they were (highly) physically active and capable of

performing prolonged walking exercise. Therefore, extrapolation of our results to all cardiac patients is difficult. Also, we should be cautious in extrapolating our results towards the (long-term) safety of prolonged walking exercise in cardiac patients. Furthermore, we were not able to measure pulmonary artery pressure during or after exercise. Exercise increases pulmonary artery pressure and hereby the right ventricular afterload, and this can have a significant effect on right ventricular function [12]. It is possible that the pulmonary artery pressure will rise more significantly during exercise in patients with *a priori* attenuated left ventricle function. Future studies might further address this issue in healthy subjects and cardiac patients. Finally, some of the medication used by the patients affects the cardiac response to exercise, such as the use of β -blockers that attenuate heart rate during exercise. This explains that cardiac patients, whilst performing exercise at similar intensity (i.e. walking speed and METs), demonstrate a lower heart rate during exercise. Moreover, angiotensin converting enzymes inhibitors may affect blood pressure response to exercise. Nonetheless, we believe that our design to continue this medication is clinically relevant as this represent the normal situation for these patients. Furthermore, as parameters of preload demonstrate similar changes after exercise between cardiac patients and controls, we believe medication use of the patients did not alter the main findings of our study.

Conclusion. Repeated prolonged walking exercise did not significantly impair overall cardiac function in cardiac patients or controls directly after exercise. Both groups demonstrated a subclinical decrease in left ventricular contractility and right ventricular early diastolic filling and an increase in cTnI levels after repeated bouts of exercise, without having significant negative consequences for the LVEF and LV strain. Interestingly, these findings were similarly present in both groups. This suggests that stable cardiac patients are capable of performing (3 days of) prolonged walking exercise without a significant overall acute

deterioration in cardiac function or a more pronounced release of cardiac biomarkers compared to controls.

ACKNOWLEDGEMENTS

We would like to thank Puck Noordam and Michelle Manders for their contribution to the cardiac ultrasound measurements. We would like to thank Margje van der Pluijm and Janwillem Kersten for their help with the study. We acknowledge Siemens Healthcare (The Hague, The Netherlands) for providing the cTnI and BNP biomarker kits and Future Diagnostics (Wijchen, The Netherlands) for biomarker analysis.

CONFLICT OF INTERESTS

None.

FUNDING

This work was supported by the Netherlands Heart Foundation (Den Haag, the Netherlands) [E Dekker-stipend, grant number 2009T064 to D.H.J.T.] and the Netherlands Organization for Scientific Research (Den Haag, the Netherlands) [Rubicon Grant, grant number 825.12.016 to T.M.H.E.].

REFERENCES

- 1 Callow AD. Cardiovascular disease 2005--the global picture. *Vascul Pharmacol* 2006;**45**:302-7.
- 2 Sofi F, Capalbo A, Cesari F, et al. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:247-57.
- 3 Thompson PD. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2003;**23**:1319-21.
- 4 McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803-69.
- 5 Leon AS. Exercise following myocardial infarction. Current recommendations. *Sports Med* 2000;**29**:301-11.
- 6 Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol* 2014;**21**:664-81.
- 7 Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med* 1998;**129**:286-93.
- 8 Cahalin LP, Chase P, Arena R, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev* 2013;**18**:79-94.
- 9 Oxborough D, Birch K, Shave R, et al. "Exercise-induced cardiac fatigue"--a review of the echocardiographic literature. *Echocardiography* 2010;**27**:1130-40.
- 10 Dawson E, George K, Shave R, et al. Does the human heart fatigue subsequent to prolonged exercise? *Sports Med* 2003;**33**:365-80.

- 11 Middleton N, Shave R, George K, et al. Left ventricular function immediately following prolonged exercise: A meta-analysis. *Med Sci Sports Exerc* 2006;**38**:681-7.
- 12 La Gerche A, Roberts T, Claessen G. The response of the pulmonary circulation and right ventricle to exercise: exercise-induced right ventricular dysfunction and structural remodeling in endurance athletes (2013 Grover Conference series). *Pulm Circ* 2014;**4**:407-16.
- 13 Adams JE, 3rd, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993;**88**:101-6.
- 14 Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. *Endocrinology* 1993;**132**:1961-70.
- 15 Shave R, George KP, Atkinson G, et al. Exercise-induced cardiac troponin T release: a meta-analysis. *Med Sci Sports Exerc* 2007;**39**:2099-106.
- 16 La Gerche A, Connelly KA, Mooney DJ, et al. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart* 2008;**94**:860-6.
- 17 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;**5**:303-11; discussion 12-3.
- 18 Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr* 1974;**32**:77-97.
- 19 Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;**37**:153-6.
- 20 Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233-70.
- 21 Middleton N, Shave R, George K, et al. Impact of repeated prolonged exercise bouts on cardiac function and biomarkers. *Med Sci Sports Exerc* 2007;**39**:83-90.

- 22 Knebel F, Spethmann S, Schattke S, et al. Exercise-induced changes of left ventricular diastolic function in postmenopausal amateur marathon runners: assessment by echocardiography and cardiac biomarkers. *Eur J Prev Cardiol* 2014;**21**:782-90.
- 23 Suzuki R, Matsumoto H, Teshima T, et al. Influence of heart rate on myocardial function using two-dimensional speckle-tracking echocardiography in healthy dogs. *J Vet Cardiol* 2013;**15**:139-46.
- 24 Dawson EA, Shave R, George K, et al. Cardiac drift during prolonged exercise with echocardiographic evidence of reduced diastolic function of the heart. *Eur J Appl Physiol* 2005;**94**:305-9.
- 25 La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 2012;**33**:998-1006.
- 26 Davila-Roman VG, Guest TM, Tuteur PG, et al. Transient right but not left ventricular dysfunction after strenuous exercise at high altitude. *J Am Coll Cardiol* 1997;**30**:468-73.
- 27 Douglas PS, O'Toole ML, Hiller WD, et al. Different effects of prolonged exercise on the right and left ventricles. *J Am Coll Cardiol* 1990;**15**:64-9.
- 28 Eijsvogels T, George K, Shave R, et al. Effect of prolonged walking on cardiac troponin levels. *Am J Cardiol* 2010;**105**:267-72.
- 29 Eijsvogels TM, Veltmeijer MT, George K, et al. The impact of obesity on cardiac troponin levels after prolonged exercise in humans. *Eur J Appl Physiol* 2012;**112**:1725-32.
- 30 Serrano-Ostariz E, Terreros-Blanco JL, Legaz-Arrese A, et al. The impact of exercise duration and intensity on the release of cardiac biomarkers. *Scand J Med Sci Sports* 2011;**21**:244-9.
- 31 Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, et al. The impact of exercise intensity on cardiac troponin I release. *Int J Cardiol* 2014;**171**:e3-4.
- 32 Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol* 2010;**56**:169-76.
- 33 Piepoli MF, Conraads V, Corra U, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011;**13**:347-57.

FIGURE LEGENDS

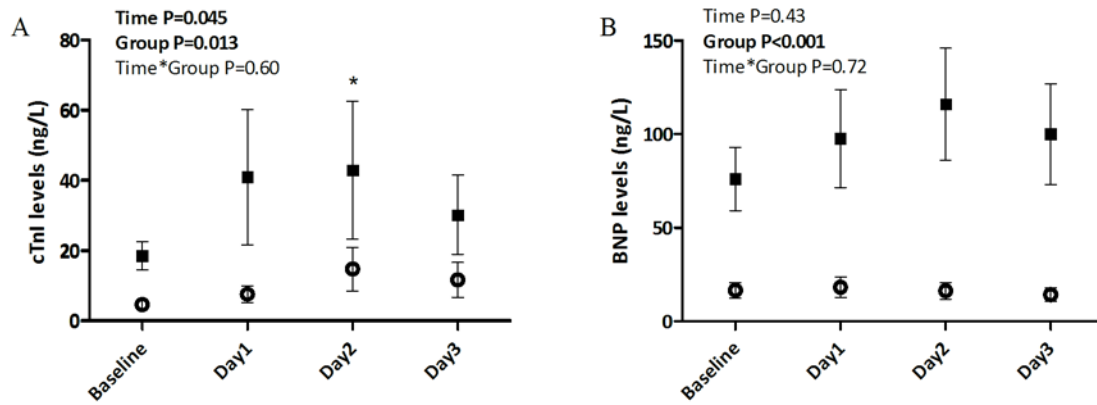


Figure 1. cTnI levels (A) and BNP levels (B) before exercise (baseline) and immediately post-exercise on day 1, day 2 and day 3 for controls (white circles) and cardiac patients (black squares). P-values refer to a linear mixed model analysis to examine whether changes in biomarkers across the 3 testing days ('Time') differs between groups ('Group', 'Time*Group'). Error bars represent SE. *cTnI levels significantly increased compared to baseline.

TABLE 1

Table 1. Subject characteristics and cardiovascular medication use of healthy controls (n=10) and cardiac patients (n=10) at baseline. Data is presented as mean±SD. P-values refer to an independent-samples *t*-test.

	Controls	Cardiac patients	P-value
Subject characteristics			
Age (yrs)	68±4	68±5	0.92
Sex (male:female)	9:1	9:1	-
Weight (kg)	82±14	81±13	0.78
BMI (kg/m ²)	25.6±3.2	26.2±4.0	0.75
BSA (m ²)	2.01±0.18	1.96±0.17	0.56
Waist circumference (cm)	97±12	96±13	0.93
Hip circumference (cm)	100±6	99±6	0.69
Waist-to-hip ratio [#]	0.96±0.07	0.97±0.09	0.65
Fat percentage (%)	30±6	32±5	0.39
Resting SBP (mmHg)	140±13	126±19	0.09
Resting DBP (mmHg)	80±7	75±9	0.16
Resting heart rate (beats/min)	64±9	57±8	0.09
Total training kilometres (km) [#]	575±711	699±687	0.57

[#]P-value relate to Mann-Whitney U test. Data on total training kilometers was missing for 1 cardiac patient. BMI; body mass index. BSA; body surface area. SBP; systolic blood pressure. DBP; diastolic blood pressure.

Table 2. Exercise characteristics of healthy controls (n=10) and cardiac patients (n=10) on the 3 walking days. P-values refer to a linear mixed model analysis that examined whether exercise parameters were different across the 3 walking days ('Time') or between groups ('Group'), and whether a different change across the 3 walking days was present between controls and cardiac patients ('Time*Group'). Data are presented as mean±SD.

	Controls			Cardiac patients			P-value		
	<i>Day1</i>	<i>Day2</i>	<i>Day3</i>	<i>Day1</i>	<i>Day2</i>	<i>Day3</i>	<i>Time</i>	<i>Group</i>	<i>Time*Group</i>
Duration (min)	424±91	470±114*	416±111	451±55	474±54*	442±66	0.001	0.60	0.50
Mean heart rate (/min) [#]	109±23	108±28	109±27	91±14	88±13	87±9	0.16	<0.001	0.45
Mean heart rate %max (%) [#]	68±14	68±17	68±16	57±8	55±7	54±5	0.16	<0.001	0.46
MET	5.2±1.0	4.4±0.5*	4.6±0.6*	5.4±0.5	4.8±0.5*	4.7±0.5*	<0.001	0.52	0.60
Walking speed (km/h)	4.7±0.9	4.1±1.0*	4.8±1.0	4.3±0.6	4.1±0.5*	4.4±0.6	0.002	0.35	0.44

*Significantly different compared to day 1. [#]A non-parametric alternative was used to perform the analysis: a Friedman test for the time-effect, a Mann-Whitney test for the group effect, and a repeated measures ANOVA on the delta's of day 2 and day 3 compared to day 1. MET; metabolic equivalent of task.

TABLE 3

Table 3. Cardiac function and structure of healthy controls (n=10) and cardiac patients (n=10) at baseline and immediately after exercise on day 1 and day 3. P-values refer to a linear mixed model analysis that examined whether cardiac function and structure were different from baseline across the 3 walking days ('Time') or between groups ('Group'), and whether a different change across the 3 walking days was present between controls and cardiac patients ('Time*Group'). Data are presented as mean±SD.

Preload	Controls			Cardiac patients			P-value		
	Pre	Day 1	Day 3	Pre	Day 1	Day 3	Time	Group	Time*Group
Heart rate (/min)	65±8 [†]	70±14*	77±12*	58±8	63±13*	64±11*	0.001	0.037	0.35
SBP (mmHg)	141±13 [†]	128±9*	130±10*	126±19	110±14*	110±17*	<0.001	0.004	0.70
DBP (mmHg)	81±7 [†]	75±9*	76±6*	75±9	65±8*	65±5*	0.001	0.002	0.43
LVEDV (mL)	97±19 [†]	99±20	99±9	141±33	123±23	123±29	0.31	0.003	0.15
LVIDd (cm) [#]	4.4±2	4.5±0.6	4.7±0.5	5.4±0.6	5.3±0.4	5.3±0.6	0.40	<0.001	0.57
E/Em [#]	8.1±2.7	7.2±2.2	6.5±2.1	9.8±5.7	9.8±5.9	9.2±6.5	0.37	0.27	0.82
LV systolic function									
LVEF, biplane (%)	60±10 [†]	56±9	55±6	48±10	46±12	42±10	0.06	0.008	0.91
LV strain (%)	-20±3 [†]	-21±3*	-19±3	-13±3	-16±4*	-14±3	0.026	<0.001	0.053
SmLV (m/s)	0.08±0.01	0.09±0.02*	0.09±0.02*	0.07±0.01	0.08±0.02*	0.08±0.02*	0.005	0.08	0.66
LVESV (mL)	42±13 [†]	40±16	44±9	74±28	65±22	73±16	0.19	0.002	0.63
SBP/ESV	3.62±0.95 [†]	3.28±1.20	3.02±0.57*	1.88±0.55	1.88±0.69	1.55±0.32*	0.028	<0.001	0.64
LV diastolic function									
E (m/s)	0.59±0.17	0.49±0.11	0.51±0.14	0.61±0.27	0.59±0.20	0.59±0.20	0.06	0.31	0.82
A (m/s)	0.66±0.13	0.65±0.13	0.65±0.10	0.74±0.32	0.71±0.27	0.77±0.29	0.34	0.34	0.48
E/A	0.87±0.12	0.76±0.08	0.77±0.11	0.86±0.29	0.85±0.22	0.77±0.13	0.12	0.58	0.33
EmLV (m/s)	0.08±0.02	0.08±0.01	0.08±0.02	0.07±0.02	0.07±0.02	0.07±0.02	0.73	0.43	0.73
AmLV (m/s) [#]	0.09±0.01	0.10±0.02	0.10±0.02	0.09±0.01	0.09±0.03	0.09±0.01	0.55	0.22	0.54
RV systolic function									
SmRV (m/s)	0.13±0.02 [†]	0.13±0.03	0.14±0.04	0.10±0.03	0.10±0.03	0.10±0.03	0.17	0.014	0.71
RV diastolic function									
EmRV (m/s) [#]	0.10±0.04 [†]	0.09±0.03	0.08±0.02*	0.08±0.02	0.08±0.03	0.06±0.02*	0.043	0.006	0.56
AmRV (m/s) [#]	0.14±0.05	0.16±0.06	0.16±0.05	0.10±0.04	0.12±0.04	0.11±0.04	0.13	0.001	0.53

[†]A non-parametric alternative was used to perform the analysis: a Friedman test for the time-effect, a Mann-Whitney test for the group effect, and a repeated measures ANOVA on the delta's of day 1 and day 3 compared to baseline. *significantly different compared to baseline (pre). [†]significantly different compared to cardiac patients at baseline. SBP; systolic blood pressure. DBP; diastolic blood pressure. LVEDV; left ventricular end-diastolic volume. LVIDd; left ventricular internal diameter end-diastole; E; peak flow velocity of the early rapid filling wave at the mitral leaflet tips. Em; peak annular tissue velocity during early filling. LVEF; left ventricular ejection fraction. LV; left ventricle. RV; right ventricle. Sm; peak annular tissue velocity during systole. LVESV; left ventricular end-systolic volume. SBP/ESV; ratio between systolic blood pressure and end-systolic volume of the left ventricle; A; peak flow velocity of the late filling wave at the mitral leaflet tips. Am; peak annular tissue velocity during late diastolic atrial contraction.

Supplementary table

Supplementary table. Cardiac function and structure of healthy controls (n=10) and cardiac patients (n=10) at baseline and immediately after exercise on day 1 and day 3. P-values refer to a linear mixed model analysis that examined whether cardiac function and structure were different from baseline across the 3 walking days ('Time') or between groups ('Group'), and whether a different change across the 3 walking days was present between controls and cardiac patients ('Time*Group'). All parameters are expressed relative to body surface area (BSA, m²). Data are presented as mean±SD.

Preload	Controls			Cardiac patients			P-value		
	<i>Pre</i>	<i>Day 1</i>	<i>Day 3</i>	<i>Pre</i>	<i>Day 1</i>	<i>Day 3</i>	<i>Time</i>	<i>Group</i>	<i>Time*Group</i>
LVEDV (mL/m ²)	49±8 [†]	50±10	51±5	73±20	63±15	64±18	0.32	0.009	0.11
LVIDd (cm/m ²) [#]	2.2±0.9	2.3±0.4	2.3±0.3	2.8±0.4	2.7±0.3	2.7±0.4	0.40	0.001	0.57
LV systolic function									
LVESV (mL/m ²)	21±6 [†]	20±8	22±5	38±17	34±13	38±9	0.20	0.003	0.60

[#]A non-parametric alternative was used to perform the analysis: a Friedman test for the time-effect, a Mann-Whitney test for the group effect, and a repeated measures ANOVA on the delta's of day 1 and day 3 compared to baseline. *significantly different compared to baseline (pre). [†]significantly different compared to cardiac patients at baseline. SBP; systolic blood pressure. DBP; diastolic blood pressure. LVEDV; left ventricular end-diastolic volume. LVIDd; left ventricular internal diameter end-diastole; LVESV; left ventricular end-systolic volume.