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Impact of Prolonged Exercise on Right Ventricular Function in Older Individuals

Majke H.D. van Bommel (1), Dr. Thijs M.H. Eijsvogels (1), Prof. Dr. Maria T.E. Hopman (1), Dr. Dick H.J. Thijssen (1)

(1) Department of Physiology, Radboud University Medical Centre Nijmegen, The Netherlands

Corresponding Author: Majke H.D. van Bommel, BSc (majkevanbommel@hotmail.com)

ABSTRACT:

IMPACT OF PROLONGED EXERCISE ON RIGHT VENTRICULAR FUNCTION IN OLDER INDIVIDUALS

BACKGROUND: Cardiovascular disease (CVD) is the leading cause of death, contributing to approximately 30% of all deaths worldwide. In contradiction with its long-term preventive effect on the development of CVD, an acute bout of exercise has potentially harmful effects on the cardiovascular system. Cardiac function is reduced immediately after prolonged strenuous exercise in young athletes, a phenomenon known as cardiac fatigue. Whether such changes also occur in older individuals, who typically demonstrate impaired cardiac function, is currently unknown.
OBJECTIVE: Examine the impact of prolonged exercise on right ventricular function in healthy older individuals.
METHODS: To examine this effect, fourteen octogenarians performed a single-day thirty-one-km self-paced march starting at 08.00 AM; systolic and diastolic cardiac function (using two dimensional-echocardiography) were measured before and immediately after exercise. During the march, heart rate and physical activity level were measured continuously.
RESULTS: All participants completed the march within 5h49min±51min at 72±12% of their maximal heart rate. Right atrial end-diastolic volume was decreased with 19% (p=0.010), whilst end-systolic volume showed a trend towards a decrease (48±12 to 41±12, p=0.058). Furthermore, right ventricular outflow, only in the parasternal-short-axis view, showed a 6% increase post-march (p=0.018) and strain rate during ventricular systole was decreased significantly (-1.7±0.4 to -1.9±0.4, p=0.027), while other strain rates were not altered after the march.
CONCLUSION: This study reveals that these octogenarians are well capable of performing a thirty-one-km walking march at moderate-intensity, whilst we revealed a reduced RV size after prolonged walking exercise. This observation is in marked contrast with previous findings in younger peers, in which a RV constriction was found, and suggests distinct changes in right ventricle function between young and older subjects.

KEYWORDS: Cardiac fatigue; prolonged exercise; octogenarians; right ventricle; echocardiography

Introduction

Cardiovascular disease (CVD) is the leading cause of death, contributing to approximately 30% of all deaths[1]. It is well-known that physical activity improves many functions within the human body and reduces symptoms of or even prevents CVD[2-8].

In contradiction with its long-term preventive effect on the development of CVD, an acute bout of exercise has been associated with potentially harmful effects on the cardiovascular system[3]. This phenomenon, called the 'exercise paradox', has gained much scientific interest and refers to the fact that cardiac health improves over a long period of time, whereas the risk of cardiovascular accidents is increased during and immediately after exercise [9]. As a result, studies have examined the immediate impact of an exercise bout on cardiac function, especially after prolonged, strenuous exercise. Recently, several studies reported that cardiac function is reduced immediately after a prolonged, strenuous bout of exercise, so-called cardiac fatigue[4, 5, 9]. In particular, right ventricular function during systole is depressed [10]. Moreover, right ventricular volume, both systolic and diastolic, was increased and the strain-rate during systole was significantly decreased post-exercise[10]. The general pattern to date shows that the acute effects of prolonged exercise include right ventricular dilatation and dysfunction. Furthermore, circulating cardiac troponin levels, as surrogate measure for cardiac damage, increase during and after moderate to high intensity exercise, reflecting the presence of some level of cardiac damage[11-15]. Typically, before exercise troponin levels are below the limit of detection, and after exercise troponin is detectable and reaches levels as seen during myocardial infarctions[3].

The aforementioned studies focused on the presence of cardiac fatigue after a bout of prolonged endurance exercise in (usually highly trained) healthy young and middle-aged men with healthy hearts. Accordingly, such results are difficult to extrapolate to other groups, such as older individuals. This latter group is of special interest given the increasing number of older individuals that participate in long-term athletic events, such as walking marches.

Advanced age is associated with a strong increase in cardiovascular risk[9]. Furthermore, older individuals are characterized by lower cardiac function compared to their younger peers[16, 17]. It is currently unknown whether a prolonged, strenuous bout of exercise in older individuals, who demonstrate a priori impaired cardiac function, leads to the typical depression in cardiac function and elevation in surrogate markers for cardiac damage. Taken into account that walking is an often performed exercise in older individuals, it is clinically relevant to examine the effect of prolonged walking

exercise on cardiac function in an older population.

Therefore, the aim of this observational study is to examine the impact of prolonged, moderate-intensity exercise on cardiac function and damage in older individuals. To examine this, octogenarians, individuals older than eighty years, will perform a single-day thirty-one-km self-paced march. We hypothesized that prolonged, moderate-intensity exercise in older individuals will lead to an acute decline in cardiac function, expressed in dilatation of the right ventricle.

Methods

Participants

Fourteen octogenarians, eight males and six females, participated in this study. All subjects provided written informed consent prior to participation. Five participants were taking cardiovascular drugs during the study, all to combat hypertension; further baseline characteristics are presented in Table 1. All subjects were registered and preparing for the Nijmegen Four Days Marches of 2014. We excluded subjects with a history of cardiovascular or cerebrovascular complication and (preventive) cardiac surgery, because of safety reasons. The study was granted approval by the local ethics committee.

Design

Participants performed a thirty-one-km self-paced walking march. To ensure that the subjects were well-trained to perform the single-day-thirty-one-km march, the study was scheduled two months before the Nijmegen Four Days Marches. The day before the march, day 1, we examined baseline characteristics, systolic and diastolic cardiac function, pulmonary function and muscle strength. The subjects also completed the International Physical Activity Questionnaire (IPAQ). On the subsequent day, subjects performed the march, starting at 8.00 AM. Within thirty minutes after completion of the march, we repeated all measurements as performed on day 1.

Procedures

Table 1 *Baseline characteristics of the participants*

	Mean±SD
Male : female	8:6
Age (years)	81.7±2.2
Height (cm)	169.6±6.9
Body mass (kg)	66.1±10.2
Hip-to-waist ratio	0.88±0.08
Systolic blood pressure, rest (mmHg)	142±22
Diastolic blood pressure, rest (mmHg)	81±12
Heart rate, rest (beats/min)	57±9

From twenty-four hours before baseline measurements, no strenuous exercise was performed. From eighteen hours before baseline measurements, no food and beverages influencing cardiac parameters (e.g. alcohol, caffeinated products and product containing high vitamin C content) were consumed, and from four hours before baseline measurements, only water was consumed. Furthermore, to minimize the impact of food on post-march cardiac function, at least two hours before finishing the walk no beverages and food were consumed. The amount of food and beverages, just as the amount and duration of breaks were noted in a diary by supervisors during walking. During the march, physical activity level and heart rate were constantly monitored using a Sensewear accelerometer and a Polar chest strap respectively. Ambient temperature during the march reached 17 °C.

Echocardiography

All echocardiographic images were acquired using a commercially available ultrasound system (Vivid Q, GE Medical, Horten, Norway) with a 1.5-4 MHz phased array transducer. After the participant had lain supine for fifteen minutes, a comprehensive examination was performed by two experienced sonographers, with the participant in the left lateral decubitus position. Each sonographer measured the same subject before and after the exercise. Furthermore, heart rate was taken from the ECG inherent to the ultrasound system. Images were recorded to DVD in raw DICOM format and data were analyzed offline by the same two experienced sonographers using commercially available software (EchoPac version 7, GE Medical, Horten, Norway). A minimum of three cardiac cycles were averaged for all peak indices and all settings were optimized to obtain maximum signal-to-noise ratio.

Convectional echocardiography

To allow accurate assessment of the right ventricle (RV), standard two-dimensional, pulsed wave Doppler and pulsed tissue Doppler (TDI) echocardiographic indices were obtained from different views [18]. Right ventricular size was measured at end diastole from the outflow. The body of the RV was assessed at three points. RV areas, end-diastolic (RVAd) and end-systolic (RVAs), were obtained by tracing around the endocardium. Right atrial (RA) volume and dimensions were measured at end-systole (RAESV) as well as prior to atrial contraction (RAPreA) and at end-diastole (RAEDV). Furthermore, as a measure for interventricular septal displacement, left ventricular eccentricity index (EI) was calculated and therefore also RV pressure and volume overload were determinable. RVOT and pulmonary artery peak velocity were obtained using a pulsed wave sample just below the pulmonary valve. A two millimeter sample volume was placed in the tricuspid annulus of the RV lateral wall and peak systolic (S'), early (E') and late (A') diastolic velocities were recorded.

Myocardial Speckle Tracking analysis

Utilizing two-dimensional myocardial speckle tracking analysis (MST), strain and strain rates derived from a modified, lateral four-chamber view[19, 20]. Regional peak longitudinal systolic strain rate (SRs'), early diastolic strain rate (SRe') and late diastolic strain rate (SRa') values were obtained for RV basal, mid and apical wall segments. In order to standardize for variable heart rates (HR), temporal data for all RV indices were obtained throughout the entire cardiac cycle using cubic spline interpolation in Microsoft Excel 2010 to provide three hundred data points for both systole and diastole[10].

Polar chest strap

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All subjects carried a Polar RS800 chest strap during the march to continuously measure heart rate. Data were used as descriptive measures and to analyze post-hoc whether between-subject differences in mean heart rate during exercise contribute to the primary outcome measures. The maximal predicted heart rates of our participants were calculated according to the formula: (208–[age*0.7])[21]

Accelerometer

During the march, all subjects carried a SenseWear Pro2 Activity accelerometer to continuously measure physical activity level. Data were used as descriptive measures and to analyze post-hoc whether between-subject differences in physical activity level during exercise contribute to the primary outcome measures.

Statistical Analysis

Pre- and post-march values for systolic and diastolic cardiac functions were analyzed using a dependent Student's t-tests. Physical activity level and heart rate were used as descriptive measurements. All values are presented as mean value ± standard deviation (SD). All analyses were carried out on Statistical Software SPSS 20.0 in which the critical alpha level was set to $p < 0.05$.

Results

All fourteen participants successfully completed the thirty-one-km march. Characteristics of the walking exercise are presented in Table 2 and confirm that participants performed prolonged (5h49min±51min), moderate-intensity (72±12% maximal heart rate) exercise. Body mass was reduced post-march (67.6±10.4 to 67.0±10.2 kg, $p<0.001$) and heart rate was increased (57±9 to 71±15 beats/min, $p<0.001$). Systolic and diastolic blood pressures were reduced post-march (142±22 to 127±16 mmHg, $p=0.004$ and 81±12 to 71±13 mmHg, $p=0.018$, respectively). Pre- and post-exercise right ventricular and atrial structural indices are shown in Table 3. RV diameter from apex to base (longitudinal, i.e. RVD3) was significantly decreased with 5% after the march ($p=0.016$), while RV diameters at the base and in the middle of the ventricle were not changed ($p=0.134$ and $p=0.734$ respectively).

Although RV systolic and diastolic areas were not significantly altered after completion of the march (right figure in Figure 1), RV:LV ratio was sig-

Table 2 *Characteristics of the walking exercise*

	Mean±standard deviation (SD)
Duration of exercise (minutes)	349±51
Heart rate, during walking (beats/min)	108±17
Percentage of predicted maximal heart rate (%)*	72±12
Physical activity, during walking (METs)	5.4±0.9

* Maximal predicted heart rate was calculated according to the formula: (208–[age*0.7]) (1)

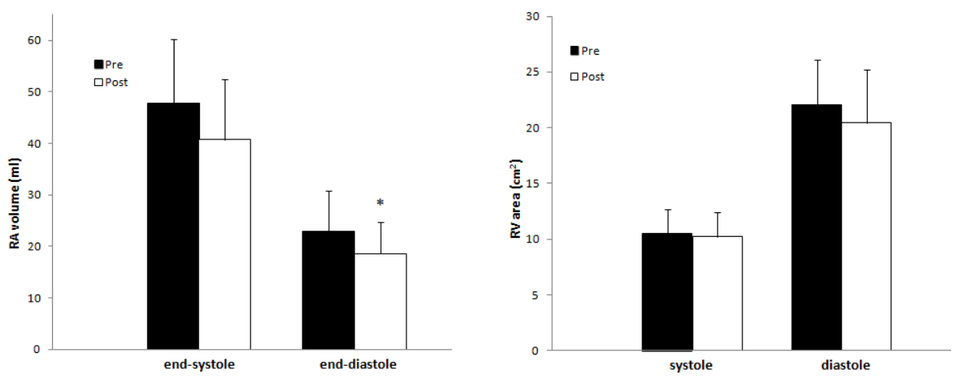

Figure 1 *Right atrial volume (left figure) and right ventricular area (right figure) in both the systolic and diastolic phase for all participants pre-march and post-march.* *significant difference ($p<0.05$)

Table 3 *RV and RA structural indices before (pre-march) and after (post-march) the 31-km march in fourteen healthy octogenarians, presented as mean ± standard deviation.*

Parameter	Pre-march Mean±SD	Post-march Mean±SD	P-value
Right ventricle			
RVD1 (mm)	41±5	40±4	0.134
RVD2 (mm)	28±4	27±5	0.734
RVD3 (mm)	84±10	80±9	**0.016**
RV systolic area (cm^2)	11±2	10±2	0.513
RV diastolic area (cm^2)	22±4	20±5	0.129
RV:LV ratio	1.0±0	0.9±0	**0.014**
RVOT PLAX (mm)	32±5	31±4	0.679
RVOT1 (mm)	32±5	31±4	0.241
RVOT2 (mm)	24±3	26±3	**0.018**
RV wall thickness (mm)	4±1	4±1	0.547
IVC diameter (mm)	16±4	17±5	0.554
Right atrium			
RA end-systolic volume (ml)	48±12	41±12	0.058
RA end-diastolic volume (ml)	23±8	19±6	**0.010**
RA area (cm^2)	16±4	15±3	0.266
Parameter	**Pre-march Mean±SD**	**Post-march Mean±SD**	**P-value**

RV, right ventricle; RVD1, RV basal diameter; RVD2, RV mid cavity diameter; RVD3, RV longitudinal diameter from apex to base; LV, left ventricle; RVOT PLAX, RV outflow tract parasternal long axis; RVOT1, RV outflow tract at the beginning of the pulmonary artery (parasternal short axis view); RVOT2, RV outflow tract measured at the mid of the pulmonary artery (parasternal short axis view); IVC, inferior vena cava; RA, right atrium.

nificantly declined (p=0.014), which probably means a change in the RV, because LV parameters were mostly unchanged. Right ventricular outflow from the parasternal short axis view (RVOT2) demonstrated a 6% increase post-march (p=0.018), whilst RV outflow from other views were not changed (p=0.679 and p=0.241). Also in the atrium, we found that RA end-diastolic volume was significantly lower (p=0.010), whilst a strong trend was observed for RA end-systolic volume to be lower (p=0.058) (left figure in Figure 1).

RV functional parameters are presented in Table 4 and strain indices are presented in Table 4 and Figure 2. The left figure in Figure 2 shows the peak longitudinal strain and the right figure shows peak longitudinal strain rate during ventricular systole.

Discussion

This study provides a comprehensive examination of the right ventricle before and after a thirty-one-km march in older individuals. A main finding is that these octogenarians are well capable of performing a thirty-one-km march. Secondly, we found that a bout of prolonged, moderate-intensity exercise in healthy octogenarians resulted in smaller right ventricular size and a lower right atrial volume, whereas strain and strain rates were minimally affected. The acute impact of prolonged exercise on cardiac function has been evaluated several times before and, generally, studies have reported the presence of a dilatation of the right ventricle. The unique observation in our study, that prolonged exercise can also cause constriction of the RV, is in marked contrast with previous findings in younger peers. This finding suggests the presence of distinct acute adaptation to exercise in

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right ventricle function between young and older individuals.

Previous studies examining cardiac function after exercise have typically included marathons, ultramarathons or ironman triathlon races as intervention. Average finishing times of these marathons ranged from 3h49min±38min to 4h16min±46 min[3, 11, 22, 23], and ironman triathlons and ultramarathons from 9h46min±1h20min to 24h32min±3h20min[10, 24, 25]. Our study, with an average finishing time of 5h49min±51min, fits within these timeframes and represents performance of prolonged exercise. Regarding the intensity of exercise, marathons and other types of prolonged exercise can be described as high-intensity with a percentage of the maximal predicted heart rate between 80 - 90%[26]. In this study the mean percentage of predicted maximal heart rate was 72±12%, reflecting a moderate-intensity exercise. Data from the accelerometer support this observation as walking by the octogenarians was performed between 3.0 and 6.0 METs, reflecting a moderate-intensity physical activity level[27]. Collectively, the walking exercise performed in this study represented a prolonged, moderate-intensity exercise which is largely in line with previous studies that have examined the impact of prolonged exercise on cardiac function. This suggests that our study was well designed to assess the impact of prolonged exercise on cardiac function in healthy octogenarians.

Baseline data provide a unique insight into the impact of advanced age on cardiac function. Previous studies on cardiac function and structure in healthy young and middle-aged subjects suggest that advanced age is associated with a smaller right ventricle and atrium. These findings are strengthened by the results of La Gerche et al.[28] and Oxborough et al.[10] in which smaller heart sizes were found in young-to-middle aged athletes compared to young athletes. Our findings are also consistent with observations of Stratton et al.[16], in which young healthy non-athletes (age, 24 to 32 years) revealed a larger right ventricle and atrium compared to older healthy non-athletes (age, 60 to 82 years), and with others who suggest that older age is associated with smaller right ventricles and atria[29-31]. These observations of a smaller heart size in older humans may be explained by the normal aging processes, as muscle atrophy and the increase in connective and adipose tissue in the right ventricle, indicating a degree of muscle loss[32]. Also physical inactivity leads to muscle loss[33]. However, the participants in this study were very active during daily life. Nevertheless, they do reveal a relatively small heart. Therefore, it seems likely that aging has a larger role in this process of changes in cardiac size, rather than activity level only.

A main finding of our study is the decrease in right atrial volume and the trend towards a decrease in right ventricular area post-march compared to pre-march. These observations are in marked contrast with other studies, primarily performed in healthy young and middle-aged groups such as the Boston Marathon[34] and the Hawaii Ironman Triathlon[35], in which a RV size increase was found after a strenuous exercise bout. Currently, two hypotheses for the increase in cardiac parameters in young individuals are considered. Firstly, heart size is increased, because the resistance against outflow of the right side of the heart is increased (i.e. pulmonary afterload). Due to inadequate dilatation of the pulmonary artery, pulmonary pressure increases and therefore less blood is able to flow out of the right side of the heart, resulting in an increased heart size in young individuals[34, 36]. Translating this to older individuals, in whom we found the opposite, a smaller heart size after exercise may relate to an increase in RV outflow. Indeed, right ventricular outflow diameter in the mid of the artery was higher after the march in older humans. Moreover, we also found a decrease in pulmonary artery pressure, indicating that the pulmonary artery in octogenarians dilated significantly. This dilation may have allowed the heart to more easily expel blood from the RV and, subsequently contributed to a smaller right heart size directly post-exercise.

The second hypothesis for the larger RV size after exercise in healthy young subjects includes the inflow tract (or preload). Based on previous literature, heart size may be increased in young individuals after exercise due to an increased venous return (or preload)[24]. One potential explanation for our observation of a decline in right ventricle and atrial mass is that, after the ~6 hour march, a lower circulating volume is present. A decrease in the circulating volume logically leads to a decline in preload of the RV, whilst such observation may be caused by dehydration after a thirty-one-km march. To support this idea, body mass was significantly decreased after finishing

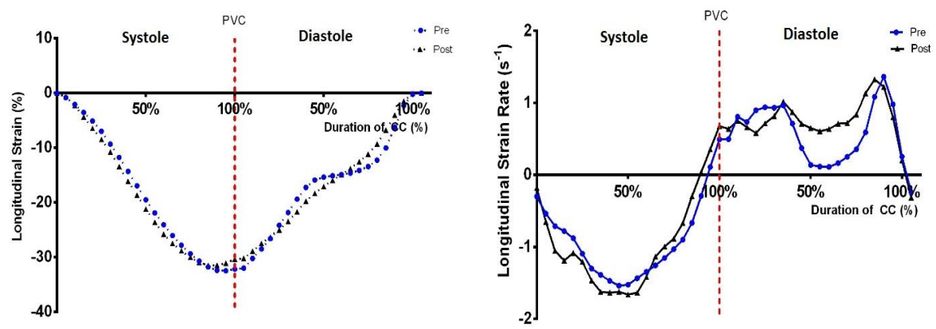

Figure 2 *Peak right ventricular longitudinal strain (left figure) and strain rate (right figure) throughout the cardiac cycle with data averaged across all participants.* PVC indicates pulmonary valve closure; CC, cardiac cycle.

the march. However, the validity of body mass as measure for dehydration can be discussed. Moreover, none of the participants met the cut-off value of >2% loss of body weight, which is widely adopted as the definition of dehydration. Furthermore, in studies examining (ultra)marathons, where less beverages are consumed and significantly more fluid is lost, no decrease in blood volumes were observed. Therefore, we believe it is unlikely that dehydration plays an important role in explaining our results.

As the increased RV size is due to an increased venous return in young subjects, we believe that the reduced RV sizes in our older individuals may be explained by a lower venous return. Venous return is not only influenced by the circulating volume, but also by other factors like the ability of the venous system to transport blood back to the heart. The quality of the venous system seems to decrease with age, and this might be due to venous valve dysfunction and/or an impaired muscle pump quality. Both, venous valves and the muscles pump of the lower extremity contribute to an adequate blood flow supply towards the vena cava and the right atrium. When these functional characteristics are impaired, more blood may be pooled in the lower extremities, leading to a lower venous return.

Focussing on cardiac function, we found that late peak diastolic filling velocity is increased after exercise, reflecting a faster filling of the right ventricle during end-diastole after exercise. This is consistent with previous studies examining cardiac fatigue[22]. However, both early diastolic filling velocity and systolic myocardial tissue velocity are both before and after the exercise lower in our study population compared to younger athletes[22]. These findings suggest that filling velocity is dependent of the cardiac cycle phase and is influenced by prolonged exercise.

Limitations

A limitation of studies examining cardiac function after prolonged exercise is the inability to measure cardiac function immediately after finishing. Consequently, the period between finishing the march and cardiac measurement differs between the participants. Therefore, in our study, post-march timing was timed consistently between subjects at 25-113 minutes after finishing. Importantly, the time between finish and cardiac assessment did not correlate with any of the cardiac parameters. Therefore, timing of the post-race cardiac measurement unlikely influenced our major outcomes. Another potential limitation is that our results cannot be simply extrapolated to octogenarians in general. The fact that our participants were able to perform a single-day thirty-one-km march within on average less than six hours, reveals that we have included a healthy, physically active and exclusive subgroup of the overall octogenarian population. Nonetheless, selection of this subgroup allowed us to validly assess the impact of advanced age on the exercise-mediated changes in cardiac function. This represents a unique design and, to the best of our knowledge, no other study attempted to assess the impact of exercise in such a group.

Clinical relevance

We found acute changes in cardiac function after a prolonged exercise in healthy older individuals. These effects could represent a stimulus for the heart for subsequent adaption to training when repeatedly exposed to this stimulus. Alternatively, the acute effects of exercise on the heart could also relate to the exercise paradox. Accordingly, the immediate change in cardiac function after exercise may relate to the increased risk for cardiac events during exercise.

Conclusion

This study revealed a smaller RV size after prolonged, moderate-intensity walking exercise in healthy octogenarians. This observation of a constriction in RV is in marked contrast with previous findings in younger peers that reveal dilatation of the RV after prolonged exercise. These distinct changes in right ventricle function between young and older subjects after exercise may relate to intrinsic characteristics of the heart (e.g. stiffening) that cause constriction, but may also relate to age-related impairment of peripheral blood flow responses that contribute to the venous return of blood. More research in this area is warranted to elucidate the responsible mechanisms and clinical relevance of this confliction between young and older well-trained individuals.

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Table 4 *RV functional indices and strains before (pre-march) and after (post-march)the 31-km march in fourteen healthy octogenarians. Data is presented as Mean±SD*

Parameter	Pre-march Mean±SD	Post-march Mean±SD	P-value
Functional indices			
EI systole	1.0±0.1	1.1±0.1	0.097
EI diastole	1.1±0.1	1.2±0.1	0.200
PA systolic pressure (mmHg)	33±5	29±4	**0.034**
Strain indices			
RV S' (cm/s)	16±2	17±4	0.174
RV E' (cm/s)	11±2	11±3	0.502
RV A' (cm/s)	19±4	23±7	**0.030**
RV E'/A'	0.6±0.1	0.5±0.1	**0.012**
Peak RV longitudinal strain (%)	-32.8±4.6	-32.2±4.6	0.495
Peak RV SRs' (s^{-1})	-1.7±0.4	-1.9±0.4	**0.027**
Peak RV SRe' (s^{-1})	1.6±0.3	1.5±0.5	0.303
Peak RV SRa' (s^{-1})	1.8±0.4	1.8±0.4	0.952
RV SRe:SRa	0.9±0.2	0.9±0.3	0.344

EI, eccentricity index; RVFAC, RV fractional area change; PA, pulmonary artery; S', systolic myocardial tissue velocity; E', early diastolic myocardial velocity; A', late diastolic filling velocity; SRs', strain rate during ventricular systole; SRe', strain rate during early ventricular diastole; SRa', strain rate during late ventricular diastole.