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Assessment of the effect of endurance training on left ventricular relaxation with magnetic resonance imaging

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The purpose of the study was to assess the effect of endurance training on the early diastolic global and regional left ventricular (LV) relaxation with three magnetic resonance imaging (MRI) techniques.

Fourteen subjects were examined with MRI before and after 3-month endurance training. Global early diastolic LV myocardial relaxation was assessed with mitral flow velocity mapping and regional LV early myocardial relaxation with myocardial tagging. LV end-diastolic and end-systolic volumes and mass were assessed with cine Magnetic resonance imaging (MRI).

Mitral flow velocity mapping analysis revealed that the time to peak early filling shortened after training (before 112 ± 32 ms, after 97 ± 21, $P < 0.05$), indicating more rapid global early myocardial relaxation. LV mass increased (97 ± 19 g, 105 ± 18, $P < 0.01$) and end-systolic volume decreased (47 ± 11 mL, 42 ± 13, $P < 0.05$). According to myocardial tagging analysis early myocardial relaxation in the septum and in the LV lateral wall increased ($P < 0.05$). Regional tagging analysis showed enhanced myocardial relaxation in the basal septum ($P < 0.05$).

Global and regional LV early diastolic relaxation improved and physiological LV hypertrophy was found after the exercise training period for 3 months in healthy sedentary subjects.

Previous echocardiography cross-sectional (Matsuda et al., 1983; Levine et al., 1991; Takemoto et al., 1992; Gledhill et al., 1994) and follow-up (Shaphiro & Smith 1983; Levy et al., 1993) training studies have shown that left ventricular (LV) diastolic function is enhanced with increased fitness. In addition, the LV diastolic dysfunction associated with normal aging is found to be less pronounced in trained persons (Takemoto et al., 1992; Levy et al., 1993). Several studies have shown that endurance training increases diastolic filling rate at rest (Levy et al., 1993; Gledhill et al., 1994; Libonati et al., 1999) and during exercise (Nixon et al., 1991; Levy et al., 1993; Gledhill et al., 1994).

Diastolic filling consist of four phases: (1) isovolumic relaxation (= time from closure of aortic valve to the opening of the mitral valve), (2) early diastolic rapid filling phase (= the early diastolic wave), (3) diastase (= during which the pressure between atrium and ventricle equalizes), and (4) late diastolic filling phase caused by atrial contraction. About 80% of LV filling occurs before atrial contraction, and the early diastolic rapid filling phase is an active myocardial process (Matsuda et al., 1983).

The purpose of our present study was to assess the effect of moderate endurance training on the diastolic properties of the LV in healthy subjects. We used, for the first time, a combination of three magnetic resonance imaging (MRI) techniques to examine the early global and regional LV relaxation: mitral flow velocity mapping, cine MRI and myocardial four-chamber tagging. Myocardial tagging is a new MRI technique to label or "tag" the myocardium by selective saturation prepulses in specific myocardial regions in planes perpendicular to the imaging plane. The change in distance between line pairs represents the regional movement of the myocardium in one direction (Reichek, 1999).

Materials and methods

Subjects and study protocol

Fourteen healthy sedentary subjects (mean age 43 years, range 23–58 years, four males) without a history of diabetes, coronary artery disease, valvular, or hypertensive disease were examined with MRI before and immediately after (range 3–5 days) a 3-month endurance-training period. The subjects that we recruited for the study were sedentary known healthy volunteers who were acquaintances of the authors. They lived in the Helsinki area and were ready to commit to a regular training program. We interviewed all subjects precisely, and selected them for the study only if they had led a sedentary life and did not exercise at all. None of the subjects was taking any medication known to influence cardiac function.

The exercise test was performed with a bicycle ergometer with continuous ECG recording with a standard ECG monitoring system (Marquette Electronics, Milwaukee, Wisconsin, USA). The initial load was 30 W, followed by increments of the load by 20 W for women and 30 W for men each minute until subjective exhaustion. The target heart rates for the training sessions were determined from the maximal heart rate for each subject. Exercise tests were performed before and after the study period.

The subjects exercised at home for 3 months using a bicycle ergometer. Training started at 60% of the maximal heart rate for 30 min a session, three times a week; this step was adopte during the first 2 weeks. Thereafter, training was gradually increased up to 75% of the maximal heart rate for 30 min a session, four times a week; this step continued during the last 3 weeks. The subjects had a continuous heart rate display (Polar Electro Inc., Oulu, Finland) during training to control the target heart rates by themselves. They had training log books to find the target heart rates for each session and note down the duration of training.

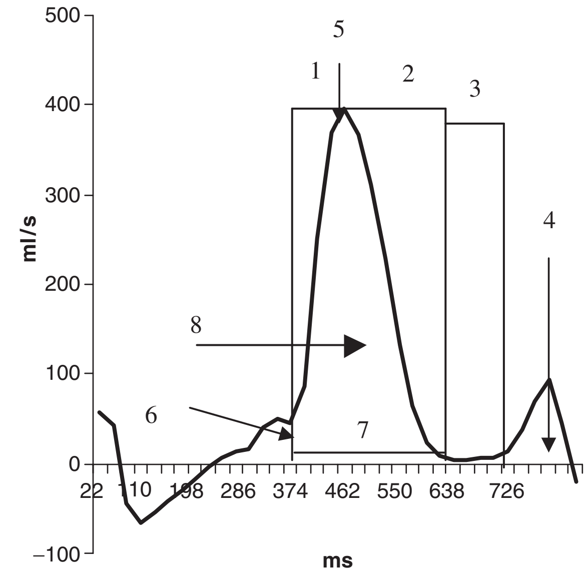

Fig. 1. Magnetic resonance flow velocity inflow curve across the mitral valve. 1, time to peak early filling = time between the early diastole and the time point at which peak early filling rate occurs (ms); 2, deceleration time of early diastolic wave (ms); 3, diastase (ms); 4, atrial filling volume = area under second peak (mL); 5, peak early filling rate = maximal flow rate of first peak (mL/s); 6, Beginning of early diastole; 7, duration of early diastole (ms); 8, early filling volume = area under first peak (mL).

MRI

All subjects were imaged with a 1.5 T Siemens Sonata MR scanner (Siemens, Erlangen, Germany) and a body array coil in the supine position. The same MRI protocol was used in studies before and after the endurance-training period, and studies were conducted by the same radiologist. All tagging and cine MR sequences were performed during prospective ECG triggering and a breath hold in the midle point of the expiratory phase to minimize the effects of respiration variation. Mitral flow velocity mapping was performed during free breathing. All subjects had sinus rhythm during imaging.

The volume flow across the mitral orifice was assessed with the MR velocity mapping with prospective gating using a two-dimensional flow-sensitive gradient echo sequence. Velocity encoding was perpendicular to the imaging plane for the mitral valve (= four-chamber view), and the imaging plane was midway between the end-systolic and end-diastolic four-chamber views (Kroft et al., 2000). Velocity sensitivity was set at 150 cm/s to avoid aliasing. Other acquisition parameters were: repetition time = 22 ms (frame rate = $45\,s^{-1}$), echo time = 4.8 ms, flip angle = 15°, matrix = 256 × 256, field of view = 260–320, and section thickness = 7 mm.

LV short axis true FISP (= fast imaging with steady-state free precession) cine series were obtained for the assessment of volumetric data of the LV at every 15 mm from the LV base to the apex (slice thickness = 7 mm, gap = 8 mm). Acquisition parameters were: repetition time = 34 ms (frame rate = $29\,s^{-1}$), echo time = 1.5 ms, flip angle = 20, matrix = 256 × 256, and field of view = 360.

Two-chamber cine images were obtained to define the plane from the LV apex to the middle of the mitral valve. The four-chamber view for tagging was set perpendicular to the two-chamber view. The four-chamber cine images were labelled with cross-section tag lines at a 90° angle to the interventricular septum. The thickness of the taglines was 2 mm and the distance between taglines was 15 mm. The acquisition parameters were: repetition time = 51 ms (frame rate = $20\,s^{-1}$), echo time = 1.5 ms, flip angle = 55°, matrix = 256 × 256, and field of view = 320 mm.

The delay in the beginning of the diastole was determined from opening of the mitral valve (mean 388 ms, range 345–448), and the end diastole from its closure. The diastolic tagging cine series were obtained by labelling the LV after this delay and following the motion of the tags to the end diastole.

Image analysis

Analysis of global early diastolic LV function

The mitral valve inflow was segmented manually with an image program from the National Institutes of Health (http://rsb.info.nih.gov/nih-image). To determine the flow volume a region of interest (ROI) was drawn at the location of the mitral valve. The ROI was superimposed on subsequent images throughout the cardiac cycle and was adjusted if any change in size or location occurred. The average velocity in the ROI measures on the phase image was then multiplied by the cross-sectional area to generate a flow volume measurement (mean blood flow = mean flow × cross-sectional area) (Szolar et al., 1996). The mitral inflow velocity curves were derived from these measurements.

Diastolic function parameters derived from the inflow curves were the time to peak early filling, the peak early filling rate, the deceleration time of early diastolic wave, the duration of early diastolic wave (Paelinck et al., 2002), and the early filling volume (Pluim et al., 1998) (Fig. 1).

Volumetric analysis

Images were traced manually. Assessment of LV volumes was performed from LV short axis images. End-diastolic and end-systolic volumes were calculated according to the modified Simpson's rule (Soldo et al., 1994), which takes into account the gap between slices. LV mass was determined by subtracting the cavity volume from the total LV volume (= cavity+muscle), and using 1.05 g/mL as the density factor of the myocardium (Pluim et al., 1998).

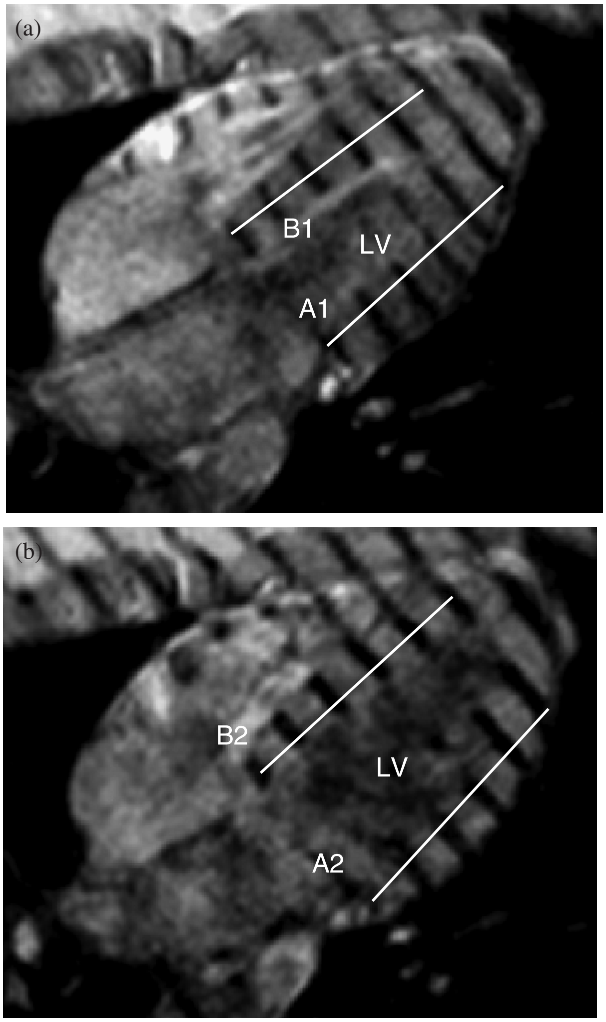

Fig. 2. (a, b) Assessment of the early diastolic myocardial relaxation velocity and relaxation fraction from four-chamber tagging images. (a) Four-chamber tagging image at the beginning of the early diastole: LV, left ventricle; A1, distance between six taglines in the LV free wall; B1, distance between six taglines in the septum. (b) Four-chamber tagging image at the end of the early diastole: LV, left ventricle; A2, distance between six taglines in the LV free wall; B2, distance between six taglines in the septum; Early diastolic myocardial relaxation velocity (mm/s^{-1}) = (B2 − B1)/relaxation time; Early diastolic myocardial relaxation fraction (%) = [(B2 − B1)/B2] × 100.

Analysis of early diastolic myocardial relaxation

The beginning and the end of the early diastole were determined from the velocity inflow curve across the mitral valve (Fig. 1). Longitudinal tagging analysis was performed manually at midmyocardium, perpendicular to the taglines. The distance between basal and apical taglines (= distance between six lines measured from the center of the taglines to avoid the partial-volume effect) was measured on the septum and the LV lateral wall at the beginning and the end of the early diastole. The early diastolic myocardial relaxation velocities and relaxation fractions were determined. (Fig. 2a, b)

Tagged images of one male were excluded because of gating problems, and those of another male because of the failure of the mitral valve MR velocity mapping before training (number of subjects = 12).

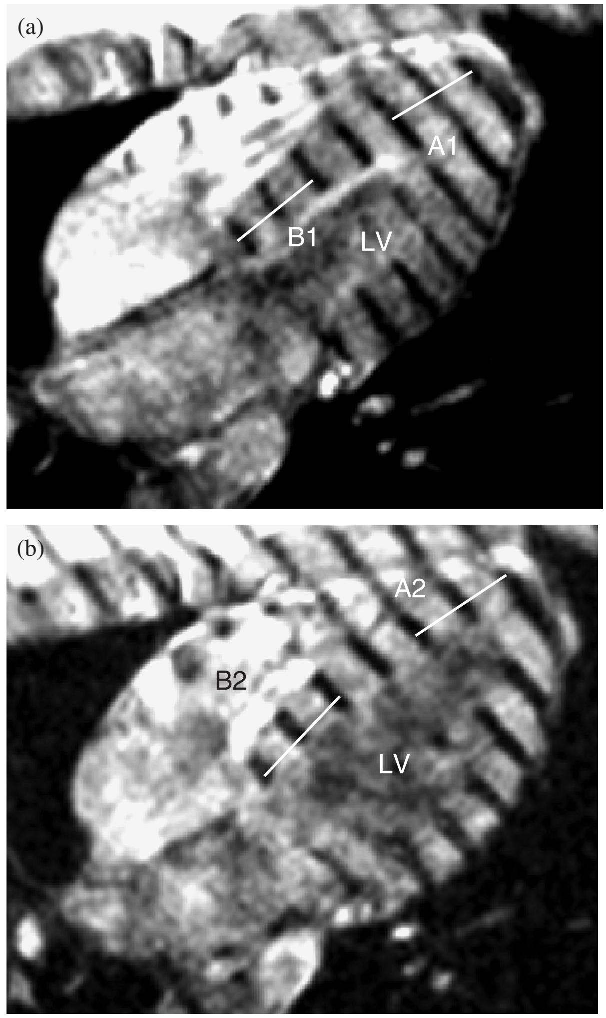

Fig. 3. (a, b) Assessment of regional differences between apical and basal parts of the septum. (a) Four-chamber tagging image at the beginning of the early diastole: LV, left ventricle; A1, distance between three apical taglines in the septum; B1, distance between three basal taglines in the septum. (b) Four-chamber tagging image at the end of the early diastole: LV, left ventricle; A2, diastolic distance between three apical taglines in the septum; B2, distance between three basal taglines in the septum.

Analysis of regional myocardial relaxation

The regional differences in the distance between three apical and three basal taglines (measured from the center of the taglines) were determined to assess diastolic myocardial relaxation in the septum and in the LV lateral wall (Fig. 3a, b). Tagged image data of one male were excluded because of gating problems (number of subjects = 13).

Statistics

Non-parametric tests were used because of the small study group. The Wilcoxon's signed-rank test was used to compare the results before and after the training period, and Spearman's two-tailed correlation coefficient was used to determine correlations. A P-value of <0.05 was considered to indicate statistical significance. Correspondence between the beginning and the length of early diastole in the mitral velocity curve and in four-chamber myocardial tagging was analyzed with the Bland and Altman (1986) method. Intraobserver variability in tagging analysis was also measured with the Bland and Altman (1986) method. All statistical analyses were performed with a commercially available software (SPSS version 11.01).

The Human Research Committee of Helsinki University Central Hospital approved this study, and all subjects gave there informed constant prior to participation.

Results

According to the training log books, the compliance with the training program was $90 \pm 2\%$ ($P<0.05$). Reasons to skip a single or several exercise training sessions were illness (mainly flu) and work-related lack of time to exercise. After training, bicycle exercise test times improved by 58 ± 53 s ($P<0.01$) and the increase in peak Watts was $9 \pm 6\%$ ($P<0.01$). The maximal heart rate did not increase during the training period (before training $180 \pm 7\,\text{min}^{-1}$; after training $180 \pm 8\,\text{min}^{-1}$, $P>0.05$). After the exercise training period for 3 months, the resting heart rate and the systolic blood pressure were found to be lower o measurement. Diastolic blood pressure at rest, weight, and body surface area did not change (Table 1).

Table 1. General comparison of the study group before and after training ($n = 14$, four males)

	Before training	After training	*P*-value*
Heart rate (beats per min)	73 ± 9	64 ± 9	<0.01
Weight (kg)	74.5 ± 15.5	73.8 ± 14.5	>0.05
Body surface area (m^2)	1.82 ± 0.21	1.81 ± 0.20	>0.05
Systolic blood pressure (mmHg)	118 ± 17	112 ± 14	<0.05
Diastolic blood pressure (mmHg)	73 ± 10	73 ± 8	>0.05

**P*-value of <0.05 indicating statistical significance. Values are mean standard deviation.

Global early diastolic LV function

The time to peak early filling shortened. The peak early filling rate, the deceleration time of early diastolic wave, and the duration of early diastole did not shorten significantly. The early filling volume did not change significantly either (Table 2).

Volumetric results

After training, the LV end-diastolic volume did not increase significantly, but the end-systolic volume decreased, and the LV mass increased (Table 3).

Early diastolic myocardial tagging

After training the early myocardial relaxation velocity increased both in the septum and in the LV lateral wall. The early relaxation fraction improved significantly in the LV lateral wall and showed a trend to increase in the septum ($P>0.05$) (Table 2). As there was a lower time resolution in the tagging image sequence than in the MR flow velocity sequence (51 vs 22 ms), the correspondence between the beginning (mean $1.2 \pm$ standard deviation 14.9 ms) and the duration (1.4 ± 22.7 ms) of early diastole was tested with the Bland and Altman (1986) method. The beginning (before training $r = 0.975$, $P<0.001$; after training $r = 0.924$, $P<0.001$) and the duration (before training $r = 0.855$, $P<0.001$; after training $r = 0.778$, $P>0.05$) of the early diastole in flow velocity curves across the mitral valve and in the tagged early diastolic analysis showed a good correlation.

Regional myocardial tagging

Regional longitudinal tagging analysis showed the trend to increase in the myocardial relaxation velocities both in the basal and apical parts of the septum and LV lateral wall ($P>0.05$), but the most pro-

Table 2. Early diastolic mitral flow velocity measurements and left ventricular early diastolic longitudinal tagging measurements in healthy subjects ($n = 13$)

	Before training	After training	*P*-value*
Flow velocity measurements			
Time to peak early filling (ms)	112 ± 32	97 ± 22	<0.05
Peak early filling rate (mL/s)	441 ± 130	420 ± 82	>0.05
Deceleration time of early diastolic wave (ms)	161 ± 30	149 ± 21	>0.05
Duration of early diastole (ms)	271 ± 30	262 ± 27	>0.05
Early filling volume (mL)	56 ± 18	55 ± 12	>0.05
Early diastolic tagging measurements			
Early septal myocardial relaxation fraction (%)	23 ± 6.0	26 ± 5.8	>0.05
Early septal myocardial relaxation velocity (mm/s)	70 ± 18	93 ± 29	<0.01
Early LV lateral wall myocardial relaxation fraction (%)	22 ± 8.5	29 ± 3.8	<0.01
Early LV lateral wall myocardial rela xation velocity (mm/s)	69 ± 26	99 ± 21	<0.01

**P*-value of <0.05 indicating statistical significance. Values are mean+standard deviation.

LV, left ventricle.

Table 3. Left ventricular volumetric data before and after a 3-month endurance training period in healthy subjects ($n = 14$)

Left ventricle	Before training	After training	*P*-value*
End-diastolic volume (mL)	121 ± 19	125 ± 23	>0.05
End-systolic volume (mL)	47 ± 11	42 ± 13	<0.05
Mass (g)	97 ± 19	105 ± 18	<0.01

**P*-value of <0.05 indicates statistical significance. Values are mean standard deviation.

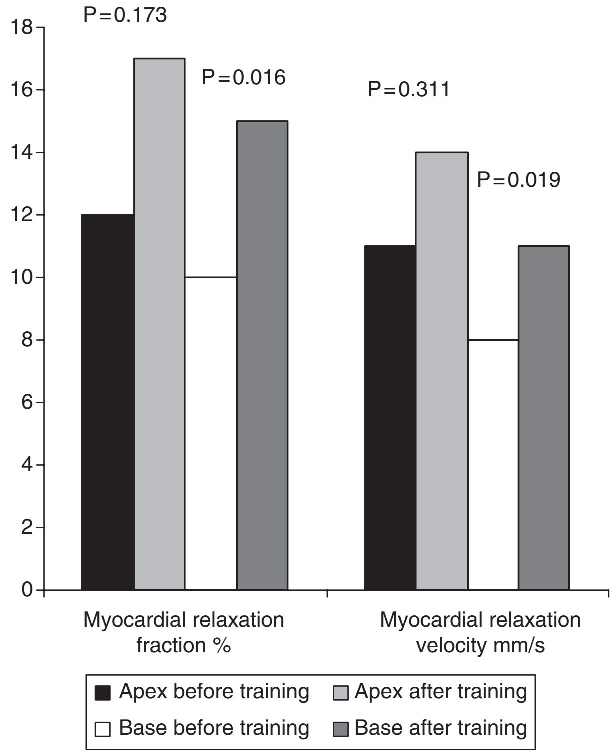

Fig. 4. Regional myocardial tagging results for the apical and the basal diastolic myocardial relaxation fraction (= proportion of regional movement during early diastole as compared with early diastolic movement %) and velocity (mm/s) of the septum before and after a three-month training period in 13 healthy subjects.

nounced increase was in the basal septum ($P<0.05$) (Fig. 4). The total amount of movement during diastole in the basal septum was 2.9 ± 1.9 mm before training and 4.4 ± 1.8 mm after training ($P<0.05$), and in the apical septum the total movement was 3.8 ± 2.2 vs 5.3 ± 2.5 mm ($P>0.05$).

Intraobserver variability of the tagging analysis

The intraobserver variability (n = 30) was 0.5 ± 2.9 mm ($P>0.05$) in the analysis of distance between six taglines and 0.1 ± 1.0 mm ($P>0.05$) in the regional analysis of three apical and basal lines (expressed as bias $\pm$ 1 standard deviation).

Discussion

Our interest was to study the effect of training on diastolic properties, because improved diastolic function could enhance ventricular repolarization and thus could have potential in reducing the risk of tachyarrhythmias in certain arrhythmia-prone patient groups (e.g. in patients with long QT syndrome). Additionally, in patients with diastolic dysfunction, better LV diastolic function could improve the functional capacity. Enhanced diastolic function as well as systolic function could also be beneficial for top athletes in terms of enhanced total LV function. The compliance for the training program reached 90% in our study, which can be considered high in previously sedentary subjects. As we know according to earlier studies, MRI is a highly accurate and reproducible non-invasive method to determine the volume and function of both ventricles morphology and function, especially if the ventricle is morphologically abnormal (Semelka et al., 1990; Soulen, 1991; Allison et al., 1993; Pattynama et al., 1993, 1994, 1995).

Previous echocardiography (Matsuda et al., 1983; Shaphiro & Smith, 1983; Finkelhor et al., 1986; Levine et al., 1991; Nixon et al., 1991; Takemoto et al., 1992; Levy et al., 1993; Gledhill et al., 1994; Fagard, 2003) and MRI (Pluim et al., 1998; Myers et al., 2002) studies have found that endurance-trained subjects had enhanced (Matsuda et al., 1983; Shaphiro & Smith, 1983; Levine et al., 1991; Nixon et al., 1991; Takemoto et al., 1992; Levy et al., 1993; Gledhill et al., 1994; Myers et al. 2000) or the same (Finkelhor et al., 1986; Pluim et al., 1998; Fagard, 2003) LV diastolic function at rest. In addition, several studies have shown that endurance training increases LV diastolic function during exercise (Nixon et al., 1991; Levy et al., 1993; Gledhill et al., 1994; Libonati et al., 1999; Fagard, 2003). In earlier studies, LV end-diastolic volume and mass had increased after endurance training in healthy subjects (Milliken et al., 1988; Ehsani et al., 1991; Nixon et al., 1991; Pluim et al., 2000; Scharhag et al., 2002; Wernstedt et al., 2002). In our study the time to the peak early filling shortened after training, indicating enhancement in the LV global early myocardial relaxation. In addition, the LV mass increased and the end-diastolic volume was maintained or showed a trend to increase as can be found in physiological LV hypertrophy. Most of the studies are cross-sectional and compare the LV diastolic filling between athletes and normal subjects (Matsuda et al., 1983; Finkelhor et al., 1986; Levine et al., 1991; Nixon et al., 1991; Takemoto et al., 1992; Gledhill et al., 1994; Pluim et al., 1998; Libonati et al., 1999; Fagard, 2003). Follow-up echocardiography studies (Shaphiro & Smith, 1983; Levy et al.,

1993) that compare the results before and after supervised training period in normal subjects are rare. As we know, there are no previous follow-up MRI studies on the effect of endurance training to LV early diastolic global and regional function assessed with myocardial tagging in normal subjects. Myers et al. (2002) studied the effects of endurance training on LV diastolic and systolic function with tagged MRI in non-ischemic cardiomyopathy patients. In their study, the LV diastolic rotational relaxation velocity increased significantly after a two-month endurance training period, but the systolic function did not change. In our study, the early diastolic myocardial relaxation in the septum and in the LV lateral wall increased. In the regional tagging analysis, we found differences in diastolic myocardial relaxation; diastolic relaxation was more pronounced in the basal septum.

Earlier studies have determined ventricular inflow curves with Doppler echocardiography (Matsuda et al., 1983; Nixon et al., 1991; Takemoto et al., 1992; Levy et al., 1993) or with MR flow methods (Soldo et al., 1994; Paelinck et al., 2002) to assess global diastolic function. It is also possible to investigate regional myocardial function with tissue Doppler echocardiography (Garcia et al., 1998; Palka et al., 1999) and tagging MRI. Myocardial velocities can be recorded at a high frame rate with Doppler echocardiography (Hatle & Sutherland, 2000). Tissue Doppler represents the component of motion of a given segment in a direction parallel to the imaging cursor. We believe that myocardial tagging is parallel to tissue Doppler in that feature. Similarly, in the MRI myocardial four-chamber tagging method, the increase in distance between taglines is related to longitudinal diastolic myocardial relaxation and diastolic filling (Mandinov et al., 2000). In the Doppler myocardial imaging study by Palka et al. (1999), athletes had more rapid early diastolic filling compared with sedentary subjects, although no differences were found in LV systolic and late diastolic function. Our longitudinal tagging results of the LV early myocardial relaxation were in concordance with these results, indicating more pronounced early myocardial relaxation after training.

We assessed LV function with mitral flow velocity mapping, cine MRI, and four-chamber tagging. Mitral flow velocity mapping enables determination of ventricular flow and reconstruction of time–velocity curves. With cine MRI, it is possible to determine LV end-diastolic and end-systolic volumes and LV mass. These two methods determine the ventricular global function. Several physiological variables affect flow velocities simultaneously and may have confounding effects on ventricular inflow (Ommen et al., 2000). The four-chamber tagging method assesses regional myocardial function, and similar to tissue Doppler, it is less sensitive to preload changes (Garcia et al., 1998). The reproducibility of the myocardial tagging method is satisfying (Paelinck et al., 2002). Also, in our study, the intraobserver variability was low ($P>0.05$). The spatial resolution of the technique was good enough, a pixel size between 1 and 2 mm, as recommended in Pons-Llado's (2005) study . The pixel size in our study was 1.25 mm. The thickness of the tagline was 2 mm. We minimized the partial-volume effect as much as possible by measuring the distance between lines from the center of the taglines. In the future, it will be possible analyze to also myocardial rotation with two- or three-dimensional tagging algorithms.

The limitations of this study are: retrospective ECG-gated sequences were not available at the time of imaging of the subjects, and thus, we used prospective gating. Late diastolic information of atrial contraction was therefore missed, and we concentrated on early diastolic results. As there are no commercial algorithms available for two- or three-dimensional tagging analysis, we concentrated on unidimensional tagging analysis in this study. The myocardial four-chamber tagging method determines only the longitudinal movement of the septum and the LV lateral wall, and it is not able to determine the rotational LV movement. However, the longitudinal movement is one component in the myocardial rotation, and therefore relative to the rotational movement of the heart. Accurate determination of functional changes requires a temporal resolution of <40 ms (frame rate $<25\,s^{-1}$) (Fujita et al., 1993; Hartiala et al., 1993). Temporal resolutions of our cine and flow sequences were 34 ms (frame rate $29\,s^{-1}$) and 22 ms (frame rate $45\,s^{-1}$), respectively. In the tagging sequence, the temporal resolution was 51 ms (frame rate $20\,s^{-1}$), lower than recommended; we therefore determined the beginning and the end of early diastole from mitral velocity inflow curves.

Perspectives

Using different MRI techniques (mitral flow velocity mapping, cine MRI and four-chamber tagging) we assessed the effect of moderate training on the diastolic properties of the LV in healthy sedentary subjects. Global early diastolic relaxation improved and physiological LV hypertrophy was found after a 3-month endurance-training period. Regional early diastolic myocardial relaxation improved significantly both in the septum and in the LV lateral wall, and relaxation was more pronounced in the basal septum. In the future, we will study the effect of endurance training on the right ventricle and both atria with MRI.

Key words: endurance training, diastolic function, magnetic resonance imaging, myocardial tagging.

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