SPORTS & EXERCISE | RESEARCH ARTICLE

Echocardiographic E/A inversion and air trapping at rest are associated with an exaggerated blood pressure response in medically controlled hypertensives during bicycle ergometry

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Abstract: Exaggerated blood pressure response during exercise is a risk factor for cardiovascular disease, but is inhomogeneously defined in the literature. We used a novel approach by taking into account both workload and blood pressure to define exercise hypertension (systolic values > 200 mmHg at 100W). We examined medically controlled hypertensives (n = 373; mean age 56.7 ± 14.8 years) and their blood pressure response during bicycle ergometry. Exercise hypertension was inversely associated with E/A wave ratio but not E/E' during resting echocardiography (p = 0.045; p = 0.293). Functional air trapping (residual volume/total lung capacity, RV/TLC) was significantly higher in the group of exercise hypertensives (43.6% ± 11.6 vs. 38.1% ± 10.0; p = 0.005). Patients treated with renin-angiotensin aldosterone system (RAAS) blockers showed lower blood pressure response during exercise than those treated with calcium channel blockers (CCBs) and thiazides (both <0.001) and also displayed higher E/A (p = 0.023) and lower E/E' values (p = 0.042). We provide evidence

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Simon Wernhart’s key research activities are physiological and pathological limitations of exercise performance with an emphasis on the cardiovascular system. He seeks to investigate prognostic factors for the development of cardiovascular disease in standard cardiological exams. The current work aims to analyze the important cardiovascular risk factor of exercise hypertension and its role in primary prevention. Further research will be dedicated to cardiorespiratory fitness (CRF) and its role in secondary prevention. Furthermore, CRF will be analyzed in cancer survivors and heart failure patients. Additionally, exercise intensity in the rehabilitation process of critically ill patients will be in the focus of future projects.

Martin Halle is the chief-investigator of multiple randomized-controlled trials analyzing the impact of exercise on diabetes, cardiovascular disease, renal insufficiency and tumors. He investigates obesity of adolescents as well as the influence of marathon running on the heart.

PUBLIC INTEREST STATEMENT

Exercise hypertension is a risk factor for cardiovascular disease. We examined medically controlled hypertensives and their blood pressure response during bicycle ergometry. Exaggerated blood pressure development during exercise (systolic values > 200 mmHg at 100W) was inversely associated with E/A wave ratio, a parameter of diastolic function in echocardiography. Hyperinflation in resting lung function testing (RV/TLC) was significantly higher in the group of exercise hypertensives (43.6% ± 11.6 vs. 38.1% ± 10.0; p = 0.005). Patients treated with renin-angiotensin aldosterone system (RAAS) blockers showed lower blood pressure response during exercise than those treated with calcium channel blockers (CCBs) and thiazides (both <0.001) and also displayed higher E/A (p = 0.023) and lower E/E' values (p = 0.042). We provide evidence
that the easily accessible parameters E/A inversion and air trapping at rest could be used in clinical routine to screen for exercise-induced hypertension in medically controlled hypertensives. We also show that RAAS blockers have a more favorable effect on blood pressure response during exercise than CCBs and thiazides.

**Subjects:** Exercise Physiology; Sports Medicine; Hypertension;

**Keywords:** exercise hypertension; diastolic function; E/A wave ratio; air trapping

1. Introduction

Elevated blood pressure is the driving risk factor to develop diastolic dysfunction, Heart failure with preserved ejection fraction (HFpEF) and (hypertensive) cardiomyopathy (Borlaug & Paulus, 2011; Desai et al., 2013). Several parameters exist to measure diastolic function in echocardiography (Gilman, Nelson, Hansen, Khandheria, & Ommen, 2007; Khouri, Maly, Suh, & Walsh, 2004; Nagueh et al., 2009; Nagueh, Middleton, Kopelen, Zoghbi, & Quiñones, 1997). Classification of diastolic function and estimation of left ventricular filling pressure by means of echocardiography remains controversial, also because of the great amount of parameters, which can be assessed (E/A, E/E', E' velocity, E-wave deceleration time, LA volume, velocity of tricuspid regurgitation jet). None of these can determine diastolic dysfunction by itself. Over the last couple of years, it has been observed that, by following the 2009 recommendations of echocardiographic assessment of diastolic function (Nagueh et al., 2009), grade I diastolic dysfunction is overestimated. The revised guidelines of 2016 seem to better classify patients according to clinical outcomes (Lancellotti et al., 2017). The term of “indeterminate diastolic function” has been coined (Nagueh et al., 2016) and seems to result in intermediate clinical outcomes between normal and diastolic dysfunction grade I (Sanchis et al., 2018).

The rise of blood pressure prior to exercise testing seems to be a predictor to develop hypertension in the future (Jae et al., 2014) and an exaggerated blood pressure response during exercise is associated with subclinical myocardial damage in otherwise normotensive, healthy individuals (Yang et al., 2014). Additionally, data from studies on exercise hypertension have shown that pathophysiological mechanisms of heart failure, such as an augmented rise of angiotensin II, come into effect in these patients (Shim et al., 2008). A high blood pressure response to exercise has recently been shown to be associated with the development of overt hypertension in athletes (Caselli et al., 2019). Hulkkonen et al. provided data in which exercise peak arterial pressure strongly depended on the individual’s cardiovascular risk profile, taking into account age, sex, diabetes, and dyslipidemia (Hulkkonen et al., 2014). Systolic blood pressure recovery ratio and heart rate recovery after exercise testing have been shown to be correlated with E/E' in pre-diabetic patients (Mahfouz, Dewedar, Elawady, Salem, & Goda, 2014).

To our knowledge, a potential association between exaggerated exercise blood pressure response and diastolic function as well as spirometric parameters at rest has not been investigated. Knowledge of easily measurable cardiopulmonary risk factors for exercise hypertension in the sports medical examination (especially diastolic function and basal spirometric parameters) at rest would be useful to better screen normotensive and physically active individuals for (covert) exercise-induced hypertension. We hypothesized that patients with higher E/E' and lower E/A in resting echocardiography have higher blood pressure response during exercise. Exaggerated blood pressure response may also be associated with functional air trapping at rest (higher ratio of residual volume/total lung capacity, RV/TLC ratio). Furthermore, we aim to analyze whether there is a class effect of antihypertensive drugs in blood pressure response and if this corresponds to the treatment recommendations of the current ESC guidelines on the management of hypertension (Williams et al., 2018).
2. Methods

2.1. Participants
In a period of six months, 1544 patients reported to our outpatient clinic for a general cardiovascular checkup. We only included patients with no history of cardiovascular events between 35 and 75 years of age (n = 373) with medically controlled hypertension, defined as documented ambulatory (out-of-hospital) measurements < 140/90mmHg. Therefore, patients’ blood pressure had to be defined as either “optimal”, “normal” or “high normal” according to current ESC guidelines (Williams et al., 2018). Patients with unstable angina or dyspnea at rest were ruled out from the analysis as well as patients with chronic obstructive lung disease and asthma. Cardiovascular risk factors, such as smoking (n = 78), diabetes (n = 16), and dyslipidemia (n = 45) were no exclusion criteria. Patients with reduced left ventricular function and high-degree valve dysfunction in resting echocardiography were excluded. Laboratory testing had be negative for acute systemic infection, renal or hepatic insufficiency.

2.2. Design of the study and testing
The checkup consisted of a clinical exam, acquisition of anthropometric data, routine lab works, resting spirometry and body plethysmography, which gained data on vital capacity, VC [l], forced expiratory volume at 1s, FEV1 [l], residual volume, RV [l], total lung capacity, TLC [l] and airway resistance, Renh [kPa s/l] as well as its indices. Transthoracic echocardiography was performed by experienced echocardiographers prior to exercise testing (Philips iE33, X5-1 probe). Two experienced echocardiographers performed the exams following the established guidelines (Gilman et al., 2007; Mitchell et al., 2019). Diastolic function was assessed by measuring the diastolic inflow pattern across the mitral valve [E/A ratio, deceleration time (DT, ms)] as well as tissue Doppler velocities (E/E' medial, lateral and averaged).

Since there was a great number of different exercise protocols due to the different anticipated performance levels of the patients, we selected the most widely used protocol with a starting workload of 25 Watt [W] and a three-minute incline of 25 W (25/25/3). This protocol is a common standard in our institution for patients with an anticipated moderate performance level (more intense protocols are used for athletes, less intense ones for elderly patients). In total, we recruited 373 participants. We analyzed two groups of participants: (1) subjects with a normal rise in blood pressure during exercise (defined as < 200 mmHg systolic pressure at 100 W, Gn) and those with an exaggerated pressure response (> 200 mmHg systolic pressure at 100 W, Ge). Blood pressure was measured at rest and every 3 min during exercise with a standard hand cuff by an experienced paramedic. Informed consent for anonymous data usage as well as institutional review board approval were obtained in advance. Patients were asked to perform until exhaustion, defined as a subjective BORG scale rating of ≥ 16 points (scale ranging from 6 to 20; 20 being maximal exertion). Medical reasons for early termination were typical angina, dizziness or disproportional dyspnea, sustained ventricular tachycardia, significant ST-segment elevation in at least two consecutive leads, descending ST-depression in two consecutive leads, new onset left bundle branch block or a drop of systolic blood pressure during exercise of > 20 mmHg.

2.3. Statistical analysis
Statistical analysis was performed with SPSS version 23.0 and Microsoft Excel 2007, normal distribution was tested with the Kolmogorov Smirnov test. Quantitative measures are described by means and standard deviations. Two-sampled t-tests were conducted to compare means between independent groups, and analysis of variance was used for the analysis of three groups. Bonferroni corrections for multiple testing were applied. Associations between quantitative measures were assessed using Pearson’s correlation coefficients. To adjust for possible confounders as age, sex, and body fat, linear regression models were fit to the data and partial correlation coefficients were estimated. A level of significance of α = 0.05 was used.
3. Results

3.1. Anthropometric data and drug effects
Mean exercise time was 12.3 min ± 3.4. We compared those subjects with a systolic blood pressure < 200 mmHg at 100 W (G\text{<}) with that > 200 mmHg at 100 W (G\text{>}) at a protocol of 25/25/3 (G\text{<} = 310 / G\text{>} = 63). Subjects of G\text{>} were older (61.8 years ± 9.0 vs. 55.7 years ± 15.5; \(p < .001\)), had higher body mass index, BMI (29.7 kg/m\(^2\) ± 6.2 vs. 26.7 kg/m\(^2\) ± 8.4; \(p = 0.010\)), and body fat content (29.7% ± 6.1 vs. 23.9% ± 5.9; \(p < .001\)) and performed worse (\(P_{\text{max}}\) in G\text{<} = 119.8 W ± 32.4 vs. G\text{>} = 144.8 W ± 48.3; \(p < .001\)). The hip-waist-ratio did not differ significantly (G\text{<}: 0.89 ± 0.1 vs. G\text{>:} 0.91 ± 0.09; \(p = 0.14\)). After adjustment for age, body fat content did not show a significant difference between the groups (\(p = 0.107\)).

All 373 patients were treated with antihypertensive mono therapy, 223 received ACE-inhibitors or angiotensin receptor blockers (ACE/ARBs), while 110 took calcium channel blockers (CCBs) and 40 were on thiazide diuretics, no beta-blockers were taken on a regular basis. Patients receiving ACE-inhibitors or ARBs showed significantly lower blood pressure responses during exercise (all were within the G\text{<} group) than CCBs (n = 25 in G\text{>} group) and thiazides (n = 38 in G\text{>} group) (both \(p < .001\)). Additionally, E/A ratio was significantly higher (\(p = 0.023\)) and E/E' significantly lower (\(p = 0.042\)) in patients on ACE-inhibitors and ARBs than CCBs or thiazides (\(p = 0.033\) and 0.021). There was no difference between CCBs and thiazides (\(p = 0.542\) and 0.345); for group and drug allocation see Figure 1.

3.2. Cardiopulmonary data
Systolic and diastolic blood pressure values were significantly higher in G\text{>} at peak performance (all \(p\)-values <.001), but not at rest (\(p = 0.45\) and 0.67, Figure 2).

Averaged E/E' (9.7 ± 2.8 vs. 8.8 ± 3.0; \(p = 0.033\)) in resting echocardiography was significantly higher in patients of G\text{>,} while E/A was significantly lower (1.0 ± 0.3 vs. 1.3 ± 0.5; \(p < .001\)). Averaged E/E' was dependent on age (\(r = 0.42\), \(p < .001\)). A regression model revealed higher values of averaged E/E' with increasing age (beta = 0.412). After correction for age, no significant difference between the groups of normal and exaggerated blood pressure response remained (adjusted mean differences: averaged E/E': \(p = 0.293\)). Deceleration time (DT) did not differ between the groups (G\text{<}: 230 ms ± 117.5; G\text{>:} 228 ms ± 49.6). However, we detected a significant difference of E/A in the groups after age adjustment (\(p = 0.045\)), with lower values in the group of exaggerated blood pressure response (beta = −0.119, \(p < .001\), Figure 3).

Additionally, G\text{>} displayed significantly worse forced expiratory ventilation in 1 s (FEV\(_1\): 2.4 l ± 0.6 vs. 3.0 l ± 0.7; \(p < .001\)) and vital capacity (VC: 3.1 l ± 0.7 vs. 3.6 l ± 1.0; \(p < .001\)) than G\text{<}, the Tiffeneau-index.
do not differ significantly. The ratio of residual volume (RV) to total lung capacity (TLC), a discriminator of functional air trapping, was significantly higher in Ge (RV/TLC: 43.6%±11.6 vs. 38.1%±10.0; p = 0.005; Figures 4(a) and 3(b)).

4. Discussion
We retrospectively analyzed medically controlled hypertensives without a history of cardiovascular events. We found two different blood pressure responses during exercise, a normal and an exaggerated response. Subjects with exaggerated responses tended to be older, had higher BMIs, waist circumference, and body fat content and had a lower fitness level, which is displayed by a significantly lower peak performance, this is backed up by existing data (Hulkkonen et al., 2014).

Our study population consisted of medically controlled mainly middle-aged hypertensives, who, at the time of evaluation, were within the required blood pressure corridor “optimal”, “normal” or “high normal” suggested by current European guidelines (Williams et al., 2018). We are aware that ambulatory 24 h measurements may provide additional information and may also provide hints on exercise hypertension during work or leisure time activities. However, we chose to analyze a “real-life scenario”, in which the general practitioner or cardiologist has to estimate a patient’s risk from a few bits of information, such as blood pressure management or easily (and quickly) accessible values from resting echo. It has been proven that exercise hypertension increases the risk to develop hypertension in the future (Manolio et al., 1994) and also increases the risk for cardiovascular events, even in the absence of resting hypertension (Allison et al., 1999). Therefore, our study population is highly relevant in primary disease prevention.

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(FEV1/VC: 80.2%±12.4 vs. 81.4%±14.5; p = 0.67) did not differ significantly. The ratio of residual volume (RV) to total lung capacity (TLC), a discriminator of functional air trapping, was significantly higher in Ge (RV/TLC: 43.6%±11.6 vs. 38.1%±10.0; p = 0.005; Figures 4(a) and 3(b)).

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> 210 mmHg in men and > 190 mmHg in females, which is believed to approximate the 90th percentile from normative data, corrected for age and sex (Allison et al., 1999; Lauer, Pashkow, Harvey, Marwick, & Thomas, 1995; Manolio et al., 1994; Mottram, Haluska, Yuda, Leano, & Marwick, 2004). The cited studies used a maximal systolic value for their definition, regardless of the timing of its measurement. We did not adhere to this “generally accepted” definition, because we also wanted to take the incline of blood pressure rise into account. A faster rise of blood pressure during early exercise may reflect the inability of the cardiovascular system to adapt to higher ventricular filling pressures. A workload of 100 W seems reasonable to compare different populations because it can be managed by most subjects. We did not differentiate between males and females in terms of blood pressure; this is debatable, but we believe this is a reasonable approximation across age and sex.

According to the current echo guidelines, all of our patients had a normal diastolic function (despite lower E/A in the group of exaggerated blood pressure response) since no single parameter can define diastolic dysfunction by itself. It is widely acknowledged that E/E’ is age-dependent (Nagueh et al., 2009, 1997, 2016; Sanchis et al., 2018); this was reproducible in our study. Older patients tend to have higher BMI and, statistically, have more cardiovascular risk factors, which may explain diastolic limitations, expressed through higher early diastolic inflow (higher E-wave) and lower tissue velocity (lower E’).

Interestingly, we found that E/A ratio was not influenced by age in our study population and that E/A was significantly lower in the group of exaggerated blood pressure response. This stands in contrast to
the generally acknowledged observation that E/A is also age-dependent (Nagueh et al., 2009), and may partly be explained by our rather young study population. It has also been shown that E/A can be increased through exercise training and this also improves microvascular perfusion in a rat model (Hotta et al., 2017). This is supported by our study, which shows that a higher fitness level is associated with lower E/A and lower blood pressure response during exercise. The A-wave reflects late diastolic, active atrial contraction and is a measure of LA stroke volume. In the exaggerated response group, E/A wave ratio was significantly lower and reflects a delayed relaxation pattern. Due to prolonged pressure decay in the left ventricle, the gradient between the left atrium and ventricle is reduced, which ultimately leads to a lower E-wave. On the other hand, the higher residual volume in the atrium is ejected in late diastole, leading to higher A-waves. We can only speculate on the reasons for a lack of age-dependency of the E/A ratio, but we assume that significant alterations in E/A take place at a more advanced age.

We have restricted our measurements to the easily assessable parameters E/A and E/E′ and did not use strain measurement, which may not always be readily available in everyday practice. A significantly lower baseline E/A in the group of exaggerated blood pressure response may be an indicator of diastolic limitation during exercise, which in turn may lead to higher blood pressure values during exercise. Unfortunately, we do not have current data on the E/A ratio during exercise. It could be assumed that during exercise, the E/A ratio further decreases due to more (active) atrial contraction, which may imply a higher atrial workload and increased LV filling pressures. This, in turn, may increase the energy demand of the left atrium and ultimately leads to limitations in exercise performance. LA strain has been recognized as a valuable tool to assess LA function and seems to be less load-dependent than LA volume (Genovese et al., 2018; Longobardo et al., 2017). LA strain analysis focuses on three phases with passive (reservoir and conduit) and active (atrial contraction) contribution. However, the wider application of strain analysis is currently hampered by unequal software solutions of different providers. Therefore, E/A ratio may be an easy tool to analyze the diastolic function and may be used as an early marker to identify patients at risk for exercise-induced hypertension. Further, (prospective) studies will be needed to evaluate the E/A ratio during exercise. Ideally, this may be combined with strain analysis of the LA.

The current ESC guidelines 2018 suggest primary treatment of hypertension with two first-line drugs, ACE-inhibitors/angiotensin receptor blockers or calcium channel blockers (Williams et al., 2018). Our study did contain a small number of hypertensive diabetics without manifest renal disease. There is a good amount of data that this group benefits from ACE inhibitors and ARBs, which were mainly used in our study population. We observed a clear class effect of this group in terms of higher E/A, lower E/E′ and lower exercise blood pressure. Shim and colleagues have shown that exaggerated blood pressure response during exercise is associated with an increased release of angiotensin II (Shim et al., 2008). Therefore, we can conclude that ACE inhibitors and ARBs have a protective effect during strenuous exercise and seem to reduce cardiac workload. Although CCBs are also first-line drugs in the treatment of hypertension, they seem to be inferior to ARBs and ACE inhibitors in our population. Both drugs reduce afterload, but ACE inhibitors and ARBs have also been associated with the preservation of myocardial contractility and delay of myocardial fibrosis (for references see ESC guidelines 2018, Williams et al., 2018).

Apart from the lower E/A ratio, we found that this group also displayed a significantly higher degree of air trapping (increased RV/TLC) at rest. Air trapping leads to an increase of functional residual capacity (FRC) and capillary constriction, resulting in higher right-ventricular after-load and rise of pulmonary capillary pressure. Additionally, flattening of the diaphragm leads to increased intra-abdominal pressure, which in turn may also hamper right ventricular pre-load. These changes may very well be worsened during increased workload. These two (stress-inducing) mechanisms may also contribute to the stress-induced sympathetic activation, which ultimately leads to exaggerated left ventricular after-load increase and exercise hypertension. Thus, air trapping may very well be a relevant co-factor in the pathogenesis of exercise hypertension. In the literature, there is evidence that hyperinflation leads to an increase in LV mass (Smith et al., 2013). However, to our knowledge, no data except our own exists on the effect of hyperinflation at rest and its influence on exercise.
hypertension. Smith et al. investigated a population of patients who were older (69 ± 6 years) than our subjects and 65% suffered from chronic obstructive pulmonary disease, while this was an exclusion criterion for our study.

To sum up, we found two parameters of the sports medical check-up which were significantly associated with exercise-induced hypertension: (1) a reduced E/A wave ratio in resting echo as a marker of increased active atrial contraction and (2) increased air trapping in lung function testing. Thus, these two parameters may alert physicians to screen for exercise-induced hypertension in normotensive individuals at rest. Our study adds valuable data on the practical relevance of easily accessible parameters, such as E/A and RV/TLC, in a general cardiologist’s or practitioner’s setting to assess the risk for exercise hypertension in outclinic patients without manifest cardiovascular disease. The chosen protocol 25/25/3 is widely used in exercise testing and ensures an exercise time between eight to 12 min for most patients in our study population. Although current guidelines down-graded the relevance of exercise ergometry to screen for manifest cardiovascular disease in subjects with an intermediate risk (Saraste et al., 2019), the role of exercise testing to assess cardiopulmonary fitness and exercise hypertension remains unquestioned.

Additionally, ACE inhibitors and ARBs seem to have more beneficial effects in terms of blood pressure response during exercise than CCBs and thiazides and also show higher E/A and lower E/E’ ratios. These sets of data support the concept of ACE inhibitors and ARBs as the preferred antihypertensive drugs in our study population.

The question remains, whether subjects with well-controlled hypertension at rest, but with an exaggerated response during exercise, need to increase their anti-hypertensive medication. Long-term studies evaluating the incidence of cardiovascular endpoints are needed to address this issue.

5. Limitations
Due to the retrospective nature of our study, we cannot claim a causal relationship between exercise-induced hypertension and lower E/A ratio and air trapping at rest. Although we stratified for potential confounders, the differences in group size may include some bias. The definition of exercise hypertension is not unified; our definition including workload and blood pressure has to be validated in larger trials.

6. Conclusion
Subjects with exaggerated blood pressure response during exercise testing were older, had higher BMIs, higher body fat content and larger waist circumference. After correction for confounders, only E/A inversion (not E/E’) was significantly associated with an exaggerated blood pressure response during exercise testing. Furthermore, subjects with exercise hypertension showed significantly more air trapping (higher RV/TLC ratio) at rest than “normal responders”. E/A inversion and dynamic air trapping may thus function as early markers and risk factors for exercise hypertension in normotensive individuals at rest. ACE inhibitors and ARBs are the drugs of choice in our population due to lower blood pressure responses during exercise and higher E/A and lower E/E’ ratios at rest.

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