Is There a Relationship Between Right Ventricular Dysfunction & Six-Minute Walk Test (6mwt) In Hypertensive Patients?

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Abstract

Background: Hypertension is the most important risk factor for death in industrialized countries. It increases hardening of the arteries thus predisposes individuals to heart disease, peripheral vascular disease and stroke, also hypertensive retinopathy and hypertensive nephropathy. The effect of hypertension on left ventricle has been documented for long time, but sparse and consistent evidence shows an impact of hypertension on the right ventricle. The RV can be studied with many imaging and functional modalities. In clinical practice, echocardiography is the mainstay of evaluation of RV structure and function. Right ventricular (RV) function has proved a major determinant of prognosis. Indeed, evidence suggests that RV dysfunction is accompanied by higher morbidity and mortality rates in several cardiovascular diseases, including congenital heart disease, heart failure (HF) with preserved (HFpEF) or reduced ejection fraction (HFrEF), coronary artery disease, and pulmonary hypertension. As RV function is a crucial determinant of short-term prognosis in several heart diseases, research has lately focused on the effect of longstanding hypertension on RV structure and function, the respective underlying mechanisms, and the potential therapeutic implications. However, RV evaluation had suffered from a relative underestimation in clinical studies compared with LV, probably due to its specific anatomic and functional features, which makes its approach more challenging.

Keywords: Right Ventricle, Exercise

Background

In accordance with most guidelines, it is recommended that hypertension be diagnosed when a person’s systolic blood pressure (SBP) in the office or clinic is ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥90 mmHg following repeated examination. High-normal BP is intended to identify individuals who could benefit from lifestyle interventions and who would receive pharmacological treatment if compelling indications were present (1).

Isolated systolic hypertension defined as elevated SBP (≥140 mmHg) and low DBP (<90 mmHg) is common in young and in elderly people. In young individuals, including children, adolescents and young adults, isolated systolic hypertension is the most common form of essential hypertension. However, it is also particularly common in the elderly, in whom it reflects stiffening of the large arteries with an increase in pulse pressure (difference between SBP and DBP). Individuals identified with confirmed hypertension (grade 1 and grade 2) should receive appropriate pharmacological treatment (2).

Right ventricular function:
The main role of the RV is to sustain an effective cardiac output. Stroke volume of the RV is predominantly generated by longitudinal shortening rather than by reduction of the cavity diameter (radial
function) as is the case in the LV. Due to the complex anatomy of the RV, echocardiographic evaluation of RV function is often difficult (3).

**Main mechanisms of RV contraction:**

The following key mechanisms are responsible for the RV pump function: (1) shortening in the longitudinal axis with traction of the tricuspid valve towards the apex; (2) inward motion of the RV free wall; (3) bulging of the interventricular septum into the RV cavity during the LV contraction and stretching the RV free wall over the septum; and (4) contraction of the right ventricular outflow tract (RVOT). So, a number of surrogate echocardiographic parameters of RV performance (such as tricuspid annular plane systolic excursion (TAPSE), peak S wave velocity of the lateral tricuspid annulus by tissue Doppler imaging (S), RV fractional area change (FAC), and RV myocardial performance index have been introduced for clinical use (4).

The adequate response of the systemic circulation to exercise is increased cardiac and stroke volume index and decreased systemic vascular resistance. This also happens in hypertensive patients, but to a lesser extent than in normotensive individuals. The possible reasons could be endothelial dysfunction, (5), increased circulating levels of catecholamines and angiotensin II, myocardial hypertrophy, or increased diastolic filling pressure (6). Another explanation for increased peripheral vascular resistance in arterial hypertension could be an increase in sodium gradient across the sarcolemma, which induces increase in Ca2+ and causes vasoconstriction, which further significantly increases blood pressure during exercise in arterial hypertension patients in comparison with normotensive (7). In contrast, hypertrophic remodeling of small arteries and arterioles, as well as reduction of precapillary arterioles, increases resistance and mean blood pressure, this further increases arterial stiffness and pulse pressure, which induces great elevation of blood pressure during exercise in arterial hypertension, (8).

The arterial remodeling in arterial hypertension, consequent changes in wall/lumen ratio, and capillary rarefaction could also decrease vasodilatation during exercise, which contributes to lower exercise capacity (9). Additionally, mitochondrial function in arterial hypertension is impaired, which contributes to lower oxygen consumption and induces oxidative stress, which also could be the reason for lower peak oxygen uptake in the arterial hypertension population (10). There is still no agreement about the impact of arterial hypertension on endothelial function. Cockcroft et al., (11) and Bruning et al., (12) found no difference in endothelium-dependent vasodilator microvasculature responses between arterial hypertensive patients and normotensive individuals, whereas other studies revealed impaired endothelium-dependent relaxation in microcirculation in arterial hypertensive patients due to oxidative stress (13,5).

The impairment of endothelium dependent relaxation in arterial hypertensive patients could be the reason of increased peripheral resistance and the cause of significantly greater exercise-induced blood pressure elevation in arterial hypertensive patients. Furthermore, increased systemic resistance leads to a reduction in cardiac output, which could be an additional cause of decreased oxygen uptake and reduced functional capacity in the hypertensive population (13). Cornelissen and Fagard (14) in a meta-analysis found that endurance training (>4 weeks) in arterial hypertensive patients results in decreased systemic vascular resistance by 7.1%, plasma norepinephrine by 29%, and plasma renin activity by 20%. Moreover, the authors showed that this regimen, regardless of drug usage, significantly decreased insulin resistance. These hemodynamic and biohumoral changes resulted in a significant decrease in resting blood pressure (-6.9/-4.9 mmHg) compared with the others (-1.9/-1.6 mmHg). Lifestyle modifications, including exercise and weight reduction, significantly improved large and small vascular remodeling. These are the reasons why exercise is considered to be an efficient additional therapy for arterial hypertension.

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Impact of right ventricle on exercise capacity in arterial hypertension:
The right ventricle has been considered as a dispensable heart chamber for overall cardiac function for a very long time. After the Multi-Ethnic Study of Atherosclerosis (MESA) and findings that undoubtedly confirmed the importance of right ventricular remodeling as an important predictor of heart failure and mortality in a population free of cardiovascular risk factors, the right ventricle was brought into focus in the domain of cardiovascular investigations (15,16).
The right ventricular hypertrophy in arterial hypertensive patients probably represents the cornerstone of reduced right ventricular systolic and impaired diastolic function. This was confirmed by many authors who studied that topic (17,18).
The mechanisms that lead to right ventricular hypertrophy are as follows: biohumoral mechanisms of myocardial interstitial fibrosis induced by catecholamines, renin – angiotensin – aldosterone system, growth factors (insulin) or inactivated inhibitors of metalloproteinase 1; Ø hemodynamic mechanisms that involve increased pulmonary vascular resistance and increased right-sided pressures and interventricular dependence, which probably has the most important role in right ventricular remodeling in arterial hypertensive patients, (7).
An additional reason for reduced exercise capacity in arterial hypertensive patients could lie in the physiology of right coronary circulation. Namely, resting right coronary blood flow is lower than left coronary blood flow, because of the lesser work of the right ventricle (19).
Endogenous nitric oxide increases the right coronary blood flow during exercise and provides adequate balance between oxygen demand and supply (20), however, the autoregulation of right coronary circulation is poor, and much worse than left coronary circulation (21).
In the right ventricle, oxygen extraction significantly increases during exercise, suggesting essential differences in blood flow regulation between these two cardiac chambers. Furthermore, right coronary vasodilation during exercise occurs significantly later than left coronary vasodilatation, which disables adequate increase in coronary blood flow and results in moderate hypoperfusion of the right ventricle and decreased right ventricular contractility. These physiological differences between right and left coronary circulation during exercise in arterial hypertensive patients with already impaired endotheliumdependent vasodilatation, possibly could explain the decreased right ventricular function and exercise capacity in this population (7).
There are only few clinical studies that concerned the relationship between the right ventricle and functional capacity in patients without pulmonary hypertension or congenital heart diseases. In these investigations, mainly systolic right ventricular parameters (ejection fraction, tricuspid annular plane systolic excursion, myocardial performance index, ventricular strain rate, systolic velocity across lateral segment of tricuspid annulus obtained by tissue Doppler) are found to be predictors of depressed functional capacity. However, these findings are not sufficient, and further studies in this field are necessary to provide answers to many questions about the influence of arterial hypertension on functional capacity (22,23).
The six minute walk test (6MWT):
The 6 min walk test (6MWT) was first used to evaluate patients with chronic respiratory diseases such as chronic obstructive pulmonary disease and respiratory failure. The test attracted the attention of cardiologists because it was easy to perform and interpret. For this reason, its role in measuring functional limitation, in evaluating the effects of therapy and in the prognostic stratification of patients with chronic heart failure has been widely investigated. The 6MWT is a simple test which does not require expensive equipment or advanced training for technicians. The test involves asking the patient to walk the longest distance possible in a set interval of 6 min, through a walking course (corridor) preferably 30-m long. The patient can stop or slow down at any time and then resume walking, depending on his/her degree of fatigue. Even though other parameters can be monitored during the test, such as arterial pressure and/or heart rate, the number of times the patient has to stop during the test, the speed of walking or even changes in respiratory gases (measured using a portable instrument) and oxygen saturation, the distance walked in 6 min is the parameter usually taken into consideration in clinical practice and also the one that has proven to be most useful in nearly all clinical studies (24). The 6MWT may be used as a tool for the measurement of functional status of a patient especially in the case of advanced diseases with multiple comorbidities who cannot perform more complex exercise tests, such as patients with HF, chronic obstructive pulmonary disease or cystic fibrosis (25). The prognostic role of 6MWT in terms of morbidity and mortality has been evaluated especially in patients with pulmonary hypertension (26) and in HF populations (27).

Furthermore, the test has been indicated before and after treatment to assess the response to various medical interventions in many patient populations including HF but also to guide cardiac rehabilitation (28). As for safety, absolute contraindications for the 6MWT include acute myocardial infarction or unstable angina (acute phase), uncontrolled arrhythmias causing symptoms or hemodynamic compromise, acute myocarditis or pericarditis, uncontrolled acutely decompensated HF (acute pulmonary edema), acute pulmonary embolism, suspected dissecting aneurysm, severe hypoxemia at rest or acute respiratory failure, acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (such as infection, renal failure, thyrotoxicosis) or mental impairment leading to inability to cooperate. Relative contraindications are resting heart rate >120 beats/min, systolic blood pressure >180 mm Hg or diastolic pressure >100mmHg. On the other hand, a test should be immediately stopped in case of chest pain, intolerable dyspnea, leg cramps, diaphoresis or any report of not feeling well (24).

The 6MWD in healthy adults has been reported to range from 400 to 700m. There are several nonstandardized reference equations for 6MWD from healthy adult populations; their value has not been established due to high variation mainly attributed to the fact that different methodologies were used in various studies (29).

Age, height, weight, sex, corridor distance, impaired cognition and need for continuous oxygen supplementation may independently affect the 6MWD in patients and therefore these factors should be taken into consideration when interpreting the results of 6MWT (30).

Because of some of the intrinsic features of the test, such as execution time (max 6 min), simplicity (walking on a flat surface), greater acceptance by patients compared to a conventional exercise test (symptom-limited), the 6MWT has come to be considered a sub-maximal test. The indications to perform a 6MWT could thus differ from those of a maximal exercise test. However, in most studies the longest distance walked during the 6MWT has shown a medium-to-high correlation with the VO2 measured at the peak of maximal exercise test. It has also been shown that the oxygen uptake at the end of the 6MWT, measured using portable instruments, shows a close correlation with the VO2 peak (31). In some patients,
the VO2 at the end of the walking test was even greater than the VO2 peak. Consequently, the 6MWT does not seem to have the features of a submaximal test. It could instead be used to assess the maximal functional capacity in patients with heart failure (30).

It has been reported that 6MWD is associated with the functional status of patients with HF and relates to established CPET measures, while it adds prognostic information over and beyond these measures. In a recent systematic review, an inverse correlation between NYHA class II–IV and 6MWD (mean values ~400m, 320 m and 225 m, respectively for NYHA class II, III and IV) was observed while an overlap in 6MWD between NYHA class I and II patients with HF (mean value ~400 m) was shown (32).

**The six-minute walk distance is a marker of functional capacity in hypertension:**

Literature on the 6MWT in patients with hypertension is limited. Clinical trials have reported low absolute values of the 6MWD in adults with grade-I or -II hypertension and comorbidities, which improved after physical rehabilitation programs (33). Cross sectional studies have suggested diminished 6MWD in women with grade-I hypertension with comorbidities, (34). Whereas another cross-sectional study demonstrated preserved 6MWD in men with grade-I hypertension without comorbidities (35). Patients with hypertension presented lower 6MWD compared with sexmatched healthy controls, highlighting that the 6MWT captures the hemodynamic-related functional capacity of patients with hypertension. Personal variables (age, body height and weight) that are considered as risk factors for CVD also have an inverse effect on the 6MWD in patients with hypertension. It appears surprising that the same factors also affect the 6MWD in healthy controls (36).

**Exercise capacity and right ventricular function: Baker et al., (37) found that RV ejection fraction at rest is more predictive of exercise capacity than LV ejection fraction in patients with chronic heart failure. Another study, showed that, in a homogenous group of patients with advanced heart failure, RV function at rest or during exercise predicts both survival and functional capacity (38).**

The mechanism through which RV dysfunction affects exercise capacity seems to be related to the elevation of pulmonary wedge pressure during exercise. Because right ventricle is very sensitive to load, an elevation of the pulmonary wedge pressure acts to increase pulmonary resistance, and thereby resistance to RV ejection. Indeed, exercise tolerance is related to the level of pulmonary wedge pressure at rest (39). Kim et al., (40) made a novel attempt at providing insight into the role of RV dysfunction on effort tolerance independent of left ventricular function in a cohort of 2051 subjects who underwent a clinically indicated resting echocardiogram and exercise single-photon emission computed tomography within a 1-month period. RV function on echocardiography was assessed both qualitatively by standard subjective visual assessment and quantitatively by measurement of tricuspid annular plane systolic excursion and peak tricuspid annular systolic velocity (S’). Both tricuspid annular plane systolic excursion and tissue Doppler imaging have been shown to be reliable measures of RV response to exercise. 6% of the population (n=123) had RV systolic dysfunction by quantitative parameters. In these patients, 19% had RV dilation and 40% had RV systolic dysfunction by qualitative assessment. The major finding of this study is that exercise duration in patients with RV dysfunction is significantly lower than that in patients without RV dysfunction (6.7±2.8 versus 7.9±2.9 minutes; P<0.001). In multivariable analysis, both LV (P=0.002) and RV (P=0.02) dysfunction were independently associated with exercise time.
References.


