Left Atrial Functional Response after a Marathon in Healthy Amateur Volunteers

Yukina Hirata, PhD [1], Kenya Kusunose, MD, PhD[1,2], Hirotsugu Yamada, MD, PhD[1,3], Sae Morita[1], Yuta Torii, MS[1], Susumu Nishio, PhD [1], Robert Zheng, MD[2], Yoshihito Saijo, MD[2], Daiju Fukuda, MD, PhD[2], Shusuke Yagi, MD, PhD[2], Takeshi Soeki, MD, PhD[2], Masataka Sata, MD, PhD[1,2].

[1]Ultrasound Examination Center, Tokushima University Hospital, Tokushima, Japan

[2]Department of Cardiovascular Medicine, Tokushima University Hospital, Tokushima, Japan

[3] Department of Community Medicine for Cardiology, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

The authors have no conflicts of interest to declare.

Short title: Left Atrial Functional Response after a Marathon

Address for Correspondence:

Kenya Kusunose, MD, PhD

Department of Cardiovascular Medicine, Tokushima University Hospital, Tokushima, Japan

2-50-1 Kuramoto, Tokushima, Japan

TEL: 81-88-633-9311, FAX: 81-88-633-7798

E-mail: kusunosek@tokushima-u.ac.jp

Abstract

Background: Middle-aged marathon runners have an increased risk of developing atrial fibrillation (AF). A previous study described that repetitive marathon running was associated with left atrial (LA) dysfunction. However, whether this change is common in marathon runners and which runners are at risk of LA dysfunction remain unknown. The purpose of this study was to determine which factors could predict LA dysfunction.

Methods and results: We prospectively examined 12 healthy amateur volunteers (9 males, 31±8 years old) who participated in a full marathon. All echocardiographic measurements and speckle-tracking echocardiography were performed before and after the marathon. The endpoint was defined as reduced LA reservoir strain one day after the marathon (non-responder group). Seven participants were in the non-responder group. Age (35±9 vs. 26±2 yrs., p=0.020), augmentation index (76±12 vs. 55±8, p=0.002), and diastolic blood pressures (83±11 vs. 70±7 mmHg, p=0.021) in the non-responder group were significantly higher compared with the responder group. In multivariate linear regression analysis, only the augmentation index was an independent predictor of reduced LA reservoir function after the marathon (β=-0.646, p=0.023).

Conclusion: The augmentation index was a predictive marker for reduction in LA reservoir function after a marathon in healthy amateur volunteers.

Key words. Marathon; left atrial reservoir function; speckle-tracking echocardiography; augmentation index

Introduction

Marathon running is becoming popular worldwide. However, there is still debate whether marathon running itself harms the cardiovascular system, especially arrhythmia [1-4]. Several studies reported that marathon runners have an increased risk of developing atrial fibrillation (AF) at middle age [3,5]. A major contributing factor for AF was left atrial (LA) structural and functional abnormality. Hence, it has been shown that marathon running is associated with LA remodeling. Furthermore, LA functional response to marathons has received attention in recent years [6]. LA function, especially LA reservoir function, is an early indicator of LA functional impairment and can provide information about LA myocardial structural and functional substrate [7,8]. Recently, LA strain analysis by 2-dimensional (2D) speckle-tracking echocardiography has been used as a sensitive marker of LA functional abnormalities even in the absence of LA geometrical changes [9,10]. Some studies have shown that athletic marathon runners have reduced LA function compared with sedentary individuals [11,12]. Repetitive marathon running may lead to decompensatory changes in the mechanical functions of the atrium, and a better understanding of the LA function after the marathon can be clinically relevant to the prognosis of marathon-induced AF. However, LA responses may vary between individuals, and the characteristics of reduced LA function is not well unknown. Thus, the aim of this study was to investigate the incidence, time course, and clinical predictors of LA dysfunction in a prospective group of healthy amateur runners.

Materials and methods

Study Participants

We enrolled 12 healthy volunteers who participated in the 2017 Tokushima Full Marathon. All participants fulfilled the following inclusion criteria: 1) sinus rhythm; 2) stable clinical condition

at the time of echocardiography; 3) absence of anemia defined by periodic health examination; 4) technically adequate 2D and Doppler echocardiograms; and 5) completed the marathon. The Institutional Review Board of the University of Tokushima approved the study protocol, and written informed consent was obtained from all participants.

Data acquisition

All participants filled out a personal questionnaire about marathons, such as amount of training and past marathon participation. We also measured body mass index (BMI), blood pressure (BP), and augmentation index (AI). Radial AI, a marker of arterial stiffness, was measured using HEM-9010AI (Omron Healthcare Co., Ltd., Kyoto, Japan). Immediately after measuring BP via the upper arm, the left radial arterial waveform was obtained using the tonometric method. Radial AI was calculated as follows: (Second peak systolic BP − diastolic BP) / (first peak systolic BP − diastolic BP) ×100 (%). We performed echocardiographic studies at three separate time points: 1) within 1 week prior to the marathon; 2) 1 day after completion of the marathon; and 3) 5 days after the marathon. The endpoint of this study was an impaired response of LA function, which we defined as decreased LA reservoir strain one day after the marathon.

Standard echocardiographic assessment

Standard transthoracic echocardiography was performed using a Vivid E95 ultrasound with an S5-1 transducer (GE Healthcare, Waukesha, WI). One experienced sonographer (H.Y.) performed all echocardiographic examinations. All measurements, except for inferior vena cava (IVC), were performed on the left side in the supine position, at the end of expiration to avoid respiratory changes. All echocardiographic measurements (2D, pulse wave Doppler, and tissue Doppler) were obtained according to American Society of Echocardiography and European Association of

Cardiovascular Imaging recommendations [13]. LV diastolic functions were assessed by ventricular inflow, with peak early (E) and atrial (A) flow velocities. Tissue Doppler imaging of septal and mitral lateral annulus were measured, and an average e' value was used. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left atrial volume (LAV) and were calculated by the biplane Simpson disk method using 2D images and indexed to the body surface area (BSA). We measured LAVi at three stages; maximum LAVi (Vmax; at the end of ventricular systole just before opening the mitral valve), minimum LAVi (Vmin; at the end of ventricular diastole just before closing the mitral valve), and atrial volume before contraction (VpreA).

2D strain echocardiography

LV and LA 2D speckle-tracking echocardiography was analyzed offline using EchoPAC ver.201 (GE Medical). All images were optimized to guarantee optimal endocardial delineation. LV global longitudinal strain (GLS) was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views. LA strain was applied to the LA myocardium in apical 4- and 2-chamber views; the software divided the atrial wall into 12 segments, and the average was calculated for analysis. The regions of interest for LA were manually determined by tracing around the endocardial surface and adjusted to the thickness of the LA wall. The cardiac cycle was defined using the onset of the P wave in electrocardiography [14]. Strain parameters before and after the marathon are shown in **Figure 1**. The peak negative strain during atrial systole represents atrial contraction (LAS pump). The sum of the absolute values of negative and positive strain peaks (LAS cond) represent the atrial reservoir strain (LAS res) [15]. To interobserver variability analysis, another sonographer (M.S), who blinded to previously obtained data, measured LA reservoir strain of all participants. An experienced observer calculated strain values twice with a time interval of 12 months between for analysis of intraobserver variability.

Statistical Analysis

Continuous variables are presented as mean ± SD and categorical variables as frequency. The Fisher exact test was used to compare categorical variables. Characteristics of the three times of echocardiographic measurements were compared by repeated measure analysis of ANOVA. A paired Student t test was used in Table 3 to compare responder and non-responder groups. Non-responder was defined as subjects showing decreased LAS res after the marathon, and those without decreased LAS classified as responder group. Linear regression analysis was used to evaluate the association between several potential values and change of LAS res before and after the marathon (ΔLAS res). ΔLAS res was calculated as follows: (LAS res after the marathon − LAS res before the marathon) / LAS res after the marathon ×100 (%). All identified variables ($p<0.10$ in the univariate model) were entered in stepwise manner into a multivariate model to determine predictors to ΔLAS res. We checked for collinearity between the independent variables and ΔLAS res using Pearson's correlation coefficient. Area under the receiver operating characteristic (ROC) curve was used to describe the prognostic LA non-responders after the marathon. Sensitivity and specificity were calculated. Optimal cut-off values were determined by the analysis of the sensitivity and specificity values derived from the ROC curve data. To determine inter- and intraobserver variability, the interclass coefficient was used. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 25, SPSS Inc., IBM Corp., Armonk, NY, USA).

Results

Baseline Population Characteristics

All participants who completed the marathon were included in the final analysis. Their baseline characteristics are shown in **Table 1**. The mean age of the 12 participants was 31±8 yrs. (range: 23-49 yrs.), and 9 (60%) of participants were male. Four participants were their first marathon, and median values of total training, amount of running distance, and endurance training were 5 [range: 2-15] times, 25 [range: 10-200] km, and 2 [range: 1-3] h/week, respectively. The mean systolic and diastolic BPs were 126±15 and 78±11 mmHg. Two participants had hypertension, and one participant was current smoker. There were no other cardiovascular risk factors. The average AI was 67±15. Correlation between age and AI is modest (r= 0.56, p=0.05). Systolic and diastolic BPs were not statistical significance but seems to be correlated with AI (systolic BP; r=0.40, p=0.196; diastolic BP r=0.53, p=0.082).

Impact of Marathon Running on Echocardiography

The echocardiographic data of the participants, before and after the marathon, are listed in **Table 2**. At baseline, all echocardiographic measurements were within normal range. No changes in heart rate (HR), LV systolic function, volume and GLS were observed before and after the marathon. Compared to baseline measurement, average mitral A-wave velocity increased one day after the marathon, resulting in decreased E/A. Mitral A-wave velocity returned to baseline 5 days after the marathon. LAVi max (20±2 vs. 26±5 ml, p<0.001), preA (14±2 vs. 18±3 ml, p<0.001), and min (10±3 vs. 15±3 ml, p<0.001) increased one day after the marathon; and returned to normal 5 days later (**Figure 2A**). Averaged LA functions showed no statistical differences between before and after the marathon (**Figure 2B**).

Impact of Marathon Running on LA volume and Function

Figure 3 shows multipoint LAVi max and LA res at baseline and post marathon. LAVi max increased after the marathon in all participants, whether LAS res increased or not. Seven participants had decreased LAS res after the marathon. Based on LA response, we divided them into two groups; non-responder group and responder group. The characteristics and echocardiographic data at baseline are listed in **Table 3**. Age (35±9 vs. 26±2 yrs., p=0.020), AI (76±12 vs. 55±8, p=0.002) and diastolic BP (83±11 vs. 70±7 mmHg, p=0.021) in the non-responder group were significantly higher than those in the responder group. No significant differences were observed with regard to marathon training data. At baseline, LAVi pre A and LAVi min in non-responder group were significantly greater compared with responder group. After the marathon, the non-responders had significantly lower LAS cond compared to the non-responders. LAS pump was no significantly between two groups. LAS pump was positively correlated with A-wave velocity 1 day after marathon (r=0.58, p=0.046). To determine the independent predictors of ΔLAS res, we performed multivariate linear regression analysis of prediction of clinical and echocardiographic variables with ΔLAS res. The univariate and multivariate analysis is presented in **Table 4**. In a stepwise multivariate model, AI was the only independent predictor of ΔLAS res. In **Figure 4,** ΔLAS res showed statistically a negative correlation with AI (r= -0.65, p=0.023). By receiver operating characteristic curve analysis, AI ≤60 can predict the LA responders, with 86% sensitivity and 80% specificity. Interobserver and intraobserver variability were good for LA res. Intraclass correlation coefficients were 0.96 (P < .001) and 0.96 (P < .001), respectively.

Discussion

Even in healthy volunteers, marathon running can transiently cause atrial burden. In the present study, echocardiographic LA parameters were transiently affected by marathon running, and LA functional responses varied among individuals. We have demonstrated that increase in AI, a marker

of arterial stiffness, can predict reduced LA reservoir function after marathon running. These results suggest that individuals, who have atherosclerotic factors including high AI, can be clinically relevant to marathon-induced LA dysfunction and lead to the AF.

LA remodeling and marathon-induced atrial fibrillation

Previous studies reported that professional athletes have an increased risk of developing AF in middle age [1,2,4,16,17]. Calvo et al. [18] analyzed 182 consecutive patients who underwent AF ablations, and 39% of spontaneous AF patients were classified as endurance athletes (endurance sport activity >3 hours per week). In professional athletes, LA functional was decreased and LA volume was greater compared to age-matched healthy sedentary men [19]. Furthermore, cardiac dimensions do not completely regress to normal levels even several years after the athlete has retired [20]. In animals, high level exercise training has been associated with atrial enlargement, fibrosis, and propensity for high-grade arrhythmias, which reverse after the cessation of training [21,22]. LA remodeling may be a physiologic adaptation to volume overload, permitting a greater volume delivery and increased cardiac output. Cardiac response returned during few days, but with this recurrent stretch of LA geometry, some individuals may be prone to the development of chronic structural changes in response to the recurrent volume overload and excessive cardiac strain [23-25]. These repetitive burdens are might predispose to serious arrhythmias such as AF. According to these results, marathon-induced LA remodeling seems to be one of the major contributing factors for developing AF [26,27]. In amateur runners, LA remodeling is not clear compared to athletes at rest. Wilhelm et al. [28] reported that individuals with more endurance training showed greater LA volumes. Furthermore, Brugger et al. [29] showed LAVi min, VpreA and Vmax, and the LA conduit and reservoir strain all increased significantly from the low to the

high training group. In our study, LAVi of all the participants transiently increased after the marathon. The results of this study are consistent with previous studies.

Impact of Marathon Running on LA function

In our data, while averaged LA reservoir strain was not significantly different between before and after the marathon, we found that LA functional response varied among individuals. Hence, we classified two groups based on LA functional response post marathon; there were 7 (58%) subjects classified non-responder group, and LA conduit strain after marathon was significantly difference between two groups. Previous studies utilizing speckle-tracking analysis, LV function parameters after marathon running were previously reported [29,30]. These studies suggest that speckle-tracking analysis is a valuable tool to detect structural and functional abnormalities in cardiovascular disease, including AF. In addition, previous studies have shown that professional athletes had reduced LA reservoir function [11,12]. LA reservoir function is the first to be affected when ventricular afterload is increased, or in cases with atrial burden [31]. Furthermore, some studies reported LA reservoir strain and LA conduit strain correlated closely with exercise capacity [32]. This suggests that LA conduit reflect of early LA remodeling causing increased stiffness and decreased elastance. LA strain is affected early and consistently in the course of LA remodeling, hense it been proposed as an early marker of LA functional decline. Based on these results, it is assumed that decreased LA reservoir function after a marathon may related to occult LA dysfunction.

Prediction of LA Functional Response after the Marathon

As we already mentioned, LA dysfunction may occur even before dilatation of LA. Previous studies reported LA functions were independent predictors of new-onset AF, even after adjustment

for LA dimensions [33,34]. These discrepancies between anatomy and function support the idea that LA strain can represent an early marker of LA dysfunction and clinical deterioration, offering additional prognostic value compared with LA dimensions. AI is a useful marker of atherosclerotic risk stratification, such as hypertension. Hypertension is one of the major contributing factor for AF [35]. A previous study reported that increase in AI was a potential risk for AF [36]. Individuals with high AI cannot adapt to changes in blood pressure smoothly, thus increasing the burden on the entire cardiovascular system. We suspect that repetitive overloading of LA stress, from events such as marathon running, could lead to decompensatory changes in mechanical function of the atrium. Our results indicate that an increase in AI is a useful marker for predicting reduced LA reservoir function after a marathon. Marathon runners, who have atherosclerotic factors, have a risk of decreased LA function after a marathon. This in turn leads to atrial enlargement, which eventually may increase the risk of AF onset. Therefore, we recommend that such individuals should take care of the cardiovascular risk factors and/or exercise with moderation.

Limitations

This study presents several limitations. First, the small number of participants included in the study limited its statistical power. We may explained the notion of chance variation. The results from our study can be interpreted as a preliminary study for future studies involving more subjects. Second, we observed echocardiographic changes across a time frame of days, not hours after the marathon. Third, there is a lack of long-time follow up data, but we have no onset of AF in this cohort beyond 20 months. Last, we analyzed relatively young volunteers with few atherosclerotic factors. Other imaging modalities have not been done. Some papers had demonstrated the relationship between marathon runners greater than 50 years of age and CAD risk by using coronary artery calcium scores (CAC) or late gadolinium enhancement (LGE) [37-39].

Unfortunately, we found it unreasonable to conduct CT on healthy young volunteers with no known coronary risk factors. To evaluate our theories, we suggest that further studies be conducted with an older population, and presumably with more atherosclerotic factors.

Conclusion

In healthy amateur volunteers who ran a full marathon, high AI can predict LA reservoir dysfunction after marathon running. It suggests that marathon runners, who have atherosclerotic factors, can be clinically relevant to occult LA dysfunction and lead to the onset of AF. Larger validation studies are needed to confirm these findings.

Disclosures

The authors have no conflicts of interest to disclose

Acknowledgments

The authors acknowledge Kathryn Brock, BA, for her work editing the manuscript. The authors gratefully acknowledge the volunteers and staff in the Ultrasound Examination Center, Tokushima University Hospital.

Funding

This work was partially supported by JSPS Kakenhi Grants (Number 17K13037 to Y.Hirata, Number 15K19381 / 17K09506 to K. Kusunose, and No. 16H05299 / 26248050 to M. Sata) and a grant-in-aid from the Takeda Science Foundation (to M.S.), the Fugaku Trust for Medical Research (to M.S.), the Vehicle Racing Commemorative Foundation (to M.S.) and Uehara Memorial Foundation (to K.K.).

References

1. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M (1998) Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. BMJ 316 (7147):1784-1785

2. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, Jenni R, Oechslin E, Luthi P, Scharf C, Marti B, Attenhofer Jost CH (2008) Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. Eur Heart J 29 (1):71-78. doi:10.1093/eurheartj/ehm555

3. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J, Investigators G (2008) Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace 10 (1):15-20. doi:10.1093/europace/eum263

4. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM (2009) Relation of vigorous exercise to risk of atrial fibrillation. Am J Cardiol 103 (11):1572-1577. doi:10.1016/j.amjcard.2009.01.374

5. Grimsmo J, Grundvold I, Maehlum S, Arnesen H (2010) High prevalence of atrial fibrillation in long-term endurance cross-country skiers: echocardiographic findings and possible predictors--a 28-30 years follow-up study. Eur J Cardiovasc Prev Rehabil 17 (1):100-105. doi:10.1097/HJR.0b013e32833226be

6. Oxborough D, Whyte G, Wilson M, O'Hanlon R, Birch K, Shave R, Smith G, Godfrey R, Prasad S, George K (2010) A depression in left ventricular diastolic filling following prolonged strenuous exercise is associated with changes in left atrial mechanics. Journal of the American Society of Echocardiography 23 (9):968-976. doi:10.1016/j.echo.2010.06.002

7. Inaba Y, Yuda S, Kobayashi N, Hashimoto A, Uno K, Nakata T, Tsuchihashi K, Miura T, Ura N, Shimamoto K (2005) Strain rate imaging for noninvasive functional quantification of the left atrium: comparative studies in controls and patients with atrial fibrillation. J Am Soc Echocardiogr 18 (7):729-736. doi:10.1016/j.echo.2004.12.005

8. Muranaka A, Yuda S, Tsuchihashi K, Hashimoto A, Nakata T, Miura T, Tsuzuki M, Wakabayashi C, Watanabe N, Shimamoto K (2009) Quantitative assessment of left ventricular and left atrial functions by strain rate imaging in diabetic patients with and without hypertension. Echocardiography 26 (3):262-271. doi:10.1111/j.1540-8175.2008.00805.x

9. Montserrat S, Gabrielli L, Bijnens B, Borras R, Berruezo A, Poyatos S, Brugada J, Mont L,

Sitges M (2015) Left atrial deformation predicts success of first and second percutaneous atrial fibrillation ablation. Heart Rhythm 12 (1):11-18. doi:10.1016/j.hrthm.2014.08.032

10. Leong DP, Penhall A, Perry R, Shirazi M, Altman M, Chong D, Bradley J, Joseph MX, Selvanayagam JB (2013) Speckle-tracking strain of the left atrium: A transoesophageal echocardiographic validation study. European Heart Journal Cardiovascular Imaging 14 (9):898-905. doi:10.1093/ehjci/jes323

11. Gabrielli L, Bijnens BH, Butakoff C, Duchateau N, Montserrat S, Merino B, Gutierrez J, Paré C, Mont L, Brugada J, Sitges M (2014) Atrial functional and geometrical remodeling in highly trained male athletes: For better or worse? European Journal of Applied Physiology 114 (6):1143-1152. doi:10.1007/s00421-014-2845-6

12. D'Ascenzi F, Pelliccia A, Natali BM, Zaca V, Cameli M, Alvino F, Malandrino A, Palmitesta P, Zorzi A, Corrado D, Bonifazi M, Mondillo S (2014) Morphological and functional adaptation of left and right atria induced by training in highly trained female athletes. Circulation: Cardiovascular Imaging 7 (2):222-229. doi:10.1161/CIRCIMAGING.113.001345

13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European association of cardiovascular imaging. European Heart Journal Cardiovascular Imaging 16 (3):233-271. doi:10.1093/ehjci/jev014

14. Hayashi S, Yamada H, Bando M, Saijo Y, Nishio S, Hirata Y, Klein AL, Sata M (2015) Optimal Analysis of Left Atrial Strain by Speckle Tracking Echocardiography: P-wave versus R-wave Trigger. Echocardiography 32 (8):1241-1249. doi:10.1111/echo.12834

15. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP, Sicari R, Smiseth OA, Smulevitz B, Takeuchi M, Thomas JD, Vannan M, Voigt JU, Zamorano JL (2011) Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 12 (3):167-205. doi:10.1093/ejechocard/jer021

16. Heidbuchel H, Anne W, Willems R, Adriaenssens B, Van de Werf F, Ector H (2006) Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. Int J Cardiol

107 (1):67-72. doi:10.1016/j.ijcard.2005.02.043

17. Abdulla J, Nielsen JR (2009) Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. Europace 11 (9):1156-1159. doi:10.1093/europace/eup197

18. Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, Nadal M, Andreu D, Vidal B, Sitges M, Brugada J (2010) Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. Europace 12 (1):30-36. doi:10.1093/europace/eup320

19. D'Ascenzi F, Cameli M, Zaca V, Lisi M, Santoro A, Causarano A, Mondillo S (2011) Supernormal diastolic function and role of left atrial myocardial deformation analysis by 2D speckle tracking echocardiography in elite soccer players. Echocardiography 28 (3):320-326. doi:10.1111/j.1540-8175.2010.01338.x

20. Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F (2002) Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. Circulation 105 (8):944-949

21. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L (2011) Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation 123 (1):13-22. doi:10.1161/CIRCULATIONAHA.110.938282

22. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, Mighiu A, Tardif JC, Tadevosyan A, Chen Y, Gillis MA, Iwasaki YK, Dobrev D, Mont L, Heximer S, Nattel S (2013) Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. J Am Coll Cardiol 62 (1):68-77. doi:10.1016/j.jacc.2013.01.091

23. Maron BJ, Pelliccia A, Spirito P (1995) Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation 91 (5):1596-1601

24. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE (2000) The athlete's heart. A meta-analysis of cardiac structure and function. Circulation 101 (3):336-344

25. Maron BJ, Pelliccia A (2006) The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation 114 (15):1633-1644. doi:10.1161/CIRCULATIONAHA.106.613562

26. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R (2008) Long-term endurance sport practice increases the incidence of lone atrial fibrillation in

men: a follow-up study. Europace 10 (5):618-623. doi:10.1093/europace/eun071

27. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H (2011) Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. Am J Cardiol 108 (4):580-585. doi:10.1016/j.amjcard.2011.03.086

28. Wilhelm M, Nuoffer JM, Schmid JP, Wilhelm I, Saner H (2012) Comparison of pro-atrial natriuretic peptide and atrial remodeling in marathon versus non-marathon runners. American Journal of Cardiology 109 (7):1060-1065. doi:10.1016/j.amjcard.2011.11.039

29. Brugger N, Krause R, Carlen F, Rimensberger C, Hille R, Steck H, Wilhelm M, Seiler C (2014) Effect of lifetime endurance training on left atrial mechanical function and on the risk of atrial fibrillation. Int J Cardiol 170 (3):419-425. doi:10.1016/j.ijcard.2013.11.032

30. Sanz-de la Garza M, Grazioli G, Bijnens BH, Sarvari SI, Guasch E, Pajuelo C, Brotons D, Subirats E, Brugada R, Roca E, Sitges M (2016) Acute, Exercise Dose-Dependent Impairment in Atrial Performance During an Endurance Race: 2D Ultrasound Speckle-Tracking Strain Analysis. JACC: Cardiovascular Imaging 9 (12):1380-1388. doi:https://doi.org/10.1016/j.jcmg.2016.03.016

31. Cioffi G, de Simone G, Mureddu G, Tarantini L, Stefenelli C (2007) Right atrial size and function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia. European Journal of Echocardiography 8 (5):322-331. doi:10.1016/j.euje.2006.06.006

32. von Roeder M, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuss G, Lucke C, Gutberlet M, Schuler G, Schuster A, Lurz P (2017) Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. Circ Cardiovasc Imaging 10 (4). doi:10.1161/CIRCIMAGING.116.005467

33. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M, Almeida AL, Choi EY, Wu C, Alonso A, Heckbert SR, Bluemke DA, Lima JA (2016) Cardiac Magnetic Resonance-Measured Left Atrial Volume and Function and Incident Atrial Fibrillation: Results From MESA (Multi-Ethnic Study of Atherosclerosis). Circ Cardiovasc Imaging 9 (8). doi:10.1161/CIRCIMAGING.115.004299

34. Pessoa-Amorim G, Mancio J, Vouga L, Ribeiro J, Gama V, Bettencourt N, Fontes-Carvalho R (2018) Impaired Left Atrial Strain as a Predictor of New-onset Atrial Fibrillation After Aortic Valve Replacement Independently of Left Atrial Size. Rev Esp Cardiol (Engl Ed) 71 (6):466-476. doi:10.1016/j.rec.2017.10.005

35. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P (2004) The burden of adult hypertension in the United States 1999 to 2000: a rising tide. Hypertension 44 (4):398-404. doi:10.1161/01.HYP.0000142248.54761.56

36. Doi M, Miyoshi T, Hirohata S, Iwabu A, Tominaga Y, Kaji Y, Kamikawa S, Sakane K, Kitawaki T, Kusano KF, Kusachi S (2009) Increased augmentation index of the radial pressure waveform in patients with paroxysmal atrial fibrillation. Cardiology 113 (2):138-145. doi:10.1159/000177951

37. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, Budde T, Mann K, Barkhausen J, Heusch G, Jockel KH, Erbel R, Marathon Study I, Heinz Nixdorf Recall Study I (2008) Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 29 (15):1903-1910. doi:10.1093/eurheartj/ehn163

38. Breuckmann F, Mohlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, Sievers B, Schlosser T, Jockel KH, Heusch G, Erbel R, Barkhausen J (2009) Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology 251 (1):50-57. doi:10.1148/radiol.2511081118

39. Karlstedt E, Chelvanathan A, Da Silva M, Cleverley K, Kumar K, Bhullar N, Lytwyn M, Bohonis S, Oomah S, Nepomuceno R, Du X, Melnyk S, Zeglinski M, Ducas R, Sefidgar M, Mackenzie S, Sharma S, Kirkpatrick ID, Jassal DS (2012) The impact of repeated marathon running on cardiovascular function in the aging population. J Cardiovasc Magn Reson 14:58. doi:10.1186/1532-429X-14-58

Figure legends

Figure 1. Example of speckle-tracking strain analysis of the left atrium before and one day after the marathon. A representative case of non-response subject before (A) and one day after the marathon (B). The other is a representative case of response subject before (C) and one day after the marathon (D). The region of interest on the LA myocardium in the apical four-and two-chamber views are illustrated by the multicolored curve superimposed on the LA at the left of the figure. The average LA strain from the 12 myocardial segments imaged in this example is displayed by the dotted white curve to the right of the figure.

Figure2. Impact of marathon running on LA volume index (LAVi) and strain. All LAVi increased one day after the marathon; returned to normal 5 days later (A). LA strain showed no significant differences between before and one day after the marathon (B).

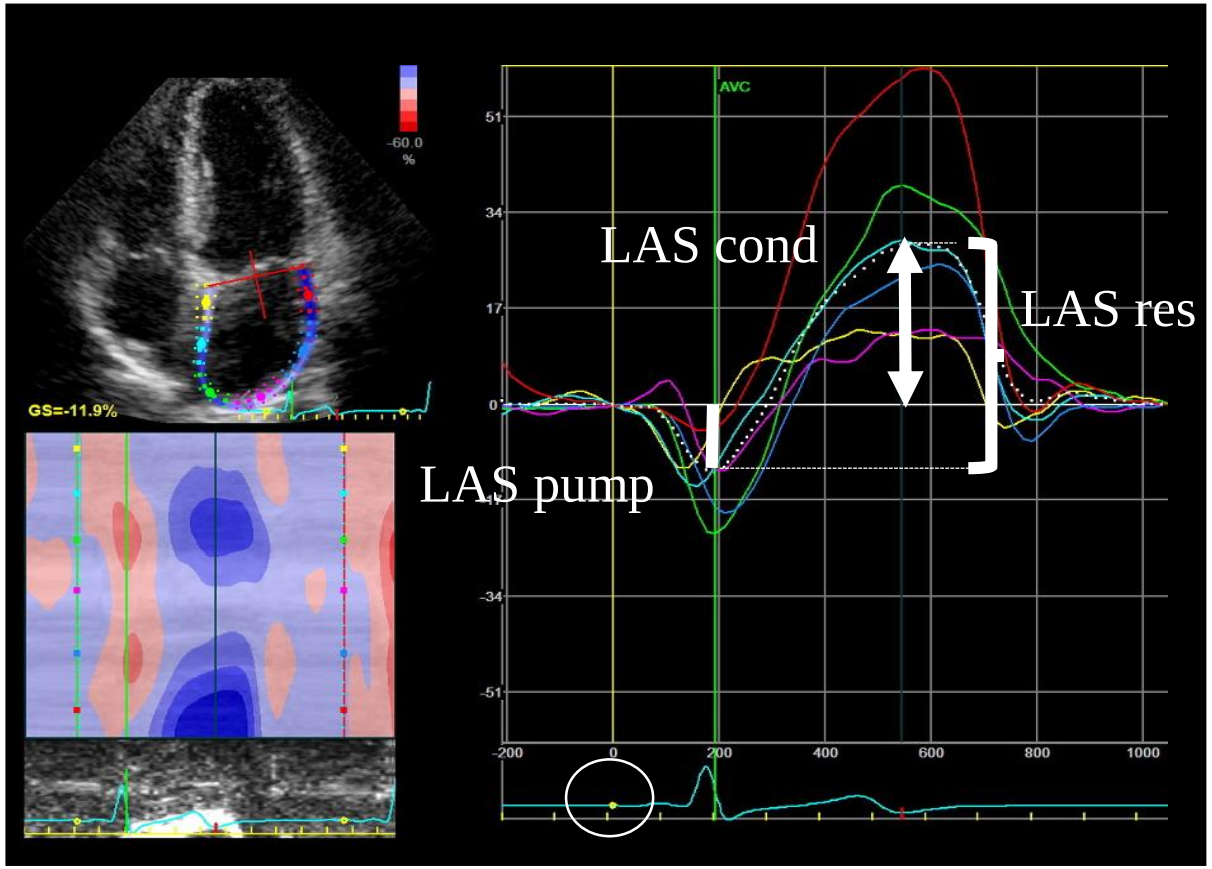
Figure3. Multipoint LAVi max and LAS res at baseline and post marathon in non-response (A) and response (B) group.

Figure4. Inverse associations between ΔLAS res and augmentation index.

Figure

Figure 1

A : Before marathon



B: One day after a marathon

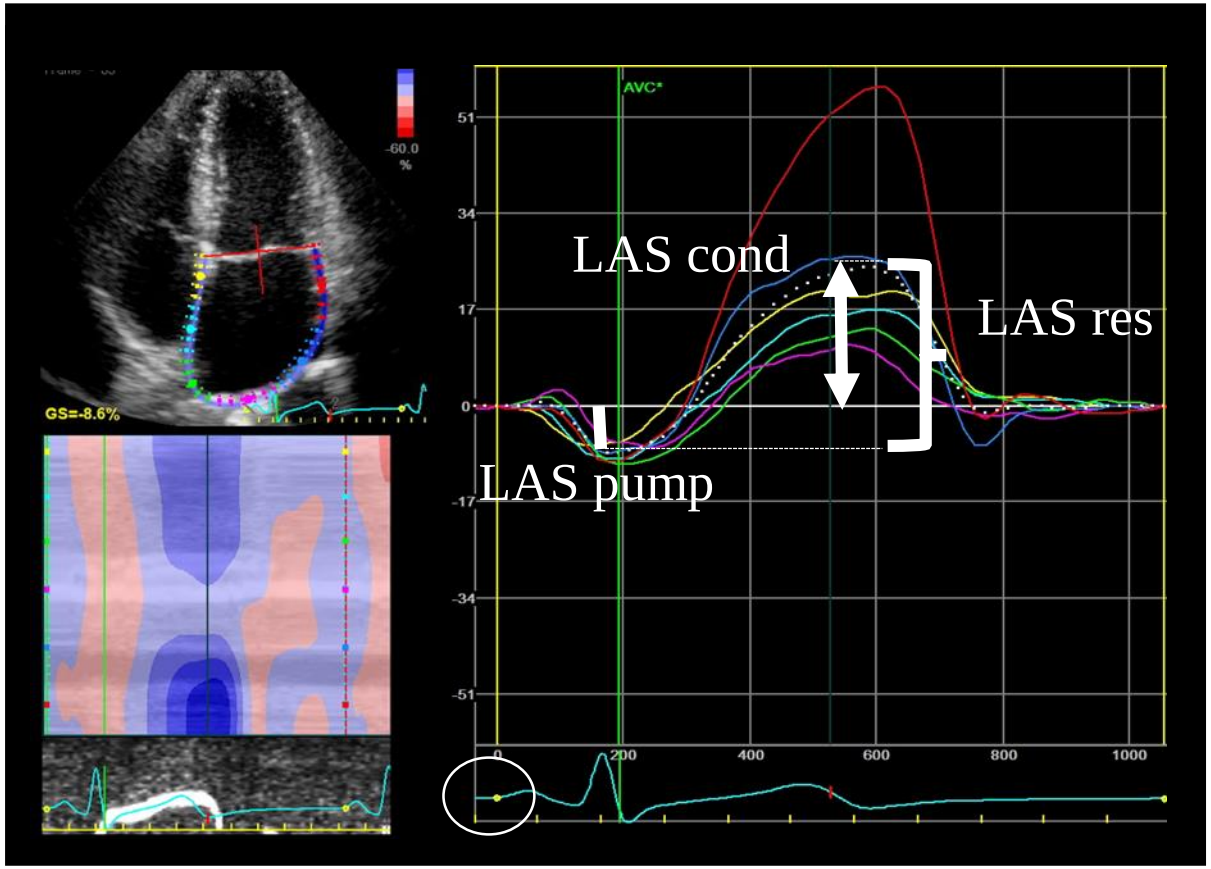
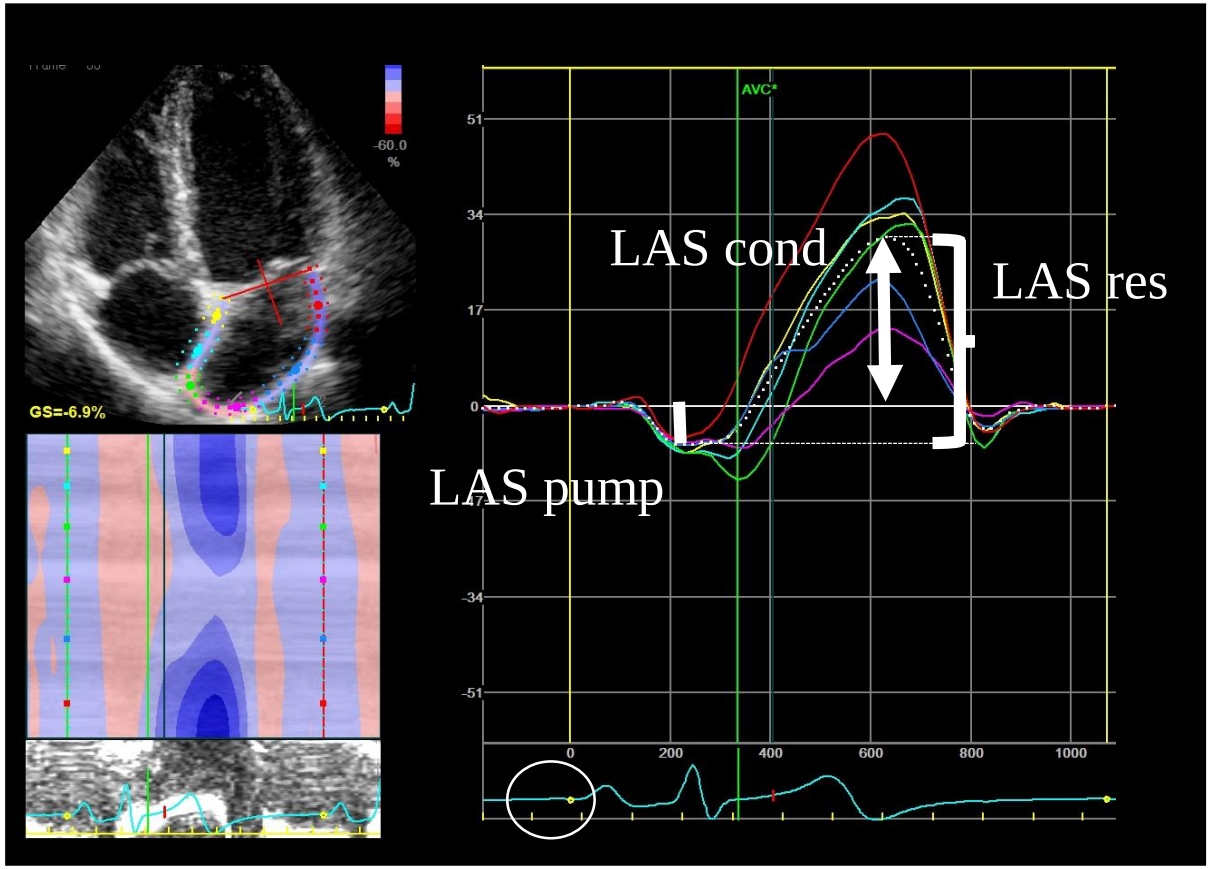


Figure 1

C : Before marathon



D: One day after a marathon

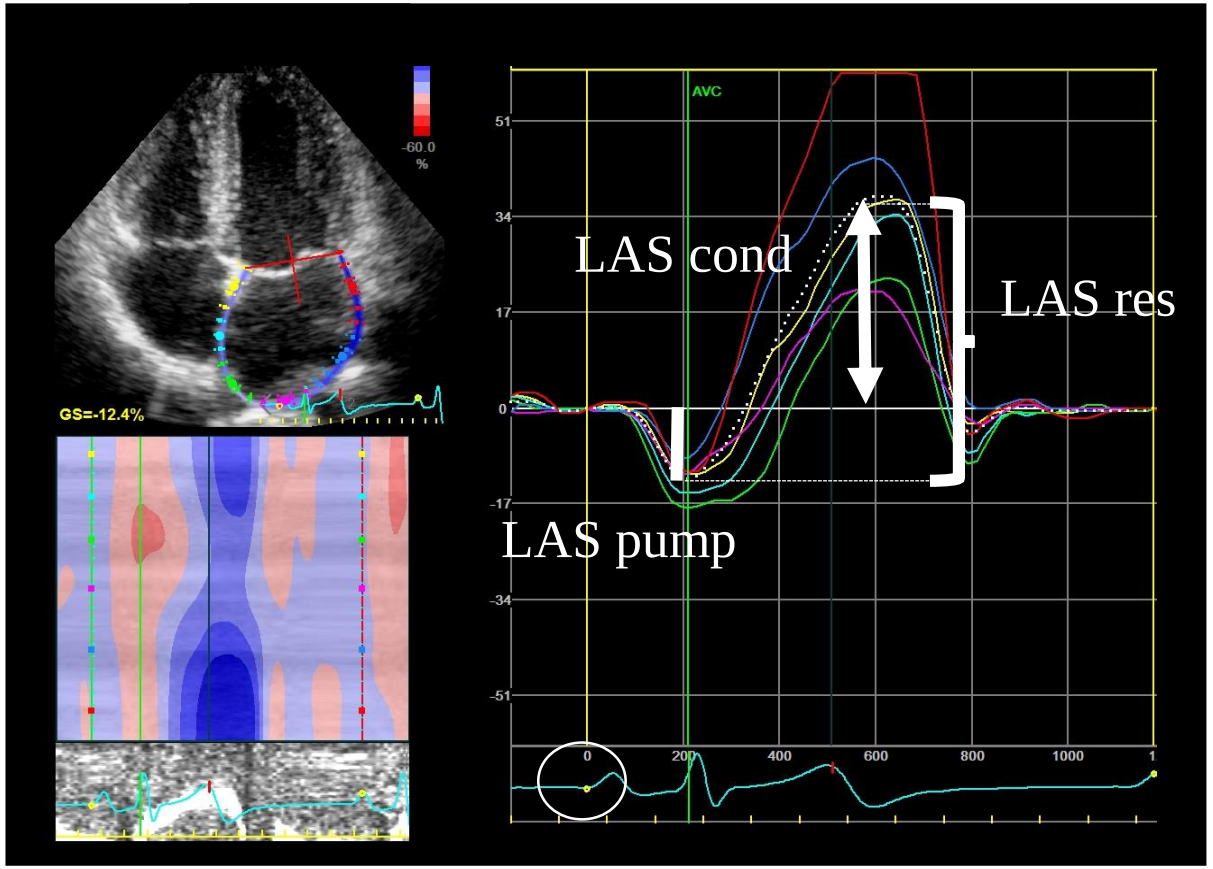


Figure 2A

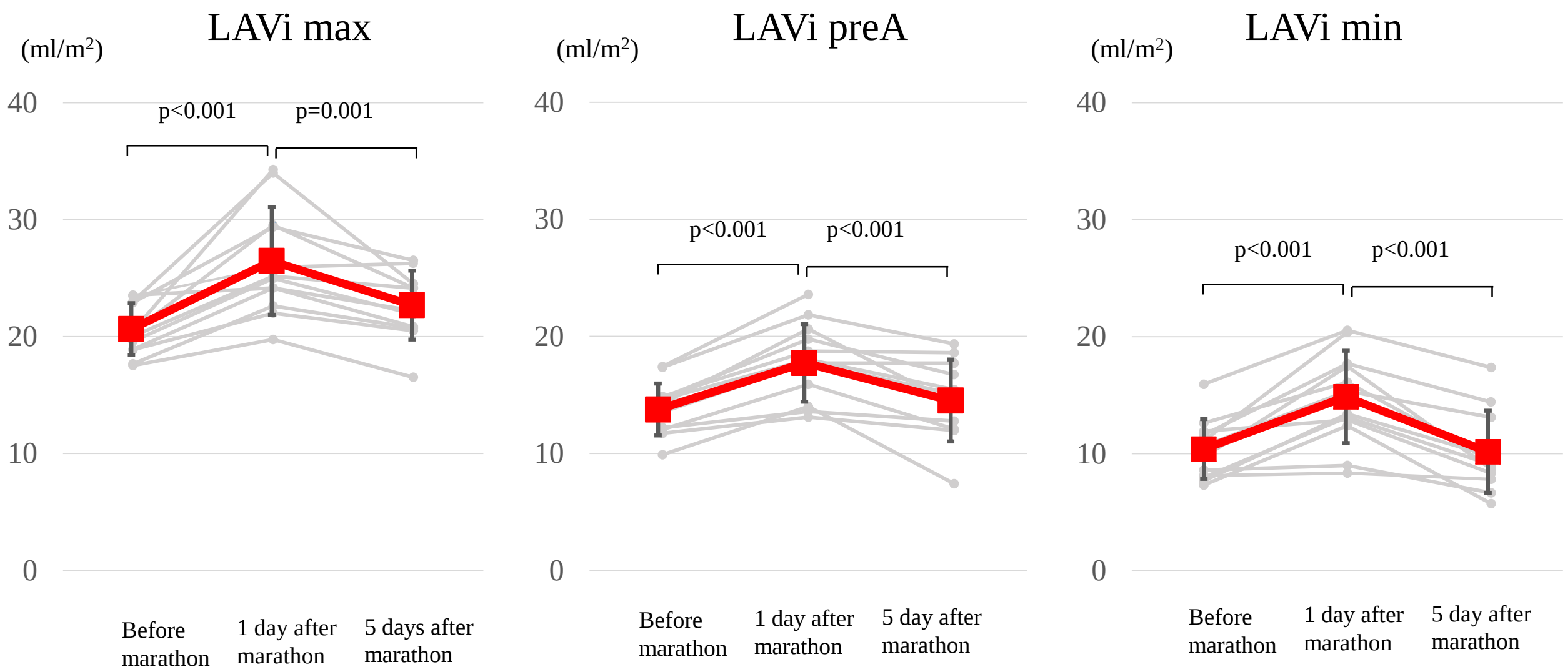
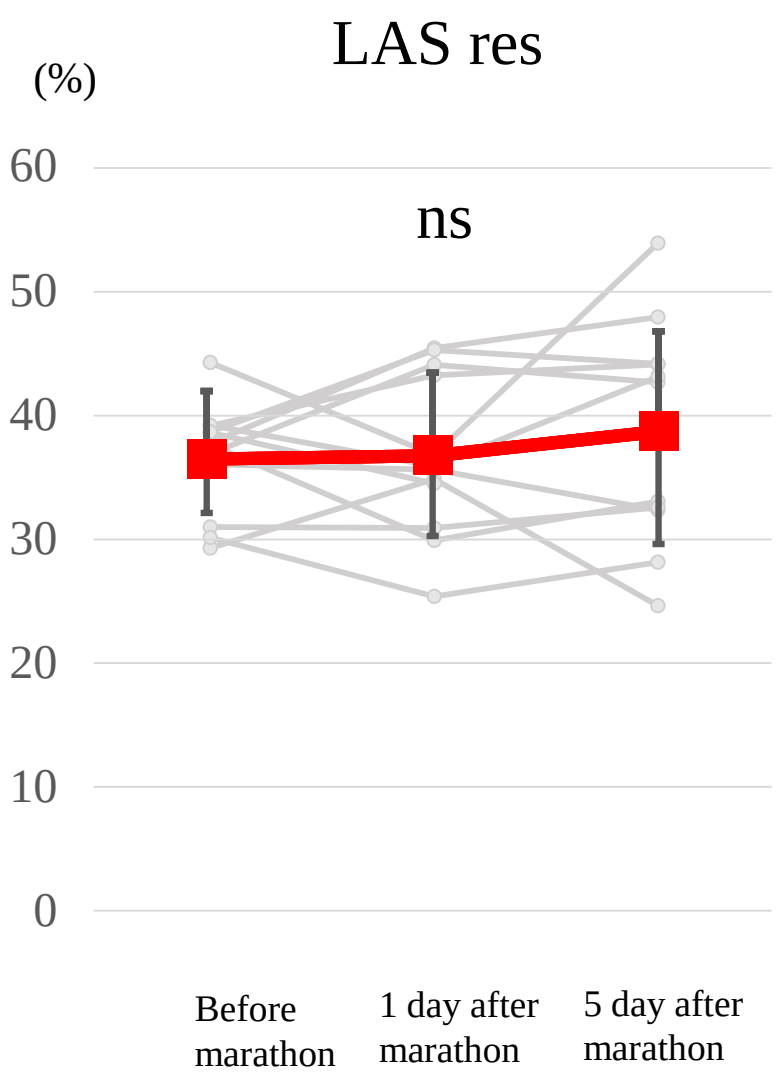
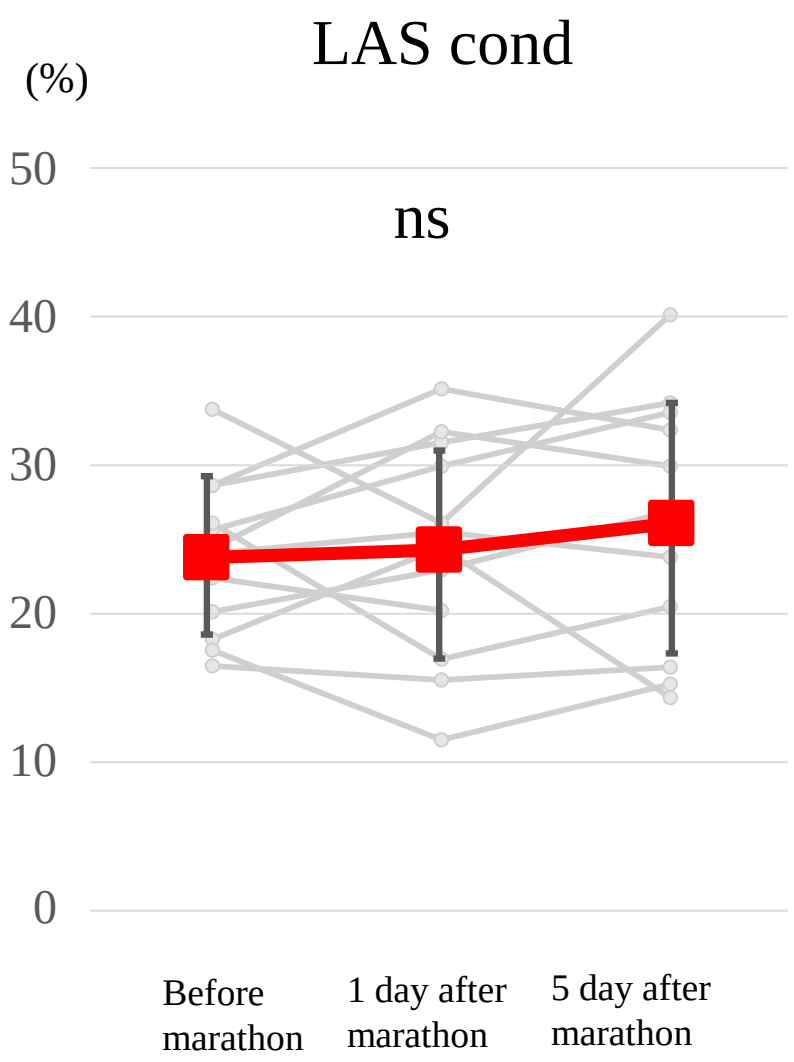

LAVi max
(ml/m²)
40
30
20
10
0
p<0.001
p=0.001
Before marathon
1 day after marathon
5 days after marathon
LAVi preA
(ml/m²)
40
30
20
10
0
p<0.001
p<0.001
Before marathon
1 day after marathon
5 day after marathon
LAVi min
(ml/m²)
40
30
20
10
0
p<0.001
p<0.001
Before marathon
1 day after marathon
5 day after marathon

Figure 2B


LAS res
(%)
60
50
40
30
20
10
0
ns
Before marathon
1 day after marathon
5 day after marathon


LAS cond
(%)
50
40
30
20
10
0
ns
Before marathon
1 day after marathon
5 day after marathon

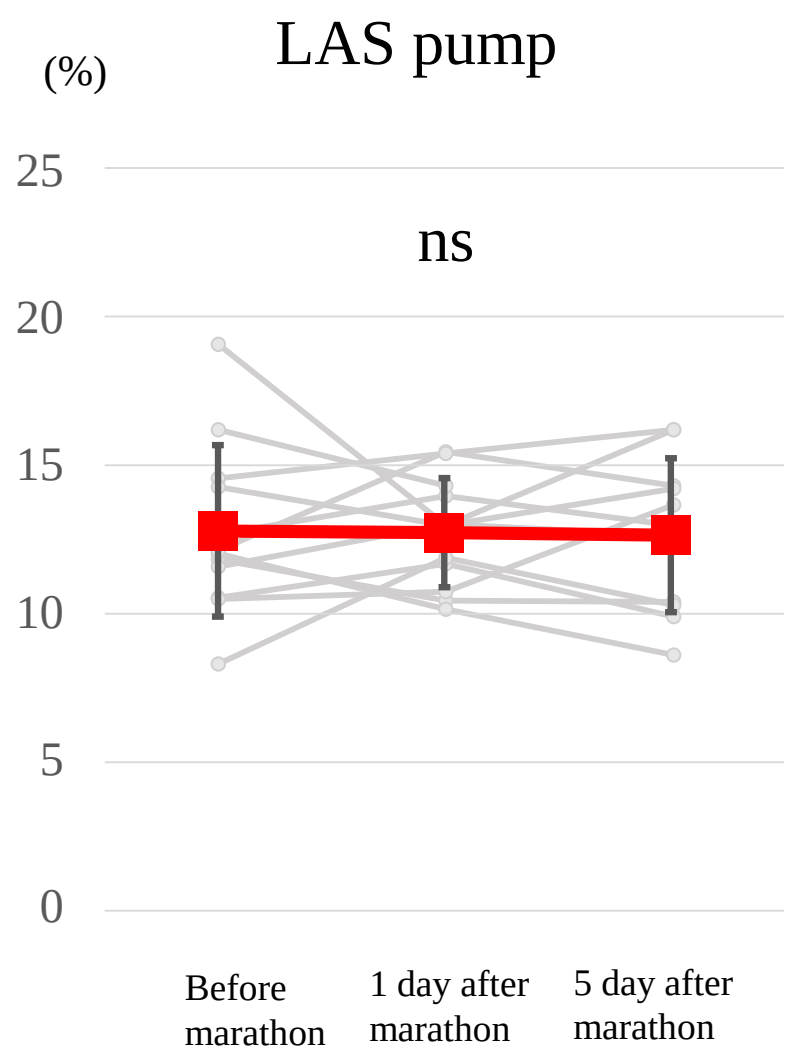

LAS pump
(%)
25
20
15
10
5
0
ns
Before marathon
1 day after marathon
5 day after marathon

Figure 3A

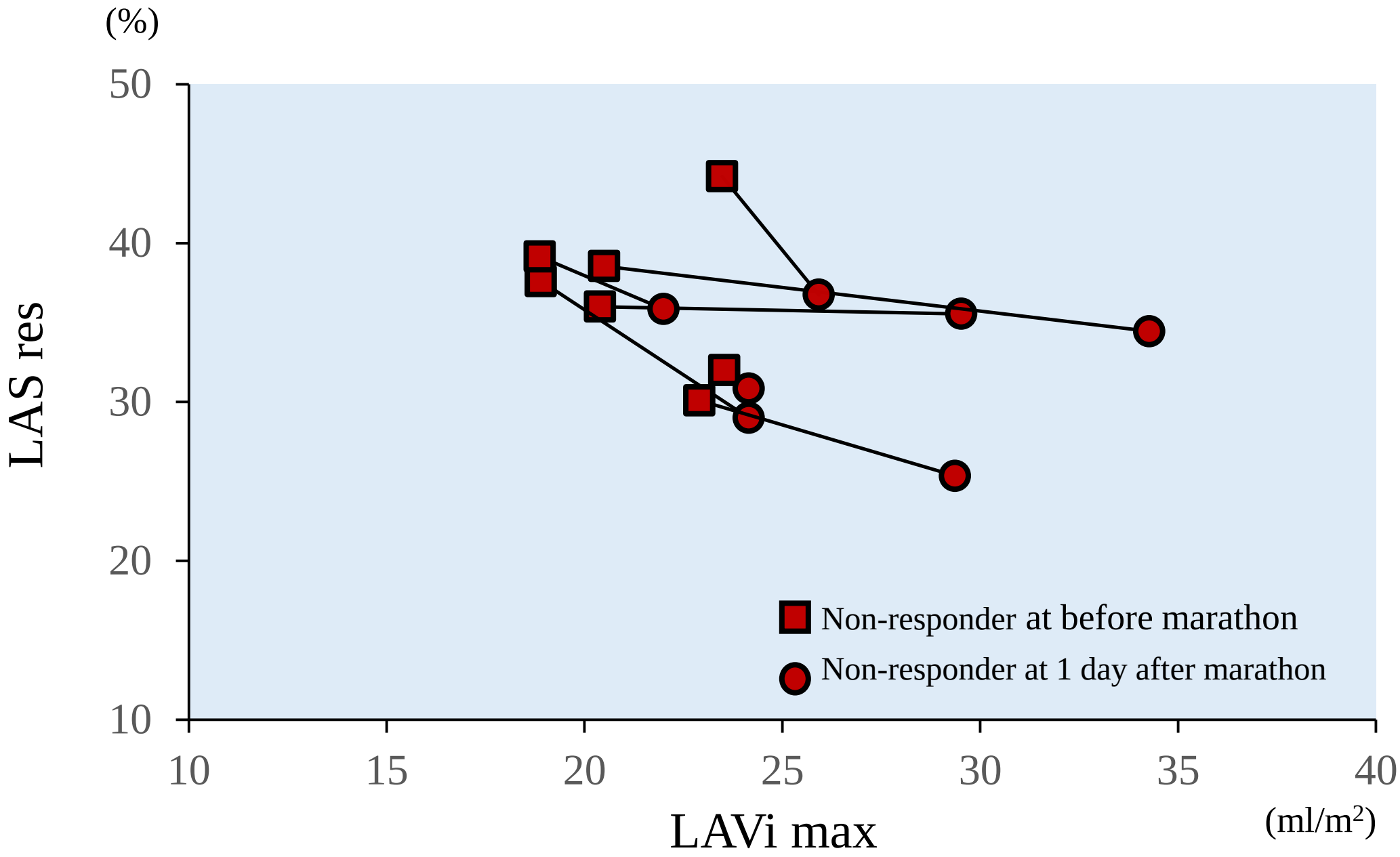

(%)
50
40
30
20
10
LAS res
10
15
20
25
30
35
40
LAVi max
(ml/m²)
Non-responder at before marathon
Non-responder at 1 day after marathon

Figure 3B

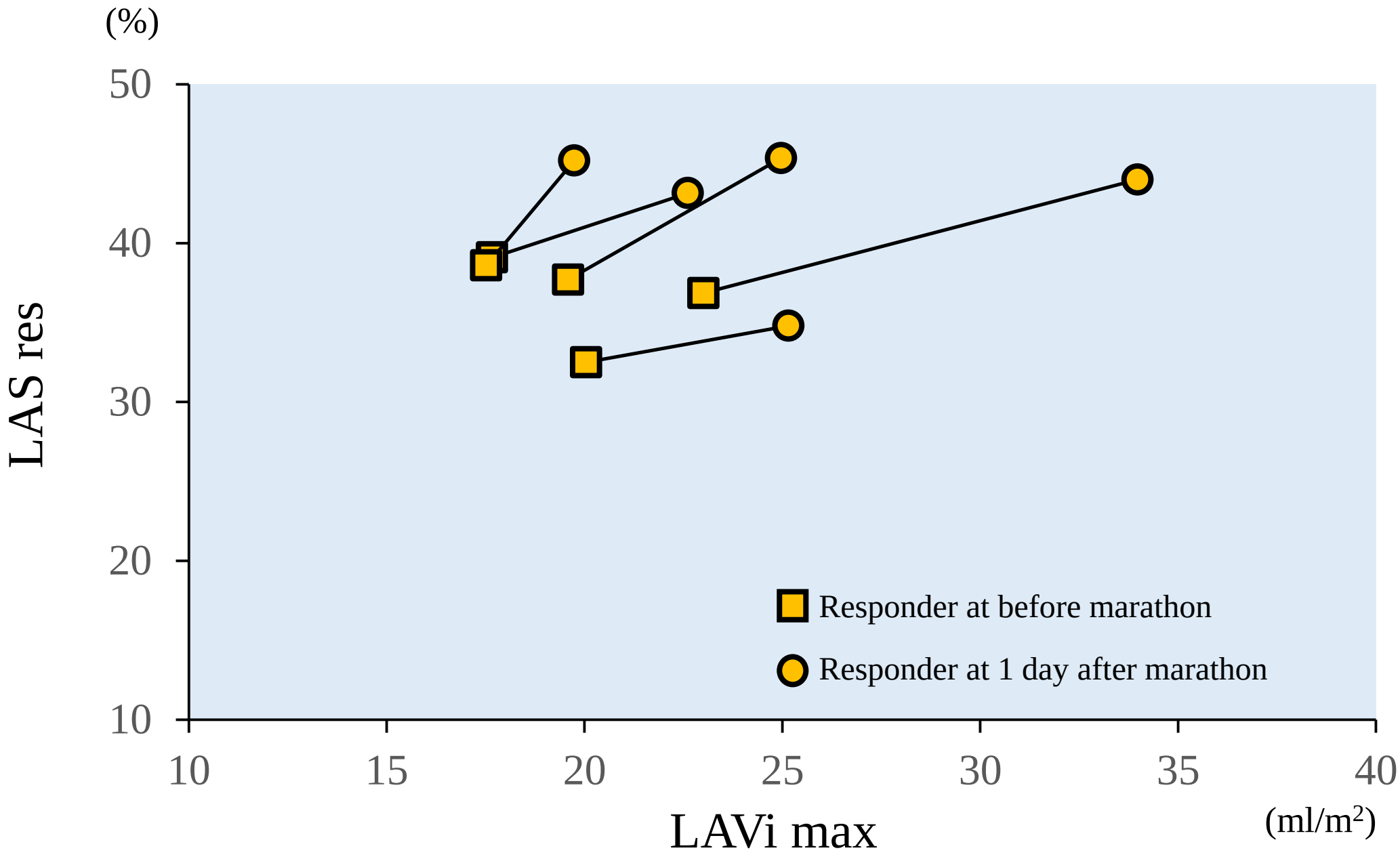
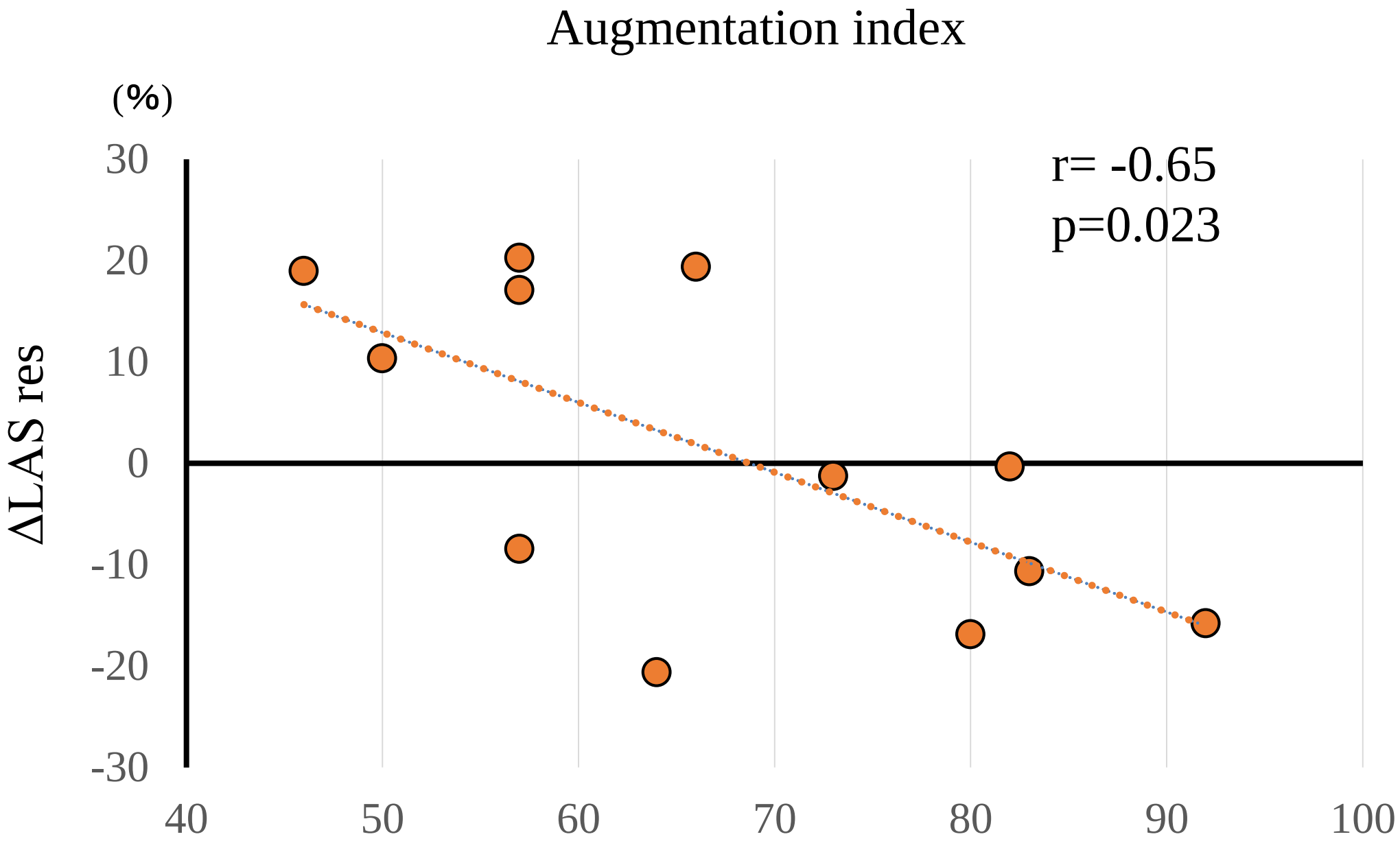

(%)
50
40
30
20
10
LAS res
10
15
20
25
30
35
40
LAVi max
(ml/m²)
Responder at before marathon
Responder at 1 day after marathon

Figure 4


Augmentation index
(%)
ΔLAS res
30
20
10
0
-10
-20
-30
40
50
60
70
80
90
100
r= -0.65
p=0.023

Table

Table1. Characteristics of 12 amateur runner participating in full marathon

	Age	Gender	BMI (kg/m^2)	Blood pressure (mmHg)	AI	Former marathon participations (time)	Training before the marathon		
							Total training (time)	Total running distance (km)	Endurance training (h/week)
A	20s	M	17.6	105/70	60.0	0	<5	10	2
B	20s	M	25.9	131/77	46.0	1-5	<5	20	1
C	20s	M	19.3	121/66	66.0	0	>20	200	2
D	20s	M	22.1	133/78	73.0	0	<5	<10	<1
E	20s	M	23.7	122/72	57.0	1-5	<5	10	<1
F	30s	M	22.2	120/74	64.0	1-5	<5	10	<1
G	30s	M	25.8	129/76	57.0	1-5	10	50	3
H	40s	M	23.8	144/80	82.0	1-5	<5	30	2
I	40s	M	24.7	145/76	92.0	≧6	>15	200	2
J	20s	F	20.1	110/66	83.0	1-5	<5	20	1
K	20s	F	19.1	106/62	57.0	1-5	>15	200	2
L	20s	F	19.7	127/64	80.0	0	5	30	2

M=Male; F=Female; BMI = body mass index; AI= Augmentation index

Table2. Echocardiographic measurement on before- and after-marathon

	Before marathon	**1 day after marathon**	**5 days after Marathon**	**P value**
Heart rate, beats/min	67±6	72±10	71±9	0.177
Stroke volume, ml	68±13	70±14	69±14	0.513
LVEDVi, ml/m^2	65±9	66±9	65±8	0.624
LVESVi, ml/m^2	23±3	24±4	23±4	0.574
LVEF, %	65±2	64±2	64±3	0.602
IVC, mm	17±4	16±6	18±4	0.417
E-wave, cm/s	76±10	74±15	80±14	0.215
A-wave, cm/s	**41±10***	**53±10***†	**44±11**†	**0.001**
E/A	**1.90±0.5***	**1.48±0.3***†	**1.91±0.5**†	**0.001**
e' average, cm/s	**13.7±3.1***	**13.4±2.7***†	**14.2±3.0**†	**0.036**
E/e'	5.6±1.3	5.8±1.4	5.9±1.5	0.912
TRPG	18.2±3.0	18.8±4.3	18.9±5.4	0.412
LV global longitudinal strain, %	19.3±1.9	19.2±1.9	19.6±1.8	0.058

LV = left ventricle; LVEDVi = left ventricle end diastolic volume index; LVESVi = left ventricle end systolic volume index; LVEF = left ventricle ejection fraction; IVC=inferior vena cava; TRPG = tricuspid regurgitation pressure gradient

Data are expressed in mean ±SD

* $p < 0.05$ versus baseline and †$p < 0.05$ versus 1 day after marathon by ANOVA analysis.

Bold values signify $p < 0.05$ by ANOVA between the 3 groups.

Table3. Baseline characteristics and echocardiographic parameters on responder and non-responder group

	Non-responder group	Responder group	p value
Age, yrs	**35±9**	**26±2**	**0.020**
Male/Female	5/2	4/1	0.380
Body mass index, kg/m^2	22.3±2.5	21.4±3.4	0.300
Systolic blood pressure, mmHg	131±16	120±12	0.111
Diastolic blood pressure, mmHg	**83±11**	**70±7**	**0.021**
Augmentation index	**76±12**	**55±8**	**0.002**
Total training, time	5±4	8±7	0.245
Total running distance, km	50±68	88±102	0.246
Endurance training, h/week	1.9±1.5	1.6±1.3	0.380
Former marathon participations, time	2.4±2.0	1.6±1.5	0.221
Marathon race time, min	323±39	308±49	0.298
Echocardiography			
Heart rate, beats/min	69±7	64±4	0.079
Stroke volume, ml	64±8	61±9	0.291
LVEDVi, ml/m^2	67±9	63±9	0.231
LVESVi, ml/m^2	25±2	22±3	0.130
LVEF, %	65±3	65±3	0.339
IVC, mm	17±5	18±3	0.416
E-wave, cm/s	72±12	78±8	0.112
A-wave, cm/s	44±12	37±4	0.104
E/A	1.7±0.5	2.1±0.5	0.107
e' average, cm/s	12.9±3.4	15.0±2.5	0.125
E/e'	5.9±1.5	5.3±0.8	0.202
LV global longitudinal strain, %	19±2	20±3	0.336
LA global longitudinal strain, % LAVi max (before marathon), ml/m^2 **LAVi preA (before marathon), ml/m^2**	11.9±2.6 21±2 **15±2**	10.8±2.7 20±2 **13±2**	0.249 0.112 **0.043**
LAVi min (before marathon), ml/m^2	**11±3**	**9±1**	**0.041**
LAS res (before marathon), %	37±5	36±4	0.448
LAS cond (before marathon), %	23±6	25±4	0.235
LAS pump (before marathon), %	14±3	11±2	0.072

LAVi max (1 day after marathon), ml/m^2	28±4	25±5	0.279
LAVi preA (1 day after marathon), ml/m^2	19±3	16±3	0.062
LAVi min (1 day after marathon), ml/m^2	16±3	13±4	0.060
LAS res (1 day after marathon), %	**33±4**	**43±5**	**<0.001**
LAS cond (1 day after marathon), %	**20±5**	**31±4**	**0.001**
LAS pump (1 day after marathon), %	13±2	12±2	0.347

LA = left atrial; LV = left ventricle; LVEF = left ventricle ejection fraction; LVEDVi = left ventricle end diastolic volume index; LVESVi = left ventricle end systolic volume index; IVC=inferior vena cava; TRPG = tricuspid regurgitation pressure gradient; LAVi= left atrial volume index; LAS= left atrial strain

Data are expressed in mean ±SD, Bold values signify $p < 0.05$ by t-test analysis

Table4. Uni- and multivariate linear regression analysis to demonstrate independent predictors of ΔLAS res (%)

	Univariate		**Multivariate (stepwise)**		
	R	**p value**	**β Unstandardized**	**Standardized β**	**p value**
Age	-0.878	0.146			
Male	5.979	0.590			
Body mass index	-0.308	0.865			
Systolic blood pressure	-0.283	0.401			
Diastolic blood pressure	**-0.706**	**0.090**	†	†	†
Augmentation index	**-0.690**	**0.023**	**-0.690**	**-0.646**	**0.023**
Total training	0.583	0.531			
Total running distance	0.036	0.556			
Endurance training	-2.382	0.759			
Former marathon participations	0.232	0.562			
Marathon race time	-0.021	0.860			
Heart rate	-0.812	0.303			
Stroke volume	-0.076	0.902			
LVEDVi	-0.274	0.624			
LVESVi	-2.166	0.257			
LVEF	2.080	0.318			
IVC	-0.391	0.771			
E-wave	0.388	0.425			
A-wave	-0.465	0.360			
E/A	10.414	0.273			
e’ average	1.525	0.335			
E/e’	-2.258	0.569			
TRPG	2.494	0.110			
LV global longitudinal strain	1.178	0.611			
LAVi max	-1.904	0.399			
LAVi preA	-3.219	0.135			
LAVi min	-2.314	0.226			
LAS res	-0.655	0.570			
LAS cond	0.061	0.950			
LAS pump	-1.543	0.369			

LA = left atrial; LV = left ventricle; LVEF = left ventricle ejection fraction; LVEDVi = left ventricle end diastolic volume index; LVESVi = left ventricle end systolic volume index; IVC=inferior vena cava; TRPG = tricuspid regurgitation pressure gradient; LAVi= left atrial volume index; LAS= left atrial strain

[†] Eliminated though the stepwise method