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Original article

Effects of a dynamic handgrip exercise on left ventricular diastolic functions in diabetes mellitus patients: A preliminary clinical data

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Background: A diabetes mellitus (DM) patients sometimes exhibit a pseudo-normal diastolic relaxation during echocardiography examination, which may lead to an incorrect diagnosis. Exercise echocardiography help uncover this hidden alteration, but conventional exercise techniques contain movement artifacts. Recently, an isotonic handgrip exercise was introduced and caused hemodynamic and diastolic changes with less movement.
Objective: To investigate hemodynamic and left ventricular diastolic that responses to a dynamic handgrip exercise (DHE) in DM patients.
Methods: 12 controls and 12 DM patients were recruited and evaluated for hemodynamic and diastolic functions at rest and 3 minutes after performing DHE.
Results: DHE increased systolic blood pressure, A wave, and lateral e' of all subjects. For DM, DHE increased E wave (0.67 ± 0.16 m/s *vs.* 0.81 ± 0.19 m/s, $P = 0.006$) and septal e' (7.17 ± 1.59 cm/s *vs.* 8.50 ± 1.62 cm/s, $P = 0.004$). A significant reduction of DT was also observed in DM (178.00 ± 40.24 ms *vs.* 155.10 ± 24.14 ms, $P = 0.041$). DHE caused negative changes of ΔE/A ratio in controls whereas positive in DM patients ($- 0.20 \pm 0.21$ *vs.* 0.06 ± 0.18, $P = 0.005$).
Conclusion: DHE induced increases of early diastole indices, E wave and e', in DM. DHE displayed a feasibility for using as an exercise stressor during echocardiography.

Keywords: Dynamic handgrip exercise, diabetes mellitus, exercise echocardiography, left ventricular diastolic function.

Left ventricular (LV) diastolic function represents a filling of blood from left atrium (LA) to LV. [1] This physiological step impacts on a stroke volume (SV). [1] Investigation tools for both LV diastolic components such trans-mitral blood flow and LV myocardial function were pulse wave (PW) Doppler echocardiography and tissue Doppler imaging (TDI), respectively.[1,2] LV diastole, measured by trans-mitral blood flow, consists of an early filling (E wave) and an atrial contraction (A wave) that correspond to velocities of trans-mitral blood flow, which produced by a pressure gradient between LA and LV. [4] In associated with trans-mitral blood flow, longitudinal LV myocardial velocity measured by TDI, displayed as 2 negative waves (e' wave and a' wave), represents myocardial function during early diastolic relaxation and atrial contraction.[3] Factors contribute to the LV diastolic function are mainly modulated by many regional myocardial functions, which include interaction between right ventricle (RV) and LV, LA function, LV systolic function, and LV systolic to diastolic synchronization. [1]

Changes of LV diastolic function in diabetes mellitus (DM) are known to be related with many factors ranged from a cellular scale to a chamber scale and can be seen by Doppler and TDI parameters.[5] In DM, increasing in LV stiffness and interstitial fibrosis cause by chronic hyperglycemia and chronic insulin resistance are correlated with alteration of LV diastolic function. [6] In a trans-mitral Doppler of DM patients, prolong isovolumetric relaxation time (IVRT),

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reduction in E wave, and raise of A wave were observed.[7] In an advance clinical stage, LV diastolic dysfunction (DD) is presented. This DD is an early maker that reflects an abnormal relaxation of LV myocardium, which is a functional change prior to a structural change of the heart, and it occurs prior to a development of LV systolic dysfunction in diabetic cardiomyopathy.[6] However, a normal diastolic pattern could be observed during resting condition in DD patients.[7] In this case, increase workload of the heart by applying exercise to the patient can unmask a pseudo-normal diastolic function and reveal a true pathology of the heart.[8]

Exercise echocardiography commonly employs treadmill or bicycle to increase cardiac workload.[9] Increasing in heart rate (HR) and systolic blood pressure (SBP) are normal responses to this moderate to high intensity exercise.[10] However, movement is a major limitation of both treadmill and bicycle during exercise echocardiography. Recently, isometric handgrip echocardiography was introduced and studied in young and elderly subjects.[11] Isometric handgrip displayed safety and feasibility to be used as a stressor by causing changes in the ratio of trans-mitral flow to lateral wall TDI (E/e') with less movement artifact. However, handgrip exercise can be performed as a dynamic exercise by squeeze-release hand grippers. Data related to hemodynamic and cardiac diastolic function responses to this dynamic handgrip exercise (DHE) is limited. In addition, as mentioned previously, pseudo-normal diastolic function could be observed in DM patients, which requires an exercise stressor to uncover an actual pathology of the patient. Therefore, the aim of this study was to investigate changes of hemodynamic and LV diastolic parameters in response to a DHE, a new exercise echocardiography technique, in DM patients.

Materials and methods

This study was conducted in accordance with the Declaration of Helsinki. Study protocols were reviewed and approved by Naresuan University institutional review board (COA no. 400/2019). All subjects provided written informed consent prior to the study. Data collections were performed between September and October 2019.

Subject recruitment

Subjects, male and female aged over 35 years diagnosed with DM type 2 by physicians and receiving glucose lowering medicines at the primary health care center, were recruited to the study. Exclusion criteria were valvular heart disease, arrhythmias, left ventricular ejection fraction (LVEF) < 50.0%, hypertension (blood pressure (BP) > 140/90 mmHg), poor echocardiography images, and patient who were unable to perform handgrip exercise (e.g. hand wound). Intense smoking and alcohol consumption were also excluded from the study. To establish a normal handgrip exercise response, healthy subjects who had normal BP (< 140/90 mmHg) with no history of chronic diseases were recruited into the control group. Medical history and basic information were obtained by using a questionnaire during subject recruitment.

Hemodynamic parameters

Baseline hemodynamic were measured at rest at the Cardio-Thoracic Technology Department Laboratory, Faculty of Allied Health Sciences, Naresuan University, Thailand. HR and BP were measured by using automatic BP monitor (Omron Corporation, Kyoto, Japan). Fasting blood sugar of DM subjects were assessed using Dextrostix (DTX) (Accu-Chek, Roche Diagnostics, Indianapolis, Indiana, USA). All echocardiographic examinations (Logiq V3, GE Health Care, Illinois, USA) were investigated by one observer, one year experience sonographer, to minimize variation. Trans-mitral pulse wave (PW) Doppler including E wave, A wave, deceleration time (DT), and iso-volumetric relaxation time (IVRT) were evaluated from apical 4 chamber (A4C) view. Early diastolic myocardial relaxation velocity (e') of left ventricle, both lateral and septal, were assessed by TDI from A4C view. Then, all measurements were repeated in all subjects at the end of 3 minutes handgrip exercise.

Handgrip exercise

To mimic a response of the heart to a low to moderate activity/exercise, we introduced a DHE to the subjects. DHE was performed with both hands on 2 kg resistance hand grippers at a minimum rate of 30 beats per minutes (bpm). A drop of the compression rate at 2nd and 3rd minutes were allowed, which depended on participant conditions (i.e. muscle fatigue or tired). Exercise was halted at the end of the 3rd minutes and all measurements were performed immediately.

Statistical analysis

Continuous variables were displayed as mean ± standard deviation (SD.) while categorical variables were displayed as number (percentage). Shapiro-Wilk test was used to assess data distribution. With normal distribution, paired *t* - test was used to compare between pre - and post - handgrip exercises in the same group whereas unpaired *t* - test was used between control and DM groups. Wilcoxon signed rank test was used to compared pre - and post - handgrip exercises of non-normal distribution data. Comparison of non-normal distribution between control and DM groups was done by Mann-Whitney test. In addition, Fisher's exact test was used for testing categorical data. GraphPad Prism 7.0 was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Twenty-four participants, 12 DMs and 12 controls, were enrolled in this study. Demographic data were summarized in Table 1. No significant differences were observed between healthy controls and DM subjects in age, gender, diastolic blood pressure (DBP), and body mass index (BMI). On the other hand, DM displayed higher systolic blood pressure (SBP) (control *vs.* DM: 121.80 ± 8.45 mmHg *vs.* 130.40 ± 11.61 mmHg, $P = 0.048$) and baseline HR (control *vs.* DM: 63.75 ± 7.35 bpm *vs.* 73.25 ± 11.53 bpm, $P = 0.025$). Average blood sugar of DM group was 133.7 ± 16.7 mg%. Numbers of handgrip exercise for 3 minutes of control and DM were 89.25 ± 2.60 times *vs.* 90.00 ± 0.85 times ($P = 0.580$), respectively.

Left ventricular diastolic parameters displayed a significantly higher of A wave velocity in DM group (controls *vs.* DM: 0.62 ± 0.13 m/s *vs.* 0.75 ± 0.16 m/s, $P = 0.045$). DM also exhibited a lower E wave but not reach a statistically significant level (controls *vs.* DM: 0.79 ± 0.17 m/s *vs.* 0.67 ± 0.16 m/s, $P = 0.092$), which contributed to a lower of E/A ratio of a DM group (controls *vs.* DM: 1.29 ± 0.21 *vs.* 0.93 ± 0.29, $P = 0.002$). DT and IVRT were similar between the two groups (Table 1).

For TDI parameter, compared to control, mitral annular early diastolic velocity (e') of DM were significantly lower in both lateral (controls *vs.* DM: 11.75 ± 1.87 cm/s *vs.* 9.33 ± 1.92 cm/s, $P = 0.005$) and septal (controls *vs.* DM: 8.83 ± 1.64 cm/s *vs.* 7.17 ± 1.59 cm/s, $P = 0.019$). An E/e' was not significantly different (controls *vs.* DM: 7.72 ± 1.71 *vs.* 8.26 ± 1.75, $P = 0.452$) (Table 2).

Table 1. Subjects characteristics.

	Controls (n = 12)	**DM (n = 12)**	***P*-value**
Age (years)	50.83 ± 2.25	54.08 ± 7.27	0.153
Female (%)	91.7 (11.0)	75.0 (9.0)	0.590
SBP (mmHg)	121.80 ± 8.45	130.40 ± 11.61	0.048
DBP (mmHg)	78.33 ± 7.05	81.17 ± 5.54	0.286
HR (bpm)	63.75 ± 7.35	73.25 ± 11.53	0.025
BMI (kg/m^2)	23.94 ± 3.39	25.26 ± 1.76	0.246

BMI, body mass index; BPM, beat per min; DBP, diastolic blood pressure; HR, heart rate; kg/m^2, kilogram per square meter; mmHg, millimeter mercury; SBP, systolic blood pressure

Table 2. Baseline left ventricular diastolic parameters.

	Controls (n = 12)	**DM (n = 12)**	***P*-value**
E wave (m/s)	0.79 ± 0.17	0.67 ± 0.16	0.092
A wave (m/s)	0.62 ± 0.13	0.75 ± 0.16	0.045
E/A ratio	1.29 ± 0.21	0.93 ± 0.29	0.002
DT (ms)	191.60 ± 32.78	178.00 ± 40.24	0.376
IVRT (ms)	80.12 ± 13.51	79.56 ± 11.17	0.913
Lateral e' (cm/s)	11.75 ± 1.87	9.33 ± 1.92	0.005
Septal e' (cm/s)	8.83 ± 1.64	7.17 ± 1.59	0.019
E/e'	7.72 ± 1.71	8.26 ± 1.75	0.452

(cm/s), centimeter per second; DT, deceleration time; IVRT, isovolumetric relaxation time; ms, millisecond; m/s, meter per second

Effects of DHE on hemodynamic parameters

DHE increased HR of DM group from 73.25 ± 11.53 bpm to 76.75 ± 11.65 bpm ($P < 0.001$) (Figure 1a). SBPs were increased in both control (baseline *vs.* handgrip: 121.80 ± 8.45 mmHg *vs.* 133 ± 11.05 mmHg, $P < 0.001$) and DM (baseline *vs.* handgrip: 130.40 ± 11.61 mmHg *vs.* 143.80 ± 13.99 mmHg, $P < 0.001$) (Figure 1b), Figure 1c.

Effects of DHE on left ventricular diastole

Handgrip exercise caused an increase of E wave in DM (baseline vs. handgrip: 0.67 ± 0.16 m/s *vs.* 0.81 ± 0.19 m/s, $P = 0.006$) (Figure 2a). After handgrip, A wave increased in both controls (baseline *vs.* handgrip: 0.62 ± 0.13 m/s *vs.* 0.80 ± 0.17 m/s, $P < 0.0001$) and DM subjects (baseline *vs.* handgrip: 0.75 ± 0.16 m/s *vs.* 0.85 ± 0.19 m/s, $P = 0.003$) (Figure 2b). DT remained unchanged in control but significantly decreased in DM (baseline *vs.* handgrip: 178.00 ± 40.24 ms *vs.* 155.10 ± 24.14 ms, $P = 0.042$) (Figure 2c). In addition, DHE caused a significantly lower DT of DM subjects compared to controls at the end of protocol (control *vs.* DM: 191.50 ± 35.53 ms *vs.* 155.10 ± 24.14 ms, $P = 0.008$). There was no significant effect of DHE on IVRT in both control and DM (Figure 2d).

DHE enhanced longitudinal tissue relaxation of lateral segment (Figure 2e) from 11.75 ± 1.87 cm/s to 12.92 ± 1.68 cm/s ($P < 0.001$) in control group and from 9.33 ± 1.92 cm/s to 10.42 ± 2.35 cm/s ($P = 0.035$) in DM group. Change of septal myocardium relaxation was only observed in DM (baseline *vs.* handgrip: 7.17 ± 1.59 cm/s *vs.* 8.50 ± 1.62 cm/s, $P = 0.004$) (Figure 2f).

In an analysis of individual changes caused by handgrip exercise, results displayed equivalent alterations in most hemodynamic and echocardiographic parameters of both control and DM groups. However, a significant difference was observed in an E/A ratio change, which control group exhibited a negative change while there was a positive change in DM group (- 0.20 ± 0.21 *vs.* 0.06 ± 0.18, $P = 0.005$).

Heart rate increase by handgrip exercise

Based on individual maximum predicted HR (MPHR), control group displayed a higher heart rate reserve (HRR) than DM group (control *vs.* DM: 105.40 ± 7.40 bpm *vs.* 92.67 ± 13.74 bpm, $P = 0.010$), which handgrip exercise elevated HR about 41.2 ± 7.6% and 46.3 ± 7.3% for control and DM ($P = 0.104$), respectively.

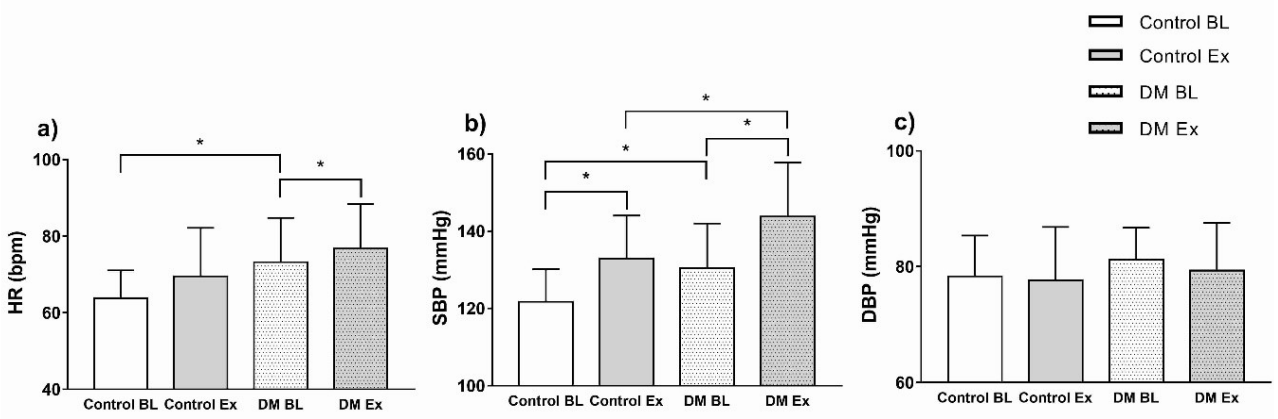

Figure 1. Effects of dynamic handgrip exercise on hemodynamic parameters (a) heart rate (b) systolic blood pressure and (c) diastolic blood pressure. BL, baseline; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, exercise; HR, heart rate; mmHg, millimeter mercury; SBP, systolic blood pressure;*$P < 0.05$

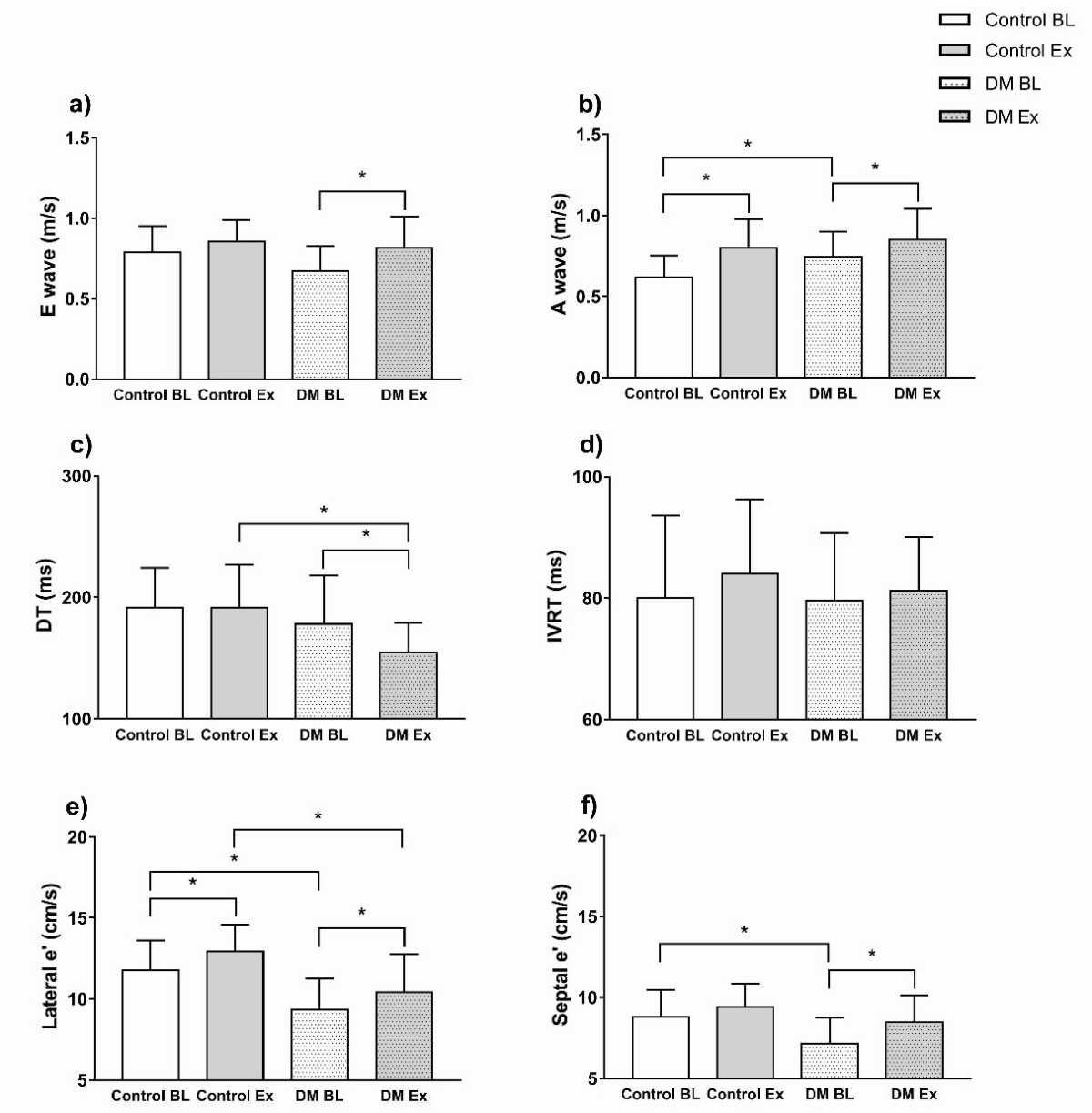

Figure 2. Effects of dynamic handgrip exercise on left ventricular diastolic parameters (a) early relaxation (b) atrial contraction (c) deceleration time (d) isovolumetric relaxation time (e) myocardium relaxation of lateral segment and (f) myocardium relaxation of septal segment. BL, baseline; DBP, diastolic blood pressure; DM, diabetes mellitus; Ex, exercise; HR, heart rate; mmHg, millimeter mercury; SBP, systolic blood pressure;*$P < 0.05$

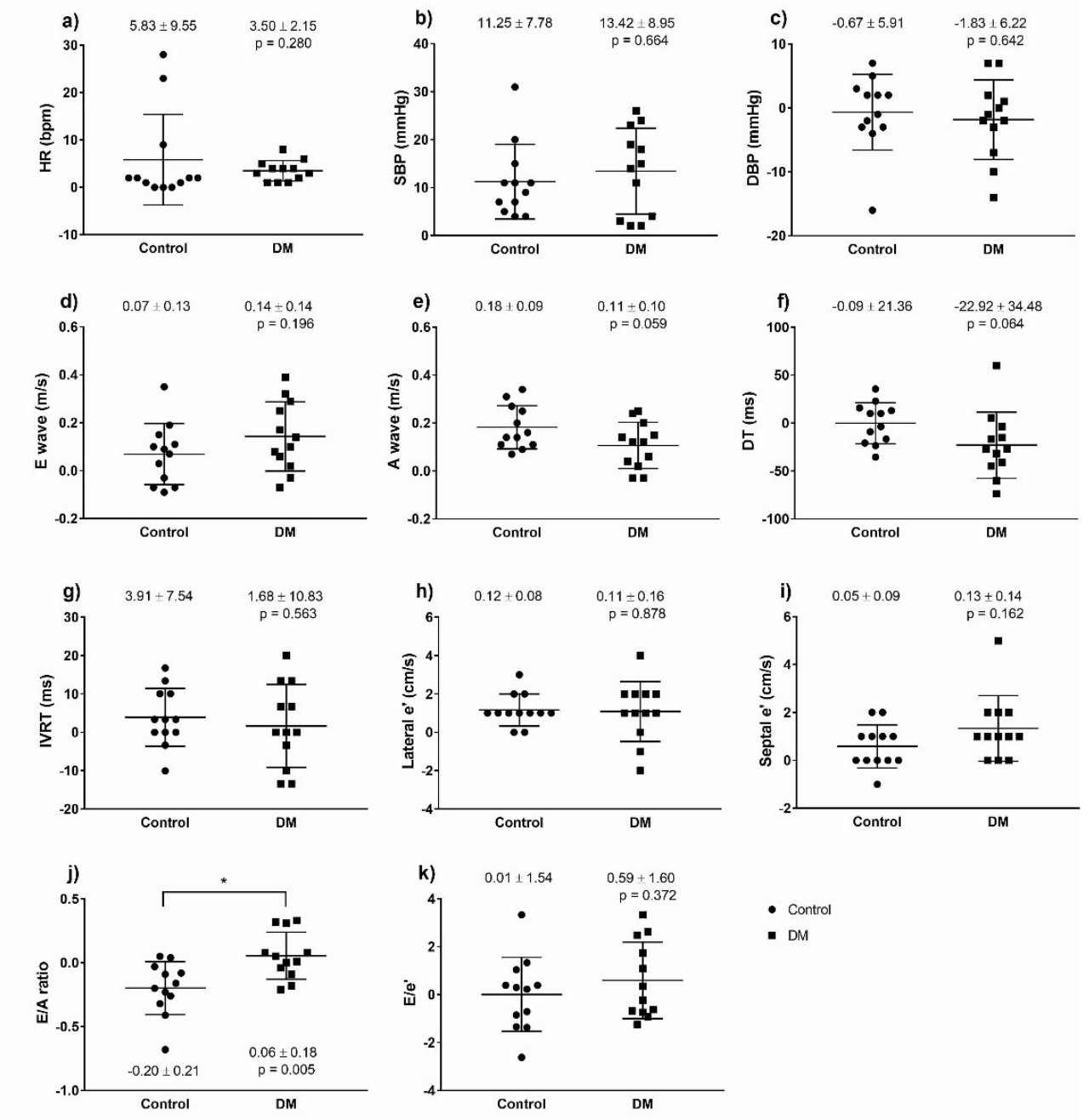

Figure 3. Mean changes of (a) heart rate (b) systolic blood pressure (c) diastolic blood pressure (d) E wave (e) A wave (f) deceleration time (g) isovolumetric relaxation time (h) lateral e' (i) septal e' (j) E/A ratio and (k) E/e' BPM = beat per min, cm/s = centimeter per second, DBP = diastolic blood pressure, DM = diabetes mellitus, DT = deceleration time, HR = heart rate, IVRT = isovolumetric relaxation time, mmHg = millimeter mercury, ms = millisecond, m/s = meter per second, SBP = systolic blood pressure, *$P < 0.05$

Discussion

In this study, we demonstrated baseline hemodynamic and resting LV diastolic parameters, using trans-mitral Doppler and TDI techniques, of DM patients compared to healthy controls and further investigated those responses to a DHE. Regarding to our findings, echocardiographic parameters displayed an alteration of mitral annular early diastolic velocity in these preserve systolic function DM patients compared to the healthy. In addition, implementation of 3 minutes dynamic handgrip as an exercise pressor, DM group exhibited similar change levels of both hemodynamic and echocardiographic variables compare to the healthy volunteers.

In DM with normal ejection fraction patient, a chronic hyperglycemia and chronic hyperinsulinemia altered LV myocardium diastole, or relaxation.[3] Our data highlighted reductions of mitral annular early diastolic velocity (e') for both septal and lateral walls in DM group. The results of this study are in line with the previous conclusions that chronic hyperglycemia and hyperinsulinemia contribute to an increase of myocardium stiffness, determined by a shorten DT after DHE, by inducing cardiomyocytes hypertrophy and increasing extra-cellular collagen deposit in diabetic cardiomyopathy patients with preserved ejection fraction phenotype.[4, 5] These structural changes was associated with LV hypertrophy caused by chronic hyperglycemia and linked to pathogenesis of diabetic cardiomyopathy.[6] Interestingly, increase myocardium stiffness had not much impact on a trans-mitral inflow as early filling velocities (E) of diabetes was a bit lower than control, but not reach a statistically significant level. Under a normal physiological relaxation, mitral annular early diastolic velocity (e') was preceded a passive early filling (E).[7] This relaxation generated a trans-mitral pressure gradient during isovolumic relaxation, which determine an E velocity under a normal LA pressure.[8] As the subjects were free from mitral stenosis, it can be confirmed that an E wave velocity reported in our study was generated by an LV relaxation. Thus, a decrease of myocardial relaxation (e') in diabetes observed in this study occurred independently from any changes of a passive early filling trans-mitral blood flow. To explain changes of LV relaxation of DM in this study, established mechanisms could be impaired calcium homeostasis, upregulated renin-angiotensin level, increased oxidative stress, mitochondrial dysfunction, and altered substrate metabolism.[9] In addition, autonomic cardiopathy was also related to a decrease diastolic function in DM patients.[10]

DHE displayed a feasibility to increase cardiac workload during echocardiographic measurement. Exercise protocol used in this study elevated HR around 41.2 - 46.3% and rose SBP around 11 – 13 mmHg form baseline. This light intensity activity displayed potentials to enhance ventricular myocardium relaxation and increase atrial contraction, which was similar to responses observed in cycle echocardiography.[11]

Exercise stress test was used to unmask a diastolic dysfunction during echocardiographic measurement in a suspected DD patients.[12] A supine bicycle was initially used as a diastolic stress echocardiography for assessing an LV filling pressure. To minimize respiratory impact and movement artifact on image quality, Samuel J, *et al*. [13] introduced an isometric handgrip exercise (IHE) to use as an exercise pressor for diastolic stress testing. IHE caused a significant change of hemodynamic and diastolic parameters in ageing individuals, i.e., increase E wave and increase A wave velocities. In a comparison, IHE produced equivalent hemodynamic responses to cycle echocardiography.[11] However, discrepancies between IHE and cycle exercise were observed in TDI parameters, which IHE exhibited negative changes of LV s' and e' velocities while cycle echocardiography showed positive changes. Generally, autonomic responses to exercises, both isometric and dynamic, initiated by withdrawal of parasympathetic tone and followed by increasing of sympathetic tone.[14, 15] Although, an underlying mechanism within in those disagreements might be due to IHE caused higher increase of mean arterial pressure than cycle exercise. Then, LV compensated by increase contractility to encounter this elevated afterload, which related to higher calcium influxes into cardiac cells. Increased intracellular calcium concentration affected on prolonged actin-myosin binding.[11] This mechanism found in IHE enhanced LV stiffness and might be associated with a negative change of LV myocardium relaxation velocity. In contrast to IHE, the DHE protocol proposed in this study eliminated an LV stiffening problem and illustrated a positive change of LV relaxation after exercise comparable to cycle echocardiography.

DHE generated a significant change in a ratio of trans-mitral Doppler (E/A) compared between healthy and DM. Myocardium of DM patient with preserved contraction showed a trend of lower early mitral inflow velocity at rest due to myocardial stiffness together with a compensated higher atrial contraction velocity. This mechanism was necessary for maintaining stroke volume in a deteriorated early relaxation.[4] After exercising, DM demonstrated trends of greater E velocity increase and lower A velocity increase than healthy subjects. In DM, reduced early relaxation, at rest, became a dominant contributor for pulling blood from LA after exercising. Consequently, without elevated LV filling pressure, atrial contraction was not much increase as a large amount of blood was passed into LV during the prior phase.

Handgrip exercise protocol used in this study was simple and concise. Protocol duration was 3 minutes comparable to IHE duration.[11, 13] Instead of using a force 40.0% of maximum voluntary contraction (an isometric pattern), our protocol utilized a dynamic handgrip at a rate 30 bpm on a 2-kg resistance hand griper. However, exercise protocol can be modified in many aspects such as frequency, duration, and resistance load. Further investigation of hemodynamic changes and cardiac function responses associated with different protocol adjustments is required to reveal a potential of DHE.

There were several points that could be considered as limitations of this prove-of-concept study. First, there was a small number of participants. Results from this first step revealed possible parameters that could be evoked by DHE. A large-scale study was required to establish responses of DHE in both healthy and DM patients. Second, study participants were dominantly female. Balance proportion between genders was required as gender difference might impact on results.[16] Third, there was a slightly higher of resting SBP in DM group. Elevated blood pressure was associated with alteration of diastolic function independent to increase LV mass.[17, 18] Co-exist between DM and HT was reported to exacerbate relaxation dysfunction more than DM or HT alone.[19] Therefore, further study in isolated hypertensive or pre-hypertensive cohorts was suggested. Finally, increase LV stiffness, caused by DM type 2, associated with LV hypertrophy.[6] Thus, in the next stage, structural parameters should be determined to provide information regard to DM related cardiac remodeling.

Conclusion

The use of DHE for echocardiography was tested in this study. DHE displayed a capability to be used as an exercise stressor during echocardiographic measurement by displaying a feasibility to enhance hemodynamic and diastolic parameters in both DM patients and healthy controls. At rest, DM patients displayed lower septal and lateral early diastolic mitral annular velocities together with higher A wave velocity. After DHE, septal early diastolic mitral annular velocity increased significantly in DM group. Different pattern of E/A ratio changes between healthy and DM were noticed. Further investigations on responses of hemodynamic and cardiac function related to modifications of DHE protocol were necessary.

Conflict of interest

The authors declare that there is no conflict of interest.

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