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Original Article

Non-invasive measurement of the response of right ventricular pressure to exercise, and its relation to aerobic capacity

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Abstract *Introduction:* Exercise echocardiography assesses exercise-induced pulmonary hypertension. The upper normal limit of right ventricular systolic pressure during exercise is not well established. Our study aims to investigate the response of right ventricular systolic pressure in relation to aerobic capacity. *Methods and results:* Cardiopulmonary exercise testing using a treadmill, and echocardiography during supine cycling, were performed in 113 healthy volunteers aged 13 to 25 years. Maximal right ventricular systolic pressure during evaluable exercise studies obtained in 108 subjects showed a Gaussian distribution only after separating the endurance trained subjects, specifically 12 athletes with Z-score of peak oxygen uptake higher than 2.0, from the normally trained group of 97 subjects. Maximal right ventricular systolic pressure during exercise in the normally trained group showed a mean of 38.0 millimetres of mercury, with standard deviation of 7.2, a median value of 39.0, and a range from 17 to 63, and the 95th percentile was 51 millimetres of mercury. In the athletes, the maximal right ventricular systolic pressure was higher, with a median of 55.5, a range from 28 to 69, this being significant, with p equal to 0.004). Of the 12 athletes, 8 (67%) showed a response of right ventricular systolic pressure to exercise exceeding 50 millimetres of mercury, but only 8 of 97 normally trained subjects (8%) showed a similar response, this also being significant, with p less than 0.001. *Conclusions:* Our study confirms the great variability in the response of right ventricular systolic pressure to exercise in healthy individuals, with 50 millimetres of mercury representing the upper normal limit. Endurance-trained athletes show higher levels, and two-thirds have abnormal responses exceeding 50 millimetres of mercury.

Keywords: Exercise echocardiography; exercise physiology; pulmonary hypertension; pulmonary circulation

Pulmonary arterial systolic pressure, and right ventricular systolic pressure, are approximately one-quarter of systemic arterial pressure, and are considered to remain nearly unchanged during exercise. Few studies, however, have investigated normal pulmonary pressures during exercise.[1–3] A known pulmonary arterial systolic pressure allows calculation of the mean pulmonary arterial pressure, which by consensus defines pulmonary arterial hypertension.[4,5] The use of invasive methods to measure pulmonary arterial pressure in healthy individuals is limited by ethical considerations. Echocardiography has been shown to provide reliable measurements compared to invasive measurement at rest,[6] and during exercise.[7,8] In the absence of an obstructed right ventricular outflow tract, the systolic pressure reflects, but does not equal, pulmonary arterial systolic pressure.[2]

International guidelines define the normal upper limits of pulmonary arterial systolic pressure at rest, but there is a general uncertainty about the upper

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limits for both pulmonary and right ventricular systolic pressures during exercise.[9,10] A value of 40 millimetres of mercury, or in some papers 45 millimetres of mercury, is proposed as the upper normal limit during exercise.[2,3,11] Recent studies, however, have shown an abnormal response of right ventricular systolic pressure above 45 millimetres of mercury during exercise in healthy, normal individuals,[12] and also in healthy carriers of mutations in the bone morphogenetic protein receptor type 2 gene.[13] Such abnormal responses have been shown to be a marker of susceptibility to high altitude pulmonary oedema.[14] Some investigators have also shown abnormal responses in endurance-trained professional athletes,[15] whereas others demonstrated a normal response.[3] It has been hypothesized that the extremely high cardiac output of such athletes exceeds their pulmonary vascular dilative capacity, and thereby may lead to pulmonary vascular pressures above normal limits.[1,15]

The pulmonary endothelium is adapted to conditions of low blood pressure. Endothelial damage is well known in different kinds of pulmonary arterial hypertension. In patients with Eisenmenger syndrome, who have untreated or complicated congenital cardiac malformations, shunting of blood from the systemic to the pulmonary circulations results in excessive pulmonary flow and endothelial sheer stress.[16]

We are not aware of any major studies on the normal range of either right ventricular or pulmonary arterial systolic pressures during exercise in healthy adolescents, including non-professional high performing athletes. Exercise echocardiography is of increasing importance as a diagnostic tool in pulmonary hypertension, and normal values of right ventricular systolic pressure during exercise are strongly needed. In this study, therefore, we aimed to investigate the normal range, in particular the upper normal limit, of right ventricular systolic pressure in adolescents and young adults during exercise, as measured by non-invasive ultrasonic techniques. Additionally, we aimed to investigate the interrelation of right ventricular systolic pressure to the aerobic exercise capacity, and to establish whether endurance-trained athletes differ from the normally trained population.

Materials and methods

Population

Healthy volunteers were recruited from hospital employees and their relatives, among college students of a nearby institution, and among local inhabitants. The volunteers were aged between 13 and 25 years, because an age- and gender-matched control group was needed at ratios of 2 to 1 for research in a young population of 45 subjects with congenital cardiac disease. The volunteers had no known heart or lung disease, albeit that mild bronchial asthma was accepted. Detection of any cardiac condition, or any serious lung condition, during the study led to exclusion.

Examination

The clinical investigation consisted of cardiopulmonary exercise testing on a treadmill, along with electrocardiography and echocardiography at rest and during exercise on a supine cycle ergometer. The participants performed a maximal exercise test with gas exchange analysis and electrocardiogram on a treadmill ergometer following the Oslo protocol[17] (Equipment: Jaeger Oxycon Delta, VIASYS Healthcare, Höchberg, Germany). Peak oxygen uptake was corrected for body weight[18] and expressed as $\mathrm{ml\,kg^{-0.67}\,min^{-1}}$.

The individual results were compared to reference values from healthy Norwegian adolescents,[19] and expressed by standard deviation, the Z-score, from the age-related mean in the reference material. Highly endurance trained individuals with a Z-score above 2.0 were defined as athletes. The others, with Z-scores equal or less than 2.0, were defined as normally trained subjects.

All echocardiographic recordings were obtained with a Vivid 7 Dimension scanner (GE Vingmed Ultrasound, Horten, Norway) and the studies were both videotaped and stored digitally. Echocardiography at rest included standard views and measurements. Right atrial pressure at rest was estimated by inferior caval venous index,[20] and the following additional specific measurements of right ventricular performance[21–24] were also included:

- Tricuspid annular plane systolic excursion in millimetres measured in M-mode.[25]
- Tricuspid annulus peak systolic velocity in centimetres per second by colour tissue Doppler imaging and by pulsed tissue Doppler imaging.[26,27]

Approximately 1 hour after treadmill testing, exercise echocardiography was performed during supine cycling with about 30 degrees head elevation and 30 degrees left side tilt (Equipment: Ergoselect 1200 EL, Ergoline, Bitz, Germany). The stepwise World Health Organisation exercise protocol was used with a starting load of 25 Watt and an increase by 25 Watt every second minute until the target heart rate of $160^{-\mathrm{min}}$ was reached. Above that level, echocardiographic recordings become futile because of upper body movement and interposition of the

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lungs. Systemic blood pressure was measured at every exercise level, as well as the maximal velocity of tricuspid regurgitation jet. The right ventricular systolic pressure was calculated from each recording by means of the modified Bernoulli equation, adding the right atrial pressure at rest to the calculated pressure gradient between right ventricle and right atrium (right ventricular systolic pressure $= 4\,V^2 +$ [right atrial pressure]).[6]

In order to detect dynamic right ventricular outflow tract obstruction that could interfere with right ventricular systolic pressure measurements, an attempt was made to measure right ventricular outflow tract velocity at the 100 Watt level. Outflow tract velocities higher than 2 meters per second lead to exclusion from the study.

Data analysis

Pressure measurements were made offline by analysis of all digitally stored still images of tricuspid regurgitation velocity. Every frame was classified as a good, reasonable or poor/impossible measurement. For every minute of exercise, measurements were summarized into a conclusive pressure value (maximum of two values per workload level) based on the best accessible Doppler measurements. Obvious outlier measurements were ignored. For approval of the entire exercise study at least the second last passed workload level had to be evaluable.

For analysis of inter-observer variability, a blinded second analyser evaluated 35 exercise echocardiographic recordings from study participants and from patients with atrial or ventricular septal defects in a similar exercise study setting. The second analyser was experienced in exercise echocardiography technique. Inter-observer agreement was expressed by a Bland-Altman-plot[28] and by Kappa statistics.[29] Variability was also expressed as deviation (%) from the average of both analysers.

Data storage and statistical analysis were executed with Microsoft Access 2003, Microsoft Excel 2003, SPSS 12.1/16.0, Analyse-it 2.11 and SigmaPlot 11.0. Offline analyses of ultrasound studies were performed on EchoPac PC 5.x (GE Vingmed Ultrasound, Horten, Norway).

Statistics

Student t-tests were performed to compare different subgroups if normal distribution was assumed. Otherwise, nonparametric tests were used for continuous variables and Chi square for categorical variables. Pearson's correlation was used to determine relation between different independent variables. A multivariate linear regression model, using the stepwise backwards elimination procedure, was used to model the relation between independent variables, specifically age, gender, exercise habits, Z-score of peak oxygen uptake, tricuspid annular plane systolic excursion and tricuspid annular peak systolic velocity, and outcome variable maximal right ventricular systolic pressure during exercise. p-values lower than 0.05 were considered statistically significant. Inter-observer variability for continuous variables was calculated by intraclass correlation coefficient. For categorical variables, inter-observer agreement was calculated by kappa statistics.

Approvals

The study complies with the Declaration of Helsinki, and it was approved by the Regional Committee for Medical Research Ethics, with all participants giving their informed consent, minors by proxy. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

We recruited 113 healthy volunteers, who passed all examinations (Table 1).

Aerobic capacity characteristics

The aerobic capacity was normally distributed (Fig. 1), with a mean Z-score of 0.31 related to the reference study.[19] Of the individuals, 13 (11.5%), with 6 female, were athletes having Z-scores higher than 2.0, and 8 of these were aged from 16 to 18 years. The athletes performed different kinds of sports, including cross country skiing, soccer, badminton, volleyball, handball, and running, and they followed a training programme on a non-professional level beside their daily school or working activity.

Cardiac characteristics

We found 3 cases of right bundle branch block in the electrocardiogram at rest, 2 in normally trained subjects and 1 in an athlete, but no incidents of arrhythmia or bundle branch block occurring during exercise. All values for shortening fraction, right ventricular systolic pressure at rest, tricuspid annular plane systolic excursion, tricuspid annular peak systolic velocity and pulsed tricuspid annular peak systolic velocity were within normal limits and normally distributed (Table 2).

Exercise echocardiography/right ventricular systolic pressure characteristics

We obtained assessable echocardiography recordings in 109 individuals (96%), among whom 12 were athletes. Maximal right ventricular systolic pressure

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Table 1. Demographics and basic characteristics.

Age group (years)	N	male/female	Age *Mean*	Height (cm) *Mean* ± *SD*	Weight (kg) *Mean* ± *SD*	BMI (kg/m^2) *Mean* ± *SD*
13–15	22	15/13	14.1	170.6 ± 11.9	62.0 ± 12.3	21.1 ± 2.6
16–18	19	22/19	16.9	168.9 ± 8.8	62.6 ± 11.6	21.8 ± 3.2
19–21	18	4/18	20.2	175.0 ± 8.6	68.3 ± 10.7	22.2 ± 2.1
22–25	21	8/14	23.3	171.8 ± 9.7	65.6 ± 17.1	22.0 ± 4.4
Overall/sum	113	49/64	18.1	171.1 ± 9.9	64.1 ± 12.9	21.8 ± 3.1

SD = standard deviation, BMI = body mass index.

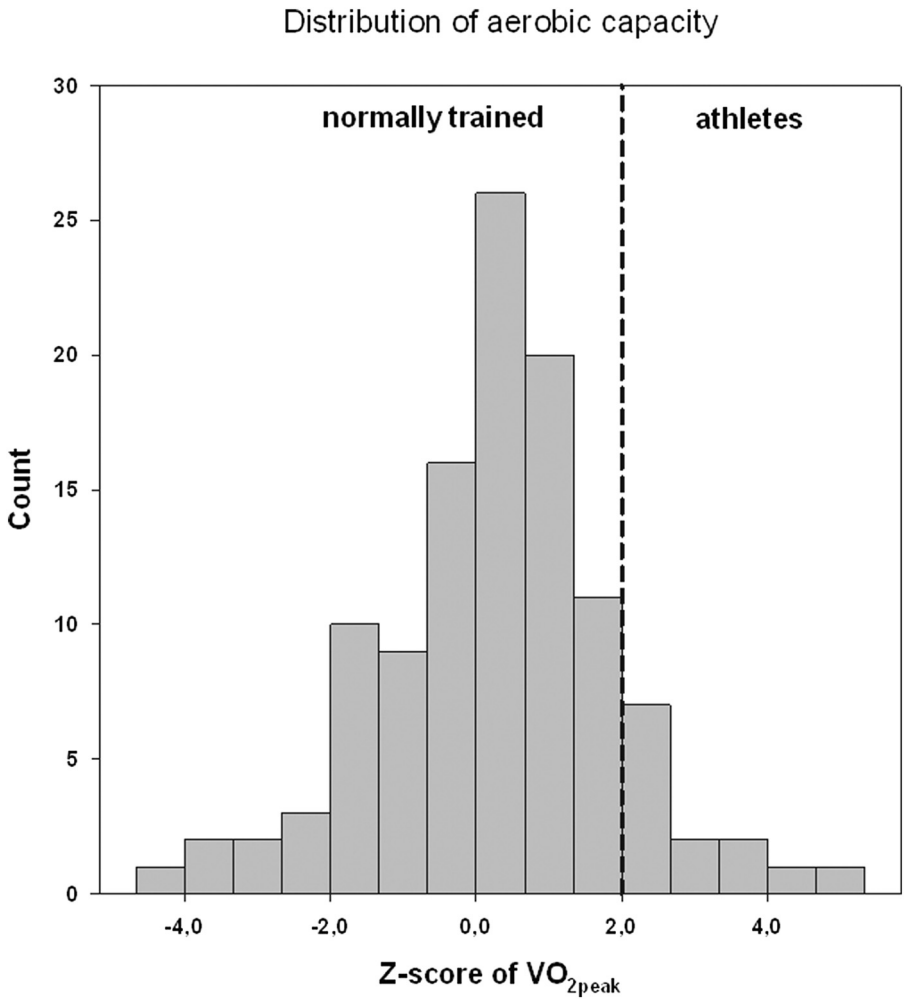

Figure 1.
Normal distribution of Z-score in peak oxygen uptake (n=113).

during exercise showed a skewed distribution towards high levels, while right ventricular systolic pressure in the normally trained group alone was normally distributed. For the whole group of 109 subjects, the maximal right ventricular systolic pressure during exercise showed a median of 39.0 millimetres of mercury, with a range from 17 to 69, and the 90th and 95th percentiles were 51 and 60 millimetres of mercury, respectively. In the normally trained group, the maximal right ventricular systolic pressure showed a mean of 38.0 millimetres of mercury, with standard deviation of 7.2, a median of 39.0, and a range from 17 to 63, with 90th and 95th percentiles at 46 and 51 millimetres of mercury. The athletes had a median maximal right ventricular systolic pressure of 55.5 millimetres of mercury, with a range from 28 to 69. The difference in maximal right ventricular systolic pressure during exercise between the normally trained group and the athletes was statistically

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Table 2. Age related measurements.

Age group (years)	Z-score of VO_{2peak} *Mean ± SD*	Athletes *N*	FS (%) *Mean ± SD*	TAPSE (mm) *Mean ± SD*	TASM (cm/sec) *Mean ± SD*	Pulsed TASM (cm/sec) *Mean ± SD*	RVSP at rest (mmHg) *Mean ± SD*	Maximal RVSP (mmHg) *Median, range*
13–15	0.33 ± 1.70	2	32.9 ± 4.5	22.6 ± 2.6	10.51 ± 1.57	11.36 ± 1.57	21.8 ± 4.8	36.0, 28–60
16–18	0.62 ± 1.73	8	32.8 ± 4.1	22.7 ± 3.5	10.76 ± 1.76	11.84 ± 1.87	22.2 ± 3.8	41.0, 24–69
19–21	0.04 ± 1.27	2	31.8 ± 4.7	23.9 ± 3.1	10.59 ± 1.84	11.91 ± 1.95	21.6 ± 2.8	37.5, 17–57
22–25	0.02 ± 1.63	1	32.7 ± 3.8	23.5 ± 3.1	10.36 ± 1.22	11.36 ± 1.47	21.5 ± 3.2	39.9, 26–51
Overall/sum	0.31 ± 1.62	13	32.6 ± 4.24	23.1 ± 3.1	10.59 ± 1.62	11.64 ± 1.74	21.9 ± 3.8	39.0, 17–69

SD = standard deviation, FS = shortening fraction, TAPSE = tricuspid annular plane systolic excursion, TASM = tricuspid annular peak systolic velocity assessed by colour Tissue Doppler Imaging, pulsed TASM = pulsed Tissue Doppler measurements of TASM, RVSP = right ventricular systolic pressure.

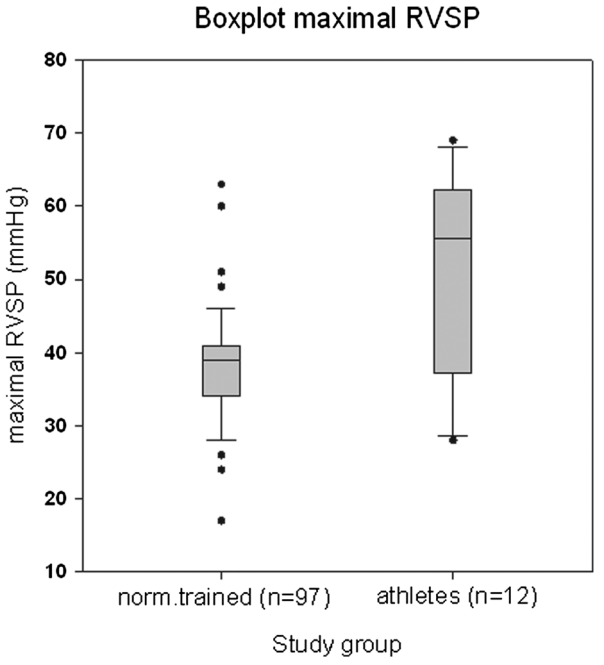

Figure 2.
Maximal right ventricular systolic pressure (RVSP) during exercise in normally trained individuals and athletes. For normal trained group there are two outliers between 1.5 and 3 box lengths outside boxes edge, one extreme case outside > 3 box lengths.

significant, the Mann-Whitney test giving a value of p equal to 0.004 (Fig. 2).

In order to investigate whether low aerobic capacity could be caused by abnormal right ventricular systolic pressure, we compared the subgroup of 8 with lowest peak oxygen uptake, and Z-scores below −2.0, with the normal group having Z-scores between −2.0 and 2.0, but found no difference in maximal right ventricular systolic pressure. For the entire normally trained group, there was no correlation between peak oxygen uptake and maximal right ventricular systolic pressure.

Normal and abnormal responders in terms of right ventricular systolic pressure, taking a cut-off for maximal right ventricular systolic pressure of greater than 50 millimetres of mercury, showed a similar pattern of slow and parallel rise of right ventricular systolic pressure and systemic systolic blood pressure during incremental exercise (Figs 3 and 4). Normal responders reached a plateau at a moderate level for exercise, whereas abnormal responders showed a continuous increase of systolic pressure throughout the entire duration of exercise (Fig. 3).

Of the 12 athletes, 10 (83%) had maximal right ventricular systolic pressures higher than 40 millimetres of mercury, as compared to 44 of the 97 (45%)

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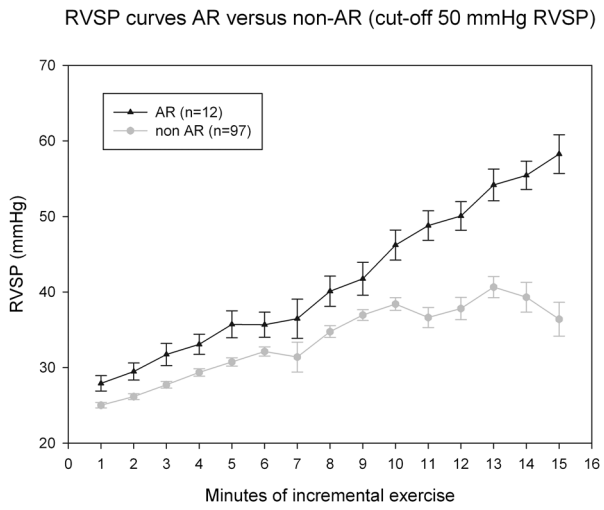

Figure 3.
Right ventricular systolic pressure (RVSP) during exercise in subjects with abnormal right ventricular systolic pressure response (AR) and normal response (non-AR) with cut-off right ventricular systolic pressure 50 mmHg. After 15 minutes, there were too few measurements to permit calculation of confidence intervals.

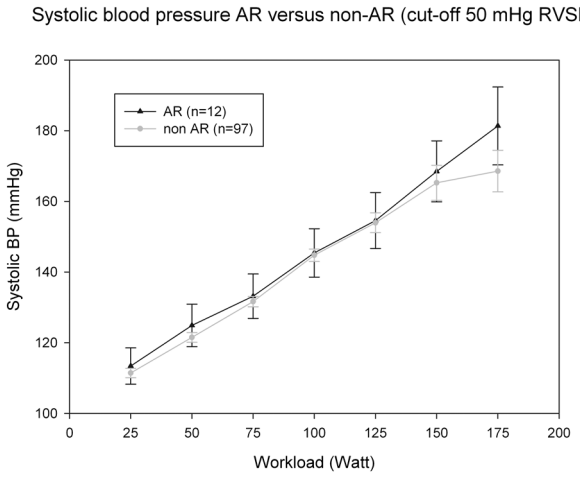

Figure 4.
Systolic blood pressure during exercise in subjects with abnormal right ventricular systolic pressure response (AR) and normal response (non-AR) with cut-off right ventricular systolic pressure 50 mmHg. After 175 Watt workload, there were too few measurements for calculation of confidence intervals.

normally trained subjects ($p = 0.025$). When using 45 millimetres of mercury as the cut off, the respective number of abnormal responders were 8 of 12 (67%) for athletes, and 16 of 97 (16%) for normally trained subjects ($p < 0.001$). With 50 millimetres of mercury taken as the cut-off, the respective numbers were again 8 of 12 (67%) for the athletes, but only 8 of 97 (8%) of the normally trained subjects ($p < 0.001$) (Table 3).

Linear regression analysis showed that age, gender, body mass index, exercise habits, Z-score of peak oxygen uptake, tricuspid annular plane systolic excursion and tricuspid annular peak systolic velocity did not have a significant predictive value for maximal right ventricular systolic pressure during exercise.

There was no difference in maximal right ventricular systolic pressure between 9 smokers and 98 non-smokers. For females there was no difference in maximal right ventricular systolic pressure between groups with regard to use of oral contraceptives.

Inter-observer variability

The analyses made by the 2 independent observers showed very good agreement. The 95% limits of agreement were −0.17/0.33 metres per second, with a positive bias of 0.06 metres per second in Doppler velocity measurements and 2 millimetres of mercury in maximal right ventricular systolic pressure between the first and second analyser (Fig. 5). There was no difference in agreement depending on low or high velocities. For tricuspid regurgitation velocities measured offline by the two observers, the intraclass correlation coefficient was 0.934 ($p < 0.001$).

In order to define abnormal pressure response to exercise, it was possible to measure inter-observer agreement for a nominal variable by Kappa statistics. With a cut-off of 45 millimetres of mercury, Kappa was 0.79, while with a cut-off of 50 millimetres of mercury, Kappa was 0.82. Following commonly used definitions, kappa from 0.6 to 0.8 means good agreement, while kappa above 0.8 means very good agreement.

Discussion

Our data has shown a great variability in right ventricular pressure response to exercise. There is no linear correlation between maximal right ventricular systolic pressure and aerobic capacity, but athletes with high aerobic capacity often show an abnormally high response. The upper normal limit of the response in normally trained individuals seems to be higher than commonly assumed.[9]

The number of examined individuals in our study is high compared to other studies with a comparable focus that investigated mixed groups of normally trained subjects and athletes made up of 20[3] to 40 individuals.[1] Our study group has a sufficient distribution of age and gender to allow conclusions to be drawn concerning adolescents and young adults. This is also supported by results for peak uptake of oxygen, which reflect reference values.

The strong correlation between non-invasive and invasive measurements has previously been

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Table 3. Abnormal right ventricular systolic pressure response during exercise in normally trained group and athletes.

Study group	N	Cut-off 40 mmHg N (%)	Cut-off 45 mmHg N (%)	Cut-off 50 mmHg N (%)
Normally trained group	97	44 (45%)	16 (16%)	8 (8%)
Athletes	12	10 (83%)	8 (67%)	8 (67%)
Chi square significance (p)		0.025	<0.001	<0.001

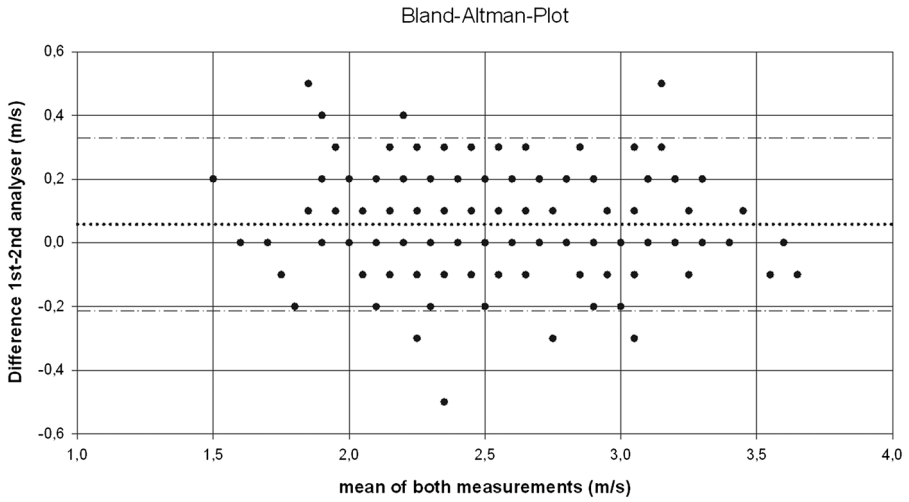

Figure 5.
Bland-Altman-Plot of inter-observer variability in measurements of the velocity of the jet of tricuspid regurgitation.

demonstrated both at rest and during exercise.[6,7,20] Thus conclusions about the response of pulmonary arterial pressure can rely, therefore, on entirely non-invasive protocols, albeit that normal values for exercise echocardiography have not previously been established. Our findings, nonetheless, confirm earlier statements[7] that exercise echocardiography as a reliable tool for assessment of the response of right ventricular pressure during exercise.

The high rate of quantifiable tests as compared to previous studies,[30] and a high degree of inter-observer agreement, reflects the technical progress. Modern ultrasound scanners and digital storage of image information facilitate detection and precise determination of small tricuspid regurgitation signals.

Doppler signal profiles of tricuspid regurgitation velocities during exercise are of variable quality, and not always easy to interpret. Signal drop-out often occurs in the middle of the profile. Measurement of the angle of velocity may be disturbed during exercise because of increased translation movement of the heart and narrowing of the area of good ultrasonic access with increasing excursion of the thorax. The described non-invasive method includes the assumption that right atrial pressure remains unchanged during exercise. From invasive studies,[7] we know that this assumption may not be totally correct, leading to a slight underestimation of pulmonary arterial pressure during exercise.

All of these technical issues potentially cause a certain underestimation of the response of right ventricular systolic pressure, and none would cause overestimation. The low inter-observer-variation confirms the high accuracy in pressure measurements.

Thus, in the absence of any obstruction to right ventricular outflow, our current non-invasive data allows conclusions to be drawn about pulmonary arterial pressure and pulmonary vascular resistance, though these parameters had not been measured. And pulmonary hemodynamics during exercise are in focus when seeking early signs of pulmonary vasculopathy.

In our study, we performed exercise echocardiography 1 hour after a maximal treadmill exercise test. This may have lowered pulmonary and systemic resistance, resulting in false low levels of pulmonary pressure. For that reason, as well as technical ones, our protocol may have caused underestimation of the response of pulmonary pressure. There are several possible ways, therefore,

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of underestimating pulmonary arterial systolic pressure by non-invasive measurement of right ventricular systolic pressure, but no obvious risk of overestimating it.

The normal range of right ventricular systolic pressure during exercise in our material is wider than in previous studies. The Gaussian distribution of maximal right ventricular systolic pressure in normally trained subjects confirms a high variability of pressure response as a physiological phenomenon rather than a technical or methodical artefact.

The data we have presented confirms a strong interrelation between high aerobic capacity and an abnormal response of right ventricular systolic pressure. The fact that separation of athletes from the normal trained group lead to normal distribution in maximal right ventricular systolic pressure during exercise suggests a specific physiological mechanism in athletes leading to high right ventricular and pulmonary pressure during exercise. This is also supported by the significant difference in the abnormal response between normal trained individuals and athletes. Cardiac output, alveolar gas diffusion and pulmonary vascular resistance were not monitored during exercise. Thus, our data does not allow a conclusion to be drawn about the theory that elevated pulmonary arterial pressure in athletes is caused by high cardiac output and limited dilative capacity on the pulmonary vessels.[1,15] The data did not give any evidence that high right ventricular systolic pressure during exercise reduces aerobic capacity in healthy individuals, since there was no difference in right ventricular systolic pressure between normally trained and totally untrained individuals.

Like earlier studies[1,15] we found that normally responding individuals reach a plateau in right ventricular systolic pressure, whereas individuals with an abnormal response continue to increase both their right ventricular and pulmonary arterial systolic pressures. There was no sudden increase of pulmonary or systemic vascular resistance in individuals with an abnormal response. The continuous increase of right ventricular systolic pressure in individuals showing an abnormal response cannot be explained by recent theories of sympathoexcitation and its influence on vasoconstriction in the pulmonary arterioles.[31] Because of their different physiology, we had to exclude the athletes in order to define normality in right ventricular systolic pressure. This leads to an upper limit of 50 millimetres of mercury for the normal response to exercise in healthy normally trained young individuals. Given that right ventricular systolic pressure reflects pulmonary arterial systolic pressure, 50 millimetres of mercury pulmonary arterial systolic pressure calculated into mean pulmonary arterial pressure results in 32.5 millimetres of mercury when using the formula $(PAMP = 0.61 * PASP + 2\,mmHg)m^4$ where PAMP and PASP are the mean and systolic pulmonary arterial pressure respectively. The result of 32.5 fits with the definition of exercise-induced pulmonary hypertension as mean pulmonary arterial pressure higher than 30 millimetres of mercury during exercise.[5]

Our results challenge the commonly used value of 40 or 45 millimetres of mercury as the upper limit of the normal response of right ventricular systolic pressure to exercise. The acceptance of a higher upper limit for normal pressure may lead to a more restrictive definition and reduced prevalence of exercise-induced pulmonary arterial hypertension.

In conclusion, we have shown exercise echocardiography to be a reliable tool in measuring right ventricular systolic pressure during exercise. Our study demonstrates a high variability in the response of this pressure to exercise among adolescents and young adults. According to our findings, 50 millimetres of mercury is the upper limit of the normal response to exercise in healthy normally trained subjects. The common definition of the normal range in right ventricular and pulmonary arterial pressures during exercise may have to be reconsidered.

Young non-professional endurance-trained athletes show an abnormally high response during exercise, with two-thirds exceeding 50 millimetres of mercury. This has to be taken in account in the selection of controls in clinical studies of exercise-induced pulmonary hypertension

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