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Stress reduces diastolic function in youth

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Abstract

Objective—The influence of mental stress on heart function is not completely clear. We hypothesize that mental stress may contribute to the attenuation of diastolic function (DF) as early as in childhood. We examined the effect of mental stress on DF and the moderator effect of race and sex on this relationship.

Methods—A bi-racial sample of normotensive subjects (n= 161; aged 15-18 years) received both the experimental and control treatments on separate visits. Mitral inflow and annulus velocities were measured every 30 minutes during a 3 hour protocol consisting of one hour rest, videogame challenge (experimental visit) and recovery.

Results—Significant hemodynamic changes were observed during experimental visit (all p's<0.01). E/A ratio progressively increased during the control visit (from 1.93±0.42 to 2.01±0.47) but decreased during the stress phase of the experimental visit (from 1.91±0.44 to 1.87±0.50, p interaction <0.001). The change in E/E' did not reach statistical significance (p<0.09). In White males, E' showed an increase from rest to stress phases (from 10.3±2.55 to 10.7±2.28 cm/sec), whereas, a decrease was observed in White females (from 11.0±2.62 to 10.6±2.53 cm/sec), Black males (from 10.5±2.31 to 9.9±2.19 cm/sec), and Black females (from 10.6±2.22 to 10.3±1.86 cm/sec, p interaction <0.04). During stress, higher A was associated with higher A', higher E/E'.

Conclusion—Recurrent episodes of mental stress may increase the risk of poor diastolic function and these adverse effects may be stronger in females and Black males.

Keywords

Mental Stress; Diastolic function; Youth

Despite the potential cardiovascular harmful effect of mental stress occurring during daily life and its hemodynamic and neuroendocrine consequences, its role on heart relaxation and filling, that is, diastolic function, has not been directly explored in childhood where cardiovascular disease has been shown to originate(1,2). Diastolic function abnormalities are important precursors of congestive heart failure(3-5).

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Pulsed Doppler echocardiography provides a means to noninvasively assess mitral inflow. Analyses of mitral inflow's early (E) and late (A) velocities provide understanding of the physiopathologic process occurring in heart filling during diastole. These flow waves occur as a result of relative pressure gradient between left atrium and left ventricle during early diastole. Previous studies (6-9) have shown the prognostic significance of transmitral inflow. Lower E/A ratio has been linked to increased cardiovascular morbidity and mortality(8). However, the dependency of mitral inflow on left ventricle preload (e.g., ventricular end-diastolic volume) and afterload (e.g., aortic pressure or wall stress) limits its reliability. Fortunately, the availability of tissue Doppler permits a better characterization of diastolic function independent of loading conditions. This technique records mitral valve annular early (E') and late (A') velocities during diastole. The mitral valve annulus motion represents LV volume changes in normal hearts rather than the pressure gradient between left ventricle and left atrium that determines the mitral inflow. Normally, higher E/A ratio and E' are optimal. Combination of early filling and early myocardial relaxation to compute the **E/E' ratio** reflects left ventricular filling pressure which is the pressure in LV at the end of diastole after it has filled up with blood from the left atrium. Filling pressure is a hallmark of diastolic function. Accurate measurement of filling pressure involves invasive acquisition of left ventricular end-diastolic pressure (LVEDP). Increased filling pressure or LVEDP is a marker of heart failure. Hillis et al.(9) provided evidence that ultrasound derived filling pressure is a predictor of survival following myocardial infarction

We hypothesized that a sustained period of increased blood pressure and heart rate during stress would impair ventricular relaxation and/or increase ventricular stiffness thus reducing diastolic filling time and leading to increased filling pressure and a greater dependence on the late filling phase. This contrasts with the normal response in which most stress related left ventricular (LV) filling occurs in early diastole due to adrenergic facilitated ventricular relaxation and/or elastic recoil that induces atrio-ventricular gradient through ventricular pressure drop, thus, obviating the need for an atrial contribution in order to maintain adequate stroke volume.

It has been shown that women have greater systolic chamber function and lower diastolic compliance than men(10-13). The reason for these differences is not clearly understood. Likewise Blacks (B) are reported to suffer a greater toll of congestive heart failure(CHF) than Whites (W)(14, 15). This disparity in CHF has been attributed to greater cluster of CVD risk factors in B. The purpose of this study was to determine if the mental stress of daily life is related to the underpinnings of cardiac malfunction risk. We evaluated whether biobehavioral stress can induce changes in diastolic function and whether race and sex moderate this action.

Mehods and Materials

Study Population

The subjects were 81 B (41 males) and 80 W (40 females) healthy normotensive adolescents aged 15 to 18 years old (mean $\pm$ SD = 17.1 ± 0.93), not on any medications, and without a history of any medical diagnosis. The mean body mass index (BMI) for W was 21.6 ± 3.3 Kg/m² and for B 24.9 ± 5.9 (**t=4.30**, $p<0.001$). All individuals had normal body mass index, blood pressure, left ventricular mass and geometry.

The protocol was approved by the Human Assurance Committee of the Georgia Health Sciences University (Medical College of Georgia). Written informed parental consent and subject assent were obtained prior to testing.

Laboratory Evaluation

Each participant received both the experimental (mental stress) and control (watching a movie) treatments. Prior to each evaluation, participants were placed on a controlled, normal sodium (4000 ± 200 mg/day) diet for 3 days prior to testing. On the fourth day, the participants were brought to the laboratory and were given breakfast. Blood samples were then drawn and urine collected. During the 1 hour pre-test “rest” phase the subjects watched movies of their own choosing from our video library. The movie selection was carefully limited to PG 13 to increase the likelihood of restful content. During the experimental visit, this was followed by a one-hour stress phase during which the subjects played a competitive video game task for a monetary reward (Snowboard, Sony Corp, Foster City CA). (Subjects improving their scores in the final stages of the game were given an additional \$20). During the control visit, the protocol was the same except that during the “stress phase” subjects watched movies. Finally, there was a one-hour post-test, “recovery” phase that was the same as the pre-test phase. Participants watched a movie in recovery period as well. During each of the one-hour phases, subjects consumed 1 12-oz. bottle of water and after each phase blood and urine samples were taken.

Hemodynamic measurements were obtained during the three hours at 10 minute intervals using the Dinamap monitor (Dinamap Compact Monitor, Tampa FL) for systolic and diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), and heart rate (HR). Simultaneous with Dinamap measurements, 40-second continuous samples of impedance waveforms were recorded using impedance cardiography (Cardiodynamics BioZ, Cardiodynamics Diego, CA) for measurement of stroke volume (SV)(16). Total peripheral resistance (TPR) was calculated using the equation $TPR = MAP/CO$.

For diastolic function, pulsed Doppler Echocardiography (Hewlett-Packard Sono 7500; Andover, MA) was used to record the mitral inflow to derive indices of left ventricular filling(17). The tracing of five consecutive cardiac cycles having the highest velocity in early filling were analyzed as previously described(18). The following parameters were examined: peak velocity of early filling (E), peak velocity of late filling (A), the ratio of early to late filling peak velocities (E/A), A corrected for HR ($CorrA = (A/(\sqrt{RR}))$), and E corrected for HR ($CorrE = (E/(\sqrt{RR}))$).

Tissue Doppler measurements were obtained by using apical 2-chamber views for evaluating the mitral valve annulus (19, 20). The sample volume was placed at the inferior annulus. The lowest possible wall filter settings and the minimum optimal gain were used as recommended by the manufacturer. Peak spectral longitudinal contraction (Sm), initial (E'), and final (A') diastolic velocities for 5 consecutive beats were analyzed; E/E' and E'/A' ratios were calculated. Doppler measurements were obtained at 30 and 60 minutes in each of the three phases (i.e., rest, stress, and recovery) during experimental and control visits.

The reproducibility of both acquiring and measuring E' and A' were determined in recordings obtained from 10 subjects. The intra observer and inter observer differences in parameter estimates were less than 10%.

Two main types of statistical analysis were used: repeated measures analysis of covariance (RmANCOVA) and Pearson product-moment correlation coefficients. The RmANCOVAs were doubly repeated (i.e., visit [control vs. experimental] and phase [rest, stress/control, recovery]) with two grouping factors (sex and race). The p-values for phase and interactions involving phase do not reflect adjustments to the degrees of freedom (e.g., Greenhouse-Geisser or Huynh-Feldt) as the effect of these adjustments was minimal. Multiple testing adjustments were not made because most of the analyses were based on *a priori* hypotheses.

B had significantly higher mean BMI than W (24.9 ± 5.9 vs. 21.7 ± 3.3 ; $t=4.30$, $p<.001$) so BMI was used as a covariate.

Results

Table 1 gives the overall estimated means ($\pm$ S.E.) for variables from pulsed and tissue Doppler measurements by visit and phase when covarying BMI. The significance of the Visit by Phase interaction is also included in Table 1. Since subjects underwent the same procedures during all three phases, it might be expected that means would not differ among the phases during the control visit. This was usually not the case, thus, the pattern of means across the phases during the experimental visit needs to be interpreted with reference to those of the control visit. For example, Figure 1 shows the nature of the Visit $\times$ Phase interaction for the E/A ratio. The decline in mean during the stress phase of the experimental visit is clearly not consistent with the increase of the control visit, whereas the increase during the recovery phase is in keeping with that of the control visit. The Visit $\times$ Phase interaction for E/E' showed a trend ($F_{(2,286)}=2.89$, $p<0.09$) with the mean values across phases of the control visit not differing significantly from one another. During the experimental visit mean values decreased from the rest to the stress phase but the decrease was not statistically significant ($F_{(1,152)}=2.78$, $p<0.09$). The amount of decrease was fairly normally distributed with nearly equal number of subjects increasing and decreasing.

Figure 2 shows the mean values of A and E and each time point during the stress and recovery phases expressed as percentage change from the mean values of the resting phase.

For Corr A and E' the two-way interaction of visit by phase was subsumed within a significant higher order interaction. For Corr A, there was a significant Visit $\times$ Phase $\times$ Race interaction ($F_{(2,300)}=3.45$, $p<0.04$), the nature of which was that, during the control visit, Corr A means declined from the rest phase to the stress phase for both races and further declined during the recovery phase. During the experimental visit mean Corr A increased for both races from the rest to stress phase but the increase for B was greater than for W; during the recovery phase the means of both races declined to similar levels.

The four- way interaction of Visit $\times$ Phase $\times$ Race $\times$ Sex interaction was significant ($F_{(2,288)}=3.66$, $p<0.03$) for E'. For the control visit, means declined from the rest phase to the stress phase and further declined to the recovery phase for both sexes and races. A similar pattern was observed during the experimental visit except by W males who did show an increase during the stress phase.

Table 2 gives the overall means of the hemodynamic variables and of urinary sodium for the three phases during both the experimental and control visits. The Visit $\times$ Phase interaction was significant for the hemodynamic variables SBP, DBP and HR but not for SV, TPR and urinary sodium. For the hemodynamic variables SBP, DBP and HR, the Visit $\times$ Phase interactions were significant because of increased responsivity during the stress phase of the experimental visit.

Effects of Race and Sex

In addition to the Visit $\times$ Phase $\times$ Race for Corr A and Visit $\times$ Phase $\times$ Race $\times$ Sex interaction for E' described above, there were also significant race and/or sex effects for Corr A ($F_{(1,150)}=3.94$, $p<0.05$ for Race $\times$ Sex interaction; B-F>B-M, W-M, W-F), A' ($F_{(1,143)}=6.46$, $p<0.02$ for Race $\times$ Sex interaction; B-F>B-M, W-M, W-F), Corr A' ($F_{(1,150)}=3.94$, $p<0.01$ for Race $\times$ Sex interaction; B-F>W-M, B-M, W-F), E/E' ($F_{(1,143)}=7.14$, $p<0.01$ for Sex; M>F), SBP ($F_{(1,155)}=38.61$, $p<0.01$ for Sex; M>F), DBP ($F_{(1,155)}=5.03$, $p<0.03$ for Race; B>W), HR ($F_{(1,156)}=8.07$, $p<0.01$ for Race $\times$ Sex interaction;

W-M,B-FM>W-F>B-M,W-MF) and TPR ($F_{(1,150)}=7.78, p<0.01$ for Sex; F>M). These effects were for all phases of the study and did not involve differential responses to the stressor.

Relationship between Pulsed and Tissue Doppler

Pearson correlations were computed between pulsed and tissue Doppler measures within the various phases of the experimental visit. A and A' were moderately correlated with each other in all phases (r range = 0.18 to 0.38, all p 's <0.03). E and E' were not significantly correlated (r range 0.01 to 0.12, all p 's >0.12). E/A ratio was significantly correlated with E/E' only during the rest phase ($r = 0.17, p<0.04$); during the stress and recovery phase the correlations were not statistically significant ($r=0.04$ and $r=0.05$, respectively; both p 's >0.54). The correlations did not differ significantly by race or sex.

Association of DF with Anthropometric and Hemodynamic measures

To enhance understanding of the nature of the changes in measures of diastolic function with stress, correlations were computed between the changes in E/A ratio and E/E' from rest to stress during the experimental visit with anthropometric and hemodynamic measures. Weight and BMI were significantly correlated with change in E/A Ratio in W but not in B. For W, $r = 0.28, p<0.02$ for weight and $r = 0.33, p<0.01$ for BMI and for B $r = 0.13, p>0.26$ for weight and $r = 0.12, p>0.30$ for BMI. Change in HR was negatively correlated with change in E/A Ratio in B ($r = -0.46, p<0.001$), the correlation was not significant in W ($r = -0.16, p>0.14$). The changes in E/A ratio from rest to stress during the experimental visit was correlated with the corresponding change in heart rate in B ($r = -0.2730, p<0.01$) and in W ($r = 0.43, p<0.001$). No significant correlations were found between changes in E/A ratio and systolic and diastolic blood pressure responses (r range -0.03 to 0.04 all p 's >0.57). Concomitant RR intervals were correlated with resting, stress, and recovery A' ($r = -.55, -.38$ and $-.36$, respectively, all p 's <0.001) but not with resting, stress, and recovery E' ($r = .16, .17$, and $.51$, respectively all p 's >.5). Changes in RR were not correlated with changes in E' ($r = .05, p>.50$) but were correlated with changes in A' and E' (all p 's >.5). ($r = -.20, p<.01$). Tables 3 shows the correlations between the hemodynamic variables and the diastolic function variables during the resting phase of the experimental visit and for the changes in these variables from the resting phase to the stress phase.

Discussion

In this cohort of healthy youth, mental stress invoked an increase in vascular tone as evidenced by increased total peripheral resistance deriving from increased blood pressure and decreased stroke volume (21). These physiological changes were paralleled with a decreased E/A ratio while normal cardiac output was maintained through sympathetically mediated acceleration of heart rate. Previous studies involving short lasting stressful tasks have reported a deleterious effect on cardiac function (22-24). Likewise, our sub-acute model of mental stress induced physiological changes that were paralleled with impediment of ventricular filling. As complicated as the relationship between stress and diastolic function could be, our design allowed clear determination of the role of mental stress since participants were compared, not only within the different testing phases (i.e., rest, stress, recovery), but also across two visits one of which included the treatment (stressor) and the other not.

To the best of our knowledge, this is the first report of sequential assessment of left ventricular filling together with myocardial velocities in youth. This dynamic assessment of diastolic function reveals that the effect of sub-acute stress is not the same as the acute response effect wherein late filling is expected to rise (22, 24). We describe a filling model

wherein the E/A ratio increases throughout the control visit, reflecting a trend toward cardiovascular homeostasis during prolonged rest. This enhancement in E/A ratio occurred due to a progressive decrease in late filling waves during prolonged rest. During the stress exposure the late filling waves did not decrease but remained constant. This is the reverse of what is observed in acute stress testing models wherein late filling has been reported to increase further inducing a decrease in E/A ratio. As in previous studies(25, 26) we found that atrial contraction, as represented by A, plays a pivotal role in adaptation of filling process to homeostasis and the stress demand, even after correcting for covariates (e.g., heart rate and body size). Overall, our model reveals that repetitive stress interferes with cardiovascular return to homeostasis.

Stress induced sympathetic stimulation is related to increased contractility that may facilitate left ventricular filling via suction effect(27, 28). Catecholamines induce elastic recoil that contributes to increase the atrioventricular pressure gradient. This allows blood to flow rapidly into the ventricles. Also, an elevated atrial contractile state occurs at high filling pressure and is a compensation mechanism for impaired early diastole. It is worth noting that in our study population E/E' a surrogate measure of LVEDP remains the same or slightly increased while A consistently increased under stress. This underlines the possibility that the teenager participants in our study may be at higher risk of developing diastolic dysfunction in stressful conditions. Whether or not our findings of a stress induced reduction of DF may represent a preclinical marker of cardiovascular dysfunction merits further investigation.

In concord with our previous studies (29-33), the prolonged protocol of mental stress (one hour) induced sustained blood pressure elevation and heart rate acceleration. In contrast to acute stressors, which may cause larger momentary increases in BP and HR (fight or flight response), our prolonged protocol reflects more closely the daily life stressful events and their toll on cardiovascular functioning. We and others have reported that the deleterious effect of sustained mental stress is linked to the activation of adrenergic and rennin angiotensin systems which could result in cardiac necrosis, myocardial ischemia, salt retention and delayed hemodynamic recovery (34-38).

In contrast to most previously conducted investigations, our study not only provides an early life depiction but also a preclinical characterization of myocardial velocities and global diastolic function. To identify early markers of malfunction, it is important to keep in mind that, in conjunction with a decreasing E/A ratio, decreasing E' values from rest to stress indicate lower compliance. In addition, decreasing E/E' represents a normal adjustment of filling pressure to the stress burden in youth who are yet unlikely to exhibit overt diastolic dysfunction. At this point, it is critical to heed the large inter-subject variation of the E/E' among our study participants. Despite the trend toward decrease, the inter-subject variability reported here may encourage the usage of biobehavioral stress to identify individuals who, either do not change or increase their E/E' during stress challenge.

Consistent with our hypothesis, in youth stress induces an increase in atrial contribution reflecting an increase in filling pressure and an attenuation of diastolic function owing to hemodynamic arousal. Our finding of race/ethnic differences in corrected A, but not in A, implies the need to covary out the effect of heart rate when comparing DF across different populations. It is worth noting that in our study E' was less dependent on heart rate and better discriminator between conditions and groups.

Strengths and Limitations

This study has several important strengths including a representative multiethnic sample of youth, the cross-over design that was preceded by a diet period to control for salt

consumption, and the use of mitral inflow and myocardial velocities parameters that were modestly correlated, therefore, poised to capture behavioral challenge induced diastolic function changes.

We did not assess catecholamines during our protocol. However, the fact that blood pressure increased and heart rate accelerated during experimental and not control visit suggests a link between sympathetic nervous system arousal during mental stress and diastolic function attenuation.

Despite the remarkable power of Doppler echocardiography to assess diastolic function, it should be noted that the noninvasive nature of this study prevents us from ruling out the presence of subclinical myocardial ischemia that has been shown to alter filling profile. Although we could not perform coronarography or scintigraphy, we chose to include only healthy individuals with no symptoms or signs of cardiac disease. Also, the young age of our participants and our inclusion/exclusion criteria limits the likelihood of recruiting individuals with known cardiovascular problems or those taking any kind of medication capable of affecting the cardiovascular system. Another limitation of diastolic function assessment is that most indices are heart rate dependent. Adjusting for heart rate allowed us to uncover race/ethnic effects in late filling which were not apparent with uncorrected A implying that HR may conceal the effect of atrial contribution to DF. Therefore, it might be useful to control for HR when using mitral inflow indices to examine DF. Along these lines we also found that BMI was associated with changes in E/A. Therefore, BMI adjustment is equally warranted when using Doppler indices to assess DF.

Although blood pressure responses seem low, they represent the expected magnitude of change for a group exposed to a biobehavioral stressor. These BP responses during a reactivity protocol are predictive of future blood pressure elevation. After the protocol we also asked subjects questions regarding their perceived anxiety, nervousness, and how relaxed they felt at each phase of the protocol. Sixty-seven percent of subjects claim to be trying hard to win the game (i.e., improve the score). We have consistently found that videogame challenge induces hemodynamic arousal after a period of PG-13 movie viewing. This is probably not due to excitement from the nature of the game but to the competitive aspect of the video game protocol. There might be a possible influence of somewhat exciting PG-13 movies on 'rest', but our findings consistently show that, in general, our subjects relax well during movie viewing as attested to by hemodynamics progressing toward homeostasis.

In summary, we report a comprehensive baseline data set for LV filling and mitral annular dynamics in healthy youth exposed to behavioral challenge. Our findings suggest that stress induces a reduction of diastolic function as reflected both by attenuation of filling and myocardial relaxation processes. Also, our data suggest that compared to W and males, B and females have reduced diastolic function despite equivalent hemodynamic arousal and similar cardiac structure. The improvement of left ventricular relaxation and filling in normal resting condition is impeded by stress induced increases in blood pressure as seen during the experimental visit. The finding of a decreased E/A and E' in response to mental stress suggests that repetitive biobehavioral stress may induce diastolic dysfunction which is a mechanism of diastolic heart failure in at risk individuals such as B and females who are more likely to develop premature congestive heart failure.

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Bibliography

1. Berenson GS, Srinivasan SR, Bao W. Precursors of cardiovascular risk in young adults from a biracial (black-white) population: the Bogalusa Heart Study. *Annals of the New York Academy of Sciences*. 1997; 817:189–198. [PubMed: 9239188]
2. Berenson GS, Wattigney WA, Tracy RE, Newman WP, Srinivasan SR, Webber LS, Dalferes ER, Strong JP. Artherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *American Journal of Cardiology*. 1992; 70:851–858. [PubMed: 1529936]
3. Zile MR, Baicu CF, Bonnem DD. Diastolic heart failure: definitions and terminology. *Prog Cardiovasc Dis*. 2005; 47:307–13. [PubMed: 16003645]
4. Ouzounian M, Lee DS, Liu PP. Diastolic heart failure: mechanisms and controversies. *Nat Clin Pract Cardiovasc Med*. 2008; 5:375–86. [PubMed: 18542106]
5. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med*. 1992; 117:502–10. [PubMed: 1503353]
6. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. *J Am Coll Cardiol*. 2001; 37:1042–8. [PubMed: 11263606]
7. Wachtell K, Bella JN, Rokkedal J, Palmieri V, Papademetriou V, Dahlof B, Blom T, Gerds E, Devereux RB. Change in diastolic left ventricular filling after one year of antihypertensive treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Circulation*. 2002; 105:1071–6. [PubMed: 11877357]
8. Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, Fabsitz RR, Howard BV, Devereux RB. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation*. 2002; 105:1928–33. [PubMed: 11997279]
9. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK. Noninvasive estimation of left ventricular filling pressure by E/E' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol*. 2004; 43:360–7. [PubMed: 15013115]
10. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol*. 1999; 33:1948–55. [PubMed: 10362198]
11. Stromberg A, Martensson J. Gender differences in patients with heart failure. *Eur J Cardiovasc Nurs*. 2003; 2:7–18. [PubMed: 14622644]
12. Celentano A, Palmieri V, Arezzi E, Mureddu GF, Sabatella M, Di Minno G, De Simone G. Gender differences in left ventricular chamber and midwall systolic function in normotensive and hypertensive adults. *J Hypertens*. 2003; 21:1415–23. [PubMed: 12817192]
13. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. *Cardiovasc Res*. 2001; 49:340–50. [PubMed: 11164844]
14. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med*. 2008; 168:2138–45. [PubMed: 18955644]
15. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008; 101:1016–22. [PubMed: 18359324]
16. Sherwood A, Carter LS, Murphy CA. Cardiac output measurements by impedance cardiography: Comparison of two alternative methodologies against thermodilution values. *Aviation, Space, and Environmental Medicine*. 1991; 62:116–122.
17. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol*. 1997; 30:8–18. [PubMed: 9207615]
18. Kapuku GK, Seto S, Mori H, Mori M, Utsunomia T, Suzuki S, Oku Y, Yano K, Hashiba K. Impaired left ventricular filling in borderline hypertensive patients without cardiac structural changes. *Am Heart J*. 1993; 125:1710–6. [PubMed: 8498315]

19. De Sutter J, De Backer J, Van de Veire N, Velghe A, De Buyzere M, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E/E'). *Am J Cardiol*. 2005; 95:1020–3. [PubMed: 15820183]
20. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol*. 1997; 30:474–80. [PubMed: 9247521]
21. Jain D, Shaker SM, Burg M, Wackers FJ, Soufer R, Zaret BL. Effects of mental stress on left ventricular and peripheral vascular performance in patients with coronary artery disease. *J Am Coll Cardiol*. 1998; 31:1314–22. [PubMed: 9581726]
22. Marabotti C, Genovesi-Ebert A, Palombo C, Giaconi S, Ghione S. Casual, ambulatory and stress blood pressure: relationships with left ventricular mass and filling. *Int J Cardiol*. 1991; 31:89–96. [PubMed: 1830035]
23. Okano Y, Utsunomiya T, Yano K. Effect of mental stress on hemodynamics and left ventricular diastolic function in patients with ischemic heart disease. *Jpn Circ J*. 1998; 62:173–7. [PubMed: 9583442]
24. Trevi GP, Gallina S, Di Giovanni P, Marchetti M, Gaeta MA, Battaglini G, Boni S, Di Sipio ML, Liberi F, Scassa E, et al. The clinical and echocardiographic parameters at rest and during mental arithmetic stress in preadolescent subjects with a hypertensive parent. *Cardiologia*. 1993; 38:437–44. [PubMed: 8221738]
25. Kapuku G, Harshfield G, Wilson M, Mackey L, Gillis D, Edmunds L, Hartley B, Treiber F. Impaired pressure natriuresis is associated with preclinical markers of abnormal cardiac structure and function. *AM J Hypertens*. 2003; 16:211A. abstract.
26. Schmitz L, Koch H, Bein G, Brockmeier K. Left ventricular diastolic function in infants, children, and adolescents Reference values and analysis of morphologic and physiologic determinants of echocardiographic Doppler flow signals during growth and maturation. *J Am Coll Cardiol*. 1998; 32:1441–8. [PubMed: 9809960]
27. Udelson JE, Bacharach SL, Cannon RO 3rd, Bonow RO. Minimum left ventricular pressure during beta-adrenergic stimulation in human subjects Evidence for elastic recoil and diastolic “suction” in the normal heart. *Circulation*. 1990; 82:1174–82. [PubMed: 1976048]
28. Courtois M, Mechem CJ, Barzilai B, Ludbrook PA. Factors related to end-systolic volume are important determinants of peak early diastolic transmitral flow velocity. *Circulation*. 1992; 85:1132–8. [PubMed: 1537111]
29. Barbeau P, Litaker MS, Harshfield GA. Impaired pressure natriuresis in obese youths. *Obes Res*. 2003; 11:745–51. [PubMed: 12805395]
30. Harshfield GA, Wilson M, Hanevold C, Kapuku G, Mackey L, Gillis D, Treiber F. Impaired stress-induced pressure natriuresis increases cardiovascular load in African American youths. *Am J Hypertens*. 2002; 15:903–906. [PubMed: 12372678]
31. Harshfield GA, Hanevold C, Kapuku GK, Dong Y, Castles ME, Ludwig DA. The association of race and sex to the pressure natriuresis response to stress. *Ethn Dis*. 2007; 17:498–502. [PubMed: 17985504]
32. Wilson ME, Harshfield GA, Ortiz L, Hanevold C, Kapuku G, Mackey L, Gillis D, Edmonds L, Evans C. Relationship of body composition to stress-induced pressure natriuresis in youth. *Am J Hypertens*. 2004; 17:1023–8. [PubMed: 15533728]
33. Harshfield GA, Treiber FA, Davis H, Kapuku GK. Impaired stress-induced pressure natriuresis is related to left ventricle structure in blacks. *Hypertension*. 2002; 39:844–7. [PubMed: 11967237]
34. Harshfield G, Wilson M, Hanevold C, Kapuku G, Mackey L, Gillis D, Treiber F. Impaired stress-induced pressure natriuresis increases cardiovascularload in African American youths. *Am J Hypertens*. 2002; 15:903–906. [PubMed: 12372678]
35. Harshfield GA, Dong Y, Kapuku GK, Zhu H, Hanevold CD. Stress-induced sodium retention and hypertension: a review and hypothesis. *Curr Hypertens Rep*. 2009; 11:29–34. [PubMed: 19146798]
36. Goldstein, DS.; Kopin, IJ. The autonomic nervous system and catecholamines in normal blood pressure control and hypertension. In: Laragh, JH.; Brenner, BM., editors. *Hypertension*:

pathophysiology, diagnosis, and management. Vol. 1. New York, NY: Raven Press; Ltd: 1990. p. 711-747.

37. Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension*. 2005; 46:1201–6. [PubMed: 16203875]
38. Carter JR, Cooke WH, Ray CA. Forearm neurovascular responses during mental stress and vestibular activation. *Am J Physiol Heart Circ Physiol*. 2005; 288:H904–7. [PubMed: 15486035]

Glossary

A	Mitral Inflow Late filling velocity
B	Black
DF	Diastolic Function
E	Mitral Inflow Early filling velocity
F	Female
M	Male
W	Whites
E'	Mitral valve annular early velocity
A'	Mitral valve annular late velocity

Figure 1. Effect of Stress on Left Ventricular Filling (mean $\pm$ SE)
E/A: early to late filling ratio

Figure 2. Time Course of Left Ventricular Filling

E: early filling

A: late filling

Table 1
The Effect of Stress on Diastolic Function (mean $\pm$ SE)

Variable	Phase			Visit × Phase Significance	
	Rest	Stress	Recovery	F	p
A (cm/s)	Experimental	42.0±0.75	42.2±0.86	F (2,300)=4.17	P<0.02
	Control	40.3±0.71	37.7±0.73		
Corrected A	Experimental	46.3±1.02	47.8±1.14	F (2,300)=6.10	p<0.003
	Control	44.7±0.94	41.6±0.99		
E (cm/s)	Experimental	77.0±0.97	74.4±0.98	F (2,300)=0.03	p<0.97
	Control	74.7±0.87	72.7±0.88		
Corrected E	Experimental	83.9±1.12	83.3±1.12	F (2,300)=1.50	p<0.23
	Control	82.1±1.03	79.3±1.01		
E/A Ratio	Experimental	1.92±0.035	1.88±0.039	F (2,300)=3.64	p<0.03
	Control	1.93±0.034	2.02±0.037		
A' (cm/s)	Experimental	4.35±0.10	4.58±0.11	F (2,286)=3.10	p<0.05
	Control	4.05±0.08	3.79±0.08		
Corrected A'	Experimental	4.78±0.12	5.17±0.14	F (2,284)=4.42	p<0.02
	Control	4.48±0.10	4.17±0.10		
E' (cm/s)	Experimental	10.7±0.20	10.4±0.19	F (2,288)=1.59	p<0.21
	Control	10.8±0.21	10.6±0.22		
Corrected E'	Experimental	11.62±0.23	11.60±0.21	F (2,286)=4.62	p<0.02
	Control	11.97±0.24	11.59±0.23		
E/E'	Experimental	7.73±0.19	7.58±0.18	F (2,286)= 2.49	p<0.09
	Control	7.32±0.17	7.32±0.18		

Table 2
Comparison of Hemodynamic Variables between Control and Experimental Visits (mean $\pm$ SE)

Variable	Phase			Visit × Phase Significance	
	Rest	Stress	Recovery	F	p
SBP (mmHG)	Experimental	109.4±0.69	111.4±0.72	108.9±0.70	F _(2,310) =7.69 p<0.001
	Control	108.6±0.65	107.9±0.69	107.4±0.70	
DBP (mmHG)	Experimental	64.1±10.46	68.3±0.49	64.9±0.51	F _(2,310) =3.07 p<0.05
	Control	63.5±0.47	63.7±0.48	64.2±0.48	
HR (beats/min)	Experimental	70.6±0.72	76.3±0.74	67.7±0.75	F _(2,312) =6.09 p<0.01
	Control	70.1±0.69	70.3±0.71	68.3±0.70	
TPR (mmHg/L.min)	Experimental	16.3±0.32	17.4±0.41	17.9±0.39	F _(2,300) =1.88 p<0.16
	Control	16.2±0.32	16.4±0.30	17.5±0.39	
SV (mmL)	Experimental	71.0±1.25	71.5±1.40	69.7±1.36	F _(2,306) =0.80 p<0.46
	Control	73.2±1.28	69.8±1.32	67.7±1.37	
Urinary Na (mEq/hr)	Experimental	7.3±0.42	9.3±0.53	9.2±1.09	F _(2,202) =0.14 p<0.87
	Control	6.9±0.40	9.1±0.67	8.2±0.53	

SBP=Systolic Blood Pressure

DBP=Diastolic Blood Pressure

HR= Heart Rate

TPR=Total Peripheral Resistance

SV= Stroke Volume

Urinary Na= Urinary Sodium

Table 3
Correlations between Hemodynamics and Diastolic Function Variables (mean $\pm$ SE)

		Baseline					Reactivity (Stress-Baseline)				
		HR (beats/min)	SBP (mmHg)	DBP (mmHg)	TPR (mmHg/L.min)	SV (ml)	HR (beats/min)	SBP (mmHg)	DBP (mmHg)	TPR (mmHg/L.min)	SV (ml)
A(cm/s)	Pearson	.55	.06	.16	-.04	-.22	.33	.12	-.02	-.12	-.04
	Sig. (2-tailed)	.001	.46	.04	.58	.01	.001	.13	.83	.14	.64
E (cm/s)	Pearson	-.14	.02	-.26	-.08	.08	.05	.07	-.08	-.14	.07
	Sig. (2-tailed)	.09	.85	.001	.28	.30	.55	.36	.27	.07	.39
E/A Ratio	Pearson	-.62	-.09	-.37	-.02	.25	-.28	-.03	.03	.05	.07
	Sig. (2-tailed)	.001	.23	.001	.75	.001	.001	.71	.66	.50	.41
A' (cm/s)	Pearson	.44	-.05	.20	.05	-.26	.10	.17	.10	-.08	.08
	Sig. (2-tailed)	.001	.54	.01	.49	.01	.22	.03	.19	.31	.32
E' (cm/s)	Pearson	-.13	-.05	-.23	-.09	.16	-.06	.15	.02	.04	.09
	Sig. (2-tailed)	.10	.55	.01	.24	.05	.45	.06	.77	.66	.26
E/E'	Pearson	.01	-.00	.04	.05	-.11	.06	-.07	-.06	-.12	-.08
	Sig. (2-tailed)	.85	.99	.65	.48	.17	.45	.39	.42	.15	.31

HR= Heart Rate

SBP= Systolic Blood Pressure

DBP= Diastolic Blood Pressure

TPR= Total Peripheral Resistance

SV= Stroke Volume

Mitral inflow out late (A) filling velocity

Mitral inflow early (E) filling velocity

Mitral valve annular out late (A') velocity

Mitral valve annular early (E') velocity