Low functional Capacity in Young Non-Complicated Hypertensive Patients is related to Left Ventricle Diastolic Function Changes Rather than Subclinical Systolic dysfunction by Abnormal Left Ventricle Strain

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Abstract

Hypertension is an elevation of systolic blood pressure (SBP) ≥140 mm Hg, or a diastolic blood pressure (DBP) ≥90 mm Hg, or using antihypertensive drugs. Arterial hypertension causes high morbidity and mortality because its harmful impact on many systems, especially the cardiovascular system. Despite good control of their blood pressure, young patients with non-complicated hypertension are usually presented with exercise intolerance which necessitate the search for possible causes. **Aim:** The present study is targeted to discover possible subtle systolic dysfunction and its correlation with exercise capacity among young age patients with chronic non complicated hypertension as well as to assign the main factors affecting exercise capacity in those patients. **Methods:** A total of 80 young age participants involved in this study. They are grouped as a group I (control subjects) , n= 40 (female: 17, male: 23) and group II (hypertensive patients), n= 40 (male: 27, female: 13) with different BMI levels. Group II further subdivided into group A (exercise capacity > 7 MET) and B (exercise capacity≤7 MET). Strain analysis was performed using propriety software on the echocardiograph. TDI and PWD are used to measure E/e' and PCWP. All participants are subjected to treadmill test using Bruce protocol in order to obtain exercise capacity and to exclude IHD. **Results:** Compared to normal subjects, non-complicated hypertensive patients have significantly reduced GLS (*P value: 0.00*) and increased PSI (*P value: 0.00*) as well as a significant increase in E/e' (*P value: 0.00*), PCWP (*P value: 0.00*) and a significant reduction in exercise capacity (*P value: 0.00*). In hypertensive patients with exercise capacity ≤7 MET versus those with exercise capacity >7 MET, there is no statistical difference between the average GLS (*P value:0.6*), average PSI (*P value: 0.07*) while significant elevation of E/e' (*P value: 0.01*) and PCWP (*P value: 0.01*) are observed in hypertensive patients with lower exercise capacity. **Conclusion:** Though significant changes in GLS, PSI and lower exercise capacity are evident in hypertensive patients in relation to healthy control subjects, Low exercise capacity in those patients is related to significant diastolic changes rather than subclinical systolic dysfunction.

Key words: Hypertension, exercise capacity, global longitudinal strain, post systolic shortening index, pulmonary capillary wedge pressure, E/e', treadmill test.

Abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure, MET: metabolic equivalent of O_2 consumption, BMI: body mass index, PCWP: Pulmonary capillary wedge pressure, IHD: ischemic heart disease, GLSP: Global longitudinal strain, PSI: Post-systolic index.

Introduction

Hypertension is an elevation of systolic blood pressure (SBP) ≥ 140 mm Hg, or a diastolic blood pressure (DBP) ≥ 90 mm Hg, or using antihypertensive drugs regardless the current blood pressure level.[1] Arterial hypertension causes high morbidity and mortality because its harmful impact on many systems, specially the cardiovascular system.[2] Before functional changes in the heart of hypertensive patient become apparent, there will be a progressive myocardial fibrosis and abnormal left ventricular (LV) geometry.[3] Diastolic impairment is major portion of this pathology, and in spite of the developing fact of its significance, it is largely underestimated awing to its difficult diagnosis as well as the absence of effective treatments.[4] Many researchers reported that despite the presence of normal systolic function as evident by ejection fraction or fractional shortening, abnormalities of diastolic indices may occur, giving the idea that diastolic dysfunction may go before or independent of systolic dysfunction. [5] Nevertheless, in all reports that study this topic, systolic function was assessed at the endocardium level, indicating a chamber function of LV, which is a physiological result of the interaction between myocardial function and geometry of left ventricle.[6] Additionally, while ordinary echocardiogram can identify variations in LV diastolic abnormalities related to left ventricle hypertrophy. LV systolic function is protected until late in the progression of the disease, making subtle changes in left ventricle contractile function troublesome to assess in the initial stages.[7] Subclinical alterations in left ventricle function can be distinguished by evaluating strain of myocardial tissue, a dimensionless estimation of deformation. Two-dimensional (2D) speckle tracking nowadays has a new echocardiographic approach for quick examination of left ventricle strains of the longitudinal, circumferential and radial fibers. This strategy evaluates myocardial movement by tracking natural acoustic reflections and interference patterns seen in two-dimensional echocardiographic pictures and has been approved with estimations gotten by MRI and sonomicrometry.[8] On the other hand, post-systolic shortening (PSS) is a longitudinal shortening after aortic valve closure, is of particular interest since it indicates, with high sensitivity, regional abnormalities. A newly occurring PSS during a stress echo is always a marker of ischemia while pre-existing PSS is only then likely to be pathologic if systolic shortening is reduced and PSS exceed 20% of the total deformation amplitude. It can be used as a prognostic marker for arrhythmic events. [9]

Methods

A total of 80 young age individuals involved in this study. In order to exclude conditions that might affect our outcomes, the following criteria are required:

a) No clinical evidence or previous history of IHD, valvular heart disease, diabetes mellitus, heart failure, respiratory disease and renal failure.

b) Not athletic.

c) Not smoker

All subjects provided information on family history, personal habits (drug ingestion, level and type of physical exercise, known disease condition and alcohol intake).

Those patients who are already diagnosed as having primary non complicated (no end organ damage) hypertension and taking single or combined antihypertensive medications (including ACEI, ARB, beta-blockers or CCB) are included in the study while those who have fluctuations in their blood pressure levels and do not take

antihypertensive medications are excluded from patients group to avoid selection bias. Duration of hypertension in months is documented for each patient. In our study we do not focus on statistical effect of treatment modality on study variables. The patients were grouped as a group I (control subjects) , n= 40 (female: 17, male: 23) and group II (hypertensive patients), n= 40 (male: 27, female: 13) with different BMI levels. In Further subsequent analysis, we exclude BMI $\geq$ 30 kg/m^2 from group II in order to minimize the effect of BMI on the study results. In regard to group II, Since exercise capacity less than 7 MET is considered low [10], they are subdivided into two subgroups: those with exercise capacity >7 MET (n=22) and those with exercise capacity $\leq$7 MET (n=18).

Echocardiography

A complete two dimensional echocardiography is achieved in all patients, using a commercially available ultrasound transducer and equipment (M5sc probe, GE, Vivid E9, 2015, USA). All acquisitions were performed by the same operator with the patients in the left lateral position.

E/e' calculation

Measurement of pulsed-wave Doppler of the early (E), late (A) of mitral inflow velocities as well as deceleration time of early filling phase of left ventricle are carried out. Using tissue Doppler in the 4-chamber view, the peak early diastolic velocity of the lateral and medial mitral annulus (e′) are measured to obtain average E/e'.

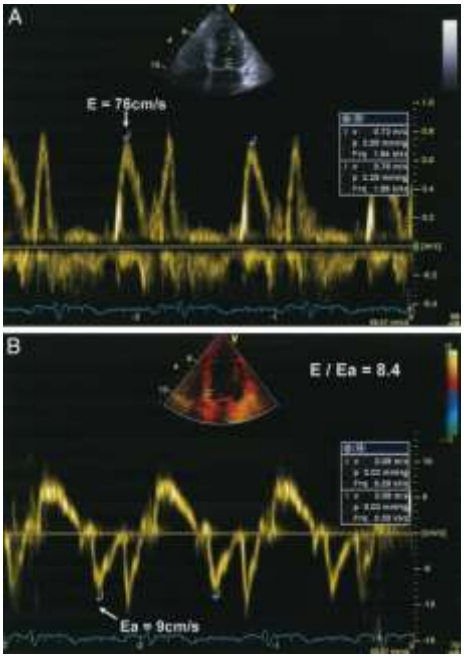

Figure 1 Calculation of E/e' ratio

Pulmonary capillary wedge pressure (PCWP) is measured in an attempt to compare our results with hemodynamic impact of diastolic dysfunction resulting from hypertension

PCWP= (E/e´ x 1.25) + 1.9 or simply 4+ E/e' (Nagueh Formula). [11]

Speckle tracking analysis

Three apical views are used for the purpose of speckle tracking analysis (two-champer, four-chamber, and long-axis). Three points on each view (the apex and two on each mitral annuli) are identified by the examiner. Peak systolic longitudinal strain in corresponding segments of every view along with defining an aortic valve closure is then identified by the software. Global longitudinal strain is obtained by taking the average strain for these three views (seventeen segments with six basal, six mid, four apical, and the one true apex). The frame rate is kept between 70 Hz and 100 Hz. The strain curve is extracted, the peak negative wave of strain during the whole cardiac cycle is referred as peak strain.[12] Post systolic index is simultaneously obtained from another map.

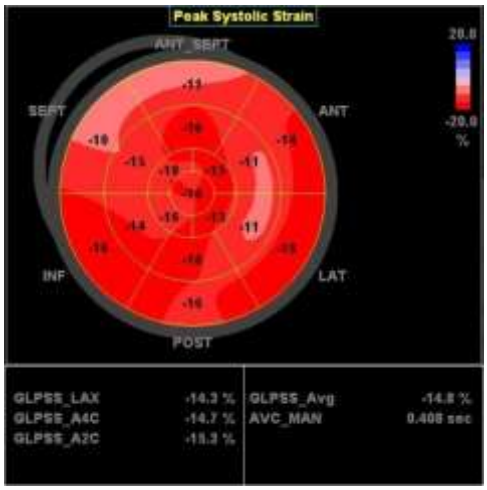

Figure 2 Bulls-eye figure of peak systolic strain

Treadmill test

All participants subjected to treadmill test using Bruce protocol in order to obtain exercise capacity and exclude the possibility of IHD. Our goal is to achieve maximal stress, i.e. when they reach ≥85% of their maximal predicted HR, which can be measured as 220-age for male and 210-age for female.[13]

Results

The mean values of the study groups (group I; control) and group II; hypertensive patients for GLS, PSI, E/e', PCWP and exercise capacity at different and matched BMI are illustrated in Table 1 and 2. In our study, there is a significant difference in GLS (P value: 0.00) and PSI (P value:0.00), E/e (P value: 0.00), PCWP (P value: 0.00) and exercise capacity (P value: 0.00) between the two groups. Hypertensive patients showed significantly lower GLS and higher PSI as well as a significant increase in E/e and PCWP and lower exercise capacity at both different and matched BMI.

Table 1: the values of GLS, PSI, E/e, PCWP and exercise capacity, according to study groups at different BMI

Data (M±SD)	Group I N=40 (male:23, female: 17) Age (23-37yr) BMI (20.8-28.7)	Group II N=40 (male:27,female: 13) Age (20-40yr) BMI (22.9-37)	P value
GLS (average) (%)	-21.1±1.4	-18.7±2.6	0.000
PSI (average) (%)	0.92±0.36	3.4±2.07	0.000
E/e'	4.3±1.01	7.71±2.31	0.000
PCWP (mmHg)	8.3±1.02	11.4±2.84	0.000
Exercise capacity (MET)	10.45±0.63	8.2±1.9	0.000

Values presented as M±SD. GLS: global longitudinal strain, PSI: post systolic index, PCWP: pulmonary capillary wedge pressure, MET: metabolic oxygen equivalent

Table 2 The values of GLS, PSI, E/e, PCWP and exercise capacity according to study groups with matched BMI

Data (M±SD)	Group I N=40 (male:23, female: 17) Age (23-37yr) BMI (20.8-28.7)	Group II N=14 (male:10, female: 4) Age (20-40yr) BMI (22.9-37)	P value
GLS (average) (%)	-21.1±1.4	-19.2±2.4	0.007
PSI (average) (%)	0.92±0.36	2.8±1.8	0.000
E/e'	4.3±1.01	6.75±1.8	0.000
PCWP (mmHg)	8.3±1.02	10.2±2.23	0.003
Exercise capacity (MET)	10.45±0.63	8.6±2.07	0.001

Values presented as M±SD. GLS: global longitudinal strain, PSI: post systolic index, PCWP: pulmonary capillary wedge pressure, MET: metabolic oxygen equivalent

Statistical analysis of different echocardiographic parameters is then conducted in relation to exercise capacity in group II (hypertensive patients). Patients group is subdivided into two subgroups: those with exercise capacity >7 MET (n=22) and those with exercise capacity ≤7 MET (n=18). In these two subgroups there is no statistical difference between the GLS (P value:0.6). Nevertheless higher PSI is documented in group B hypertensive patients with low exercise capacity, but statistically still not significant (*P value: 0.07*). E/e' and PCWP are significantly elevated in patients with lower exercise capacity as shown in figure 1,2,3 and 4.

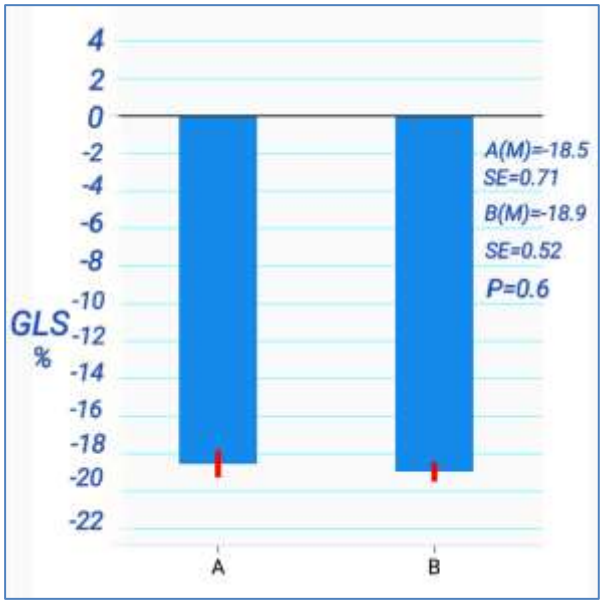

Figure 3: Average global longitudinal strain (GLS), (%) in group A (exercise capacity >7 MET, n:22) and group B (exercise capacity ≤7 MET, n:18)

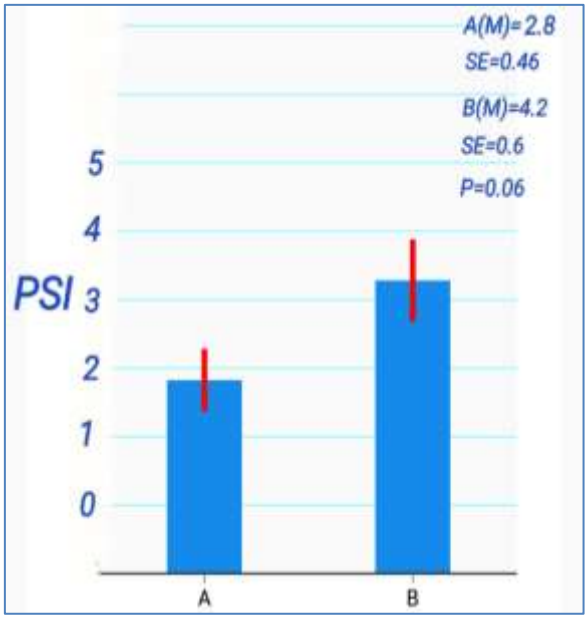

Figure 4: Average post systolic index (PSI), (%) in group A (exercise capacity >7 MET, n:22) and group B (exercise capacity ≤7 MET, n:18)

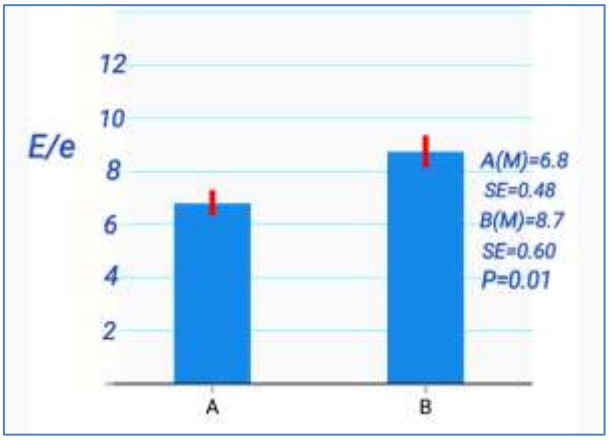

Figure 5: E/e' ratio in group A (exercise capacity >7 MET, n:22) and group B (exercise capacity ≤7 MET, n:18)

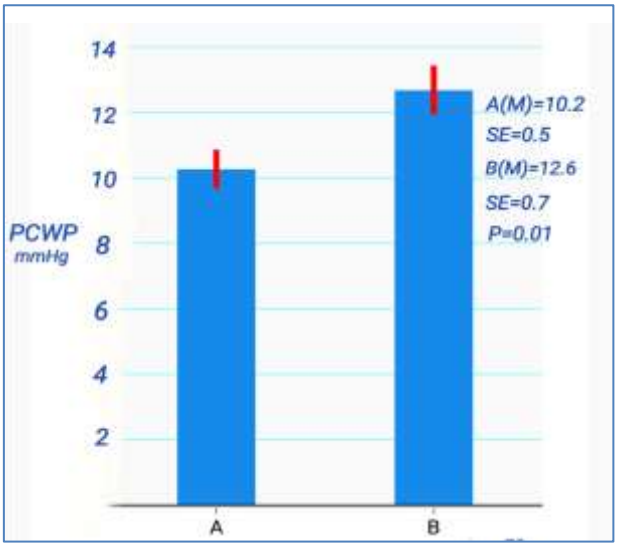

Figure 6: Pulmonary capillary wedge pressure (PCWP), (mmHg) in group A (exercise capacity >7 MET, n:22) and group B (exercise capacity ≤7 MET, n:18)

Discussion

Hypertension is a common disease and has multiple effects on CVS, especially the heart, in our study the blood pressure was 137.7±15.5/86±13.4 mm Hg in non-complicated hypertensive patients (all of them are receiving antihypertensive medications) and 119.3±18.5/75±11.4 mm Hg in normotensive control subjects. Body mass index is more in patients group (30.5±4.01kg/m2) compared to normotensive (24.9±2.2kg/m2) individuals. In our study at different BMI levels, hypertensive patients showed significantly lower global longitudinal strain and more post-systolic index, additionally, we demonstrated that there is significantly higher E/e and PCWP compared to normotensive individuals. These findings are consistent with a study by Shantanu P. *et al*, 2013[12] in which the shortening of longitudinal fiber was less in the patients with systemic hypertension and normal EF and FS than the corresponding

segments in the control group. The possible cause of reduced LV longitudinal strain in hypertensive individuals might be attributed to the existence of regional subendocardial ischemia and fibrosis of perivascular and interstitial regions.(14) Myocardial post-systolic shortening index has variable duration and amplitude in its characteristic waves. In one third of healthy individuals, post systolic contraction may occur in some myocardial segments and it is functionally not significant. On the other hand, post systolic contraction may indicates myocardial insults as ischemic damage together with abnormal strain. Post-systolic contraction takes place in an energetically demanding segments.(15) Asanuma et al. (16), showed that speckle tracking derived PSI is the most useful echo parameters referring to myocardial injury during ischemia. In our patients PSI is significantly elevated, though in non-pathological limit indicated that serial subclinical myocardial changes has been occur in those patients group. Diastolic dysfunction is the main component of LV function that has been affected by systemic hypertension and it is independent of LV systolic function, namely you may found abnormal diastolic parameters with normal or supra-normal systolic function.(17) We approached the results of a study by Giovanni de S *et al*, 2000 who showed that abnormal diastolic indices can be revealed in hypertensive patients in the presence of normal or supernormal systolic function.(17) We also showed significant increment in E/e' and PCWP and significant reduction in exercise capacity in hypertensive patients compared to control subjects with matched BMI. These results are approach to those groups of hypertensive patients with different BMI including obese subjects, indicated that these changes result mainly from hypertension effect. Diastolic function is an important factor in maintaining normal exercise capacity since it plays a major part in producing a maximal cardiac output. Throughout the exercise, the preservation of adequate left ventricular filling to safeguard a normal cardiac output comprises the capability to attain diastolic filling rates larger than the ejection rates during systole.(18) Though all of our patients are using antihypertensive medications with blood pressure level of (137.7±15.5/86±13.4 mmHg), but their exercise capacities of some what are still limited and well correlated with diastolic indices changes indicated that treatment may not influence exercise capacity, perhaps due to poor affection on diastolic function. Little W. *et al,* 2006 reported poor improvement in diastolic function in hypertensive subjects despite the use of effective anti-hypertensive drugs.(19) we disagree with Ljubica G *et al* (20) who showed that only lower GLS% appeared as an independent predictor of exercise capacity <7 METs while our study revealed no significant change in GLS. We postulate that antihypertensive medications may modulate systolic function, including GLS in both subgroups.

Conflict of Interests.

There are non-conflicts of interest .

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الخلاصة

ارتفاع ضغط الدم هو ارتفاع في ضغط الدم الانقباضي (140 ≤ (SBP ملم زئبق، أو ضغط الدم الانبساطي (90≤ (DBP ملم زئبق، أو باستخدام الأدوية الخافضة لضغط الدم. ارتفاع ضغط الدم الشرياني يسبب ارتفاع معدلات المراضة والوفيات بسبب تأثيره الضار على العديد من النظم ، وخاصة نظام القلب والأوعية الدموية. على الرغم من التحكم الجيد في ضغط الدم لديهم، فإن المرضى الصغار الذين يعانون من ارتفاع ضغط الدم غير المعقد عادةً ما يعانون من عدم تحمل التمرينات التي تستلزم البحث عن الأسباب المحتملة. **الهدف:** تهدف هذه الدراسة إلى اكتشاف الخلل الوظيفي الانقباضي الدقيق المحتمل وارتباطه بقدرة التمرين لدى صغار السن المصابين بارتفاع ضغط الدم المزمن غير المعقد وكذلك تحديد العوامل الرئيسية التي تؤثر على قدرة التمرينات لدى هؤلاء المرضى. **الأساليب:** ما مجموعه 80 من المشاركين في سن مبكرة المشاركة في هذه الدراسة. يتم تجميعها في المجموعة الأولى (الأشخاص الخاضعين للمراقبة)، ن = 40 (أنثى: 17 ، ذكور: 23) والمجموعة الثانية (مرضى ارتفاع ضغط الدم)، ن = 40 (ذكور: 27 ، أنثى: 13) مع مستويات مختلفة من مؤشر كتلة الجسم. تنقسم المجموعة الثانية إلى المجموعة "أ" (قدرة التمرين< 7 (METو) Bقدرة التمرين ≥ 7 .(METتم إجراء تحليل الإجهاد باستخدام برنامج الحماية على مخطط صدى القلب. يتم استخدام TDI و PWD لقياس E / e ، و .PCWPيتعرض جميع المشاركين لاختبار المطحنة باستخدام بروتوكول بروس من أجل الحصول على القدرة على ممارسة الرياضة واستبعاد امراض اقفرار شرايين القلب .**النتائج:** بالمقارنة مع الأشخاص الطبيعيين ، فإن مرضى ارتفاع ضغط الدم غير المعقد قد قللوا بشكل كبير) GLSقيمة (P: 0.00 وزادوا) PSIقيمة (P: 0.00 بالإضافة إلى زيادة ملحوظة في E / e ، (قيمة (P: 0.00،) PCWPقيمة (P: 0.00 وانخفاض كبير في قدرة التمرين (قيمة .(P: 0.00في مرضى ارتفاع ضغط الدم الذين لديهم قدرة ممارسة MET 7 ≥ مقابل أولئك الذين لديهم قدرة ممارسة< MET 7 ، لا يوجد فرق إحصائي بين متوسط) GLSقيمة (P: 0.6، متوسط) PSI قيمة (P: 0.07في حين يرتفع بشكل ملحوظ من E/e ، (قيمة (P: 0.01و PCWP)قيمة (P: 0.01لوحظت في مرضى ارتفاع ضغط الدم مع انخفاض القدرة على ممارسة الرياضة. الخلاصة: على الرغم من حدوث تغييرات كبيرة في GLS و PSI وانخفاض القدرة على ممارسة التمرينات الرياضية لدى مرضى ارتفاع ضغط الدم فيما يتعلق بالمواضع الخاضعة للمراقبة الصحية ، إلا أن انخفاض القدرة على ممارسة التمرينات الرياضية لهؤلاء المرضى يرتبط بالتغيرات الانبساطية الكبيرة بدلاً من الخلل الوظيفي الانقباضي تحت الإكلينيكي.