

ORIGINAL RESEARCH

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The Effect of Acute Allergic Reactions on Diastolic Heart Function

Abstract

Purpose: Diastolic heart failure is characterized by the presence of heart failure symptoms despite preserved systolic function. Cytokines released during allergic reactions may impair diastolic heart function, either through their direct toxic effects or by inducing coronary artery spasm. The purpose of this study was to examine the effects of acute allergic reactions on diastolic heart function.

Methods: Fifty patients, randomly selected from those who were admitted to the emergency room between May 2010 and December 2010 with the complaints of rash and itching, and who were subsequently diagnosed with allergic reactions based on the clinical and laboratory findings, were included in the study as the allergy group. Thirty healthy volunteers, in whom the diagnosis of allergy was ruled out based on the clinical and laboratory data, were used as the control group. Diastolic heart functions were evaluated in patients presenting with allergic reaction as well as in control subjects.

Results: There was no significant difference between the two groups in terms of basal systolic functions, diameters of the cavities and wall thicknesses, and biochemical parameters. Color M mode flow progression velocities, E ratios, E/A ratios and mitral lateral annulus tissue Doppler velocities measured by echocardiography at Day 0 and Day 5 were significantly altered in the allergy group ($p < 0.05$).

Conclusion: Impairment in diastolic functions was observed following acute allergic reactions. Acute allergic reactions could be a cause of mortality and morbidity if they lead to the development of diastolic heart failure.

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Allergy is excessive and abnormal reaction of our body's immune system that is triggered against essentially harmless substances normally found in the environment. At the initial phase of an allergic reaction, various mediators are released from the mast cells, which, in turn, cause further effects [1]. These mediators may exert effects on all the body's systems, but particularly on the respiratory system, circulatory system and gastrointestinal tract.

The heart performs the task of pumping and distributing the blood throughout the body organs and tissues in a cycle of systole and diastole. The systolic phase is related to the contraction of the ventricles, which generates a pressure that drives blood out of the heart; whereas diastolic phase is related to relaxation of ventricles, which allows the ventricles to refill with blood. A left ventricular end-diastolic pressure above 12 mmHg indicates the presence of diastolic dysfunction which leads to increased pressure in the atrium and backwards in the pulmonary vascular bed, potentially resulting in associated symptoms [2].

Histamine, serotonin, leukotriene (neutral proteases, arachidonic acid), cytokines and chemokines, which are released from mast cells during an allergic reaction, are known to exert adverse effects on the cardiovascular system. These vasoactive and myocardium-repressing factors unfavorably affect myocardial function; thus, diastolic function may be impaired following an acute allergic reaction [3].

In this study, our goal was to examine whether or not the mediators released from the mast cells during allergic reactions have a measurable effect on diastolic heart function.

Materials and Methods

Sixty-seven patients were randomly selected among those who were admitted to the emergency room between May 2010 and December 2010 with the complaints of rash and itching, and were subsequently diagnosed with allergy based on the clinical and laboratory findings, were considered for including in the study as the allergy group. Of these, 17 patients were excluded from the study for various reasons. Thirty healthy volunteers who were admitted to the Cardiology Outpatient clinic, and in whom the diagnosis of allergy was ruled out based on the clinical and laboratory data, were used as the control group.

The inclusion criteria for this study were as follows: the diagnosis of allergy established by an experienced emergency medicine specialist based on the physical examination and laboratory findings, age between 18 and 50 years, presence of normal left ventricular systolic functions on performed echocardiography; and, volunteer subjects with normal ventricular function and without any chronic illness. No gender specifica-

tion was made during the recruitment process. All patients were informed of the study prior to their participation and their consents were obtained before their inclusion in the study. Our study was approved by local ethics committee.

The exclusion criteria for this study were as follows: sustained acute coronary syndrome (i.e., acute myocardial infarction) at the time of enrollment, presence of heart failure, diabetes mellitus (type 1 or 2), hypertension, severe valvular heart disease, chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic renal failure, age below 18 or above 50 years, pregnant women and presence of atrial fibrillation or severe arrhythmia.

Medical histories were obtained from the subjects and routine physical examination was performed. Complete blood count, routine biochemistry were obtained, brain natriuretic peptide (BNP), serotonin, histamine and Troponin-I levels were measured, and electrocardiography and echocardiography were performed.

Electrocardiography

12-lead, 3-channels electrocardiography recordings were obtained with a paper speed of 25 mm/s using a Nihon Kohden (Tokyo, Japan) electrocardiography device and at least three QRS complexes were recorded for each derivation. ECGs were evaluated for the evidences of acute coronary syndrome, left ventricular hypertrophy, AV block and bradycardia.

Echocardiography

All subjects underwent transthoracic echocardiography in left lateral supine position in the cardiology clinic of the Department of Cardiology. ECG were performed by the same cardiologist using a 3 MHz adult probe and Vivid 7 Dimension/Vivid 7 Pro echocardiography device (Horten, Norway) and harmonic imaging, in accordance with the recommendations of the American Society of Echocardiography [4]. Parasternal long axis, short axis, apical four chamber and two chamber views were obtained, and left ventricular systolic and diastolic functions were evaluated by M-mode, B-mode, pulse wave Doppler (PW-Doppler) and continuous wave Doppler (CW-Doppler) methods. Posterior wall thickness, interventricular septum thickness, left ventricular end-systolic diameter, left ventricular end-diastolic diameter were measured. Pulmonary artery pressure (PAP) was calculated by adding 10-15 mmHg to the functional flow gradient measured at tricuspid valve using continuous wave Doppler (CW-Doppler) with apical four chamber view. Ejection fraction was measured using Simpson's method from apical four chamber and apical two chamber

views. Flow progression velocity (Vp) was recorded by color M-mode echocardiography and lateral mitral annulus tissue Doppler velocities (Sm, Em, Am) were recorded by tissue Doppler method. Valvular defects, if any, were graded and recorded accordingly.

Blood Tests

12 ml of blood sample was drawn from the left antecubital vein from all patients upon admission to the emergency room and again on Day 5. All blood samples were analyzed at the same day in the Biochemistry Laboratory of Firat University Faculty of Medicine using an OLUMPUS 2700 auto-analyzer. Routine biochemical parameters (glucose, urea, creatinine, Na and K), CK-MB and troponin-I levels were measured and a complete blood count (hemoglobin, hematocrit, platelets, leucocyte) was performed; the results were recorded separately for each patient. For the measurement of BNP, serotonin and histamine levels, 5 ml of venous blood samples were drawn into two separate biochemistry and complete blood count tubes; after waiting 10 minutes for the blood to coagulate, the tubes were centrifuged at 5000 rpm for 3 minutes. Sera was stored at -20°C until analysed. All samples were analysed at the Central Laboratory of Firat University Faculty of Medicine. BNP was meas-

ured using IMMULITE®2000 immunoassay system and recorded in pg/mL. Serotonin levels were determined by fluorometric method and Eureka Lab Division kits using a Hewlett Packard 1100 series HPLC and the results were recorded in µg/L. Histamine levels were studied in sera obtained from complete blood count tubes using Biotek El 800 device based on ELISA method and recorded in ng/mL.

Statistical Analysis

SPSS (statistical package for social sciences for Windows, version 18.0) was used in statistical analyses. Apart from descriptive statistical methods (mean, standard deviation), in the evaluation of quantitative data, the Mann-Whitney U test was used in inter-group comparisons of parameters that do not display normal distribution or homogeneity. The Wilcoxon test was used in intra-group comparisons of parameters that do not display normal distribution. The Chi-square test was used in the analysis of qualitative data (Yates-corrected Chi-Square test with 2x2 contingency tables was used). The level of significance was set at $p < 0.05$ with 95% confidence interval.

Table 1. Comparison of the baseline measurements between the groups

Variables	Group 0	Group 1	p*
Sex (n,%)			
Female	15 (50%)	26 (52%)	0.99
Male	15 (50%)	24 (48%)	
Heredity (n,%)			
Yes	12 (40%)	22 (44%)	0.907
No	18 (60%)	28 (56%)	
Age (mean ± S.D.)	30.90 ± 8.82	30.20 ± 8.590	0.792
Leucocyte (10 ⁹ /L)	6.94 ± 1.67	9.86 ± 3740	0.001
Hemoglobin (g/dL)	15.28 ± 1.61	14.31 ± 1.82	0.03
Urea (mg/dL)	26.63 ± 6.04	28.02 ± 7.24	0.55
Creatinine (mg/dL)	1.00 ± 0.16	0.89 ± 0.27	0.11
CK-MB (U/L)	15.20 ± 4.07	15.48 ± 4.76	0.83
AST (U/L)	20.80 ± 7.17	19.98 ± 6.81	0.55
ALT (U/L)	22.67 ± 12.08	20.64 ± 16.58	0.84
Serotonin (µg/L)	67.85 ± 26.12	92.43 ± 17.76	0.001
Histamine (ng/mL)	0.54 ± 0.21	1.58 ± 0.76	0.001
BNP (µg/L)	33.37 ± 10.55	45.49 ± 26.28	0.85

*Mann-Whitney U test Group 0:

Control Group; Group 1: Study Group

Results

Fifty patients [mean age: $30,20 \pm 8,590$ years; 48% (n=24) were male; 52% (n=26) were female] were randomly selected among those who were admitted to the emergency department of Firat University Faculty of Medicine between May 2010 and December 2010 with the complaints of rash and itching, and who were subsequently diagnosed with allergic reaction based on the clinical and laboratory findings, were included in the study as the allergy group. Thirty healthy volunteers [mean age: $30,90 \pm 8,821$ years; 50% (n=15) were male; 50% (n=15) were female] admitted to the Cardiology Outpatient clinic, in whom the diagnosis of allergy was ruled out based on the clinical and laboratory data, were used as the control group. There was no significant difference in terms of age, heredity and age for the two groups ($p>0.05$) (Table 1).

There was no statistical difference between the groups in terms of hemoglobin, urea, creatinine, CK-MB, AST, ALT and BNP levels ($p>0.05$) (Table 1). Leucocyte, serotonin and histamine values were significantly higher in the study group ($p<0.05$).

Mitral flow progression velocity (Vp) and E velocity were found to be significantly different between the control group and the study group, when the results of echocardiographic examination performed at Day 0 are compared ($p<0.05$). There was no significant difference in terms of the other echocardiographic parameters (Table 2).

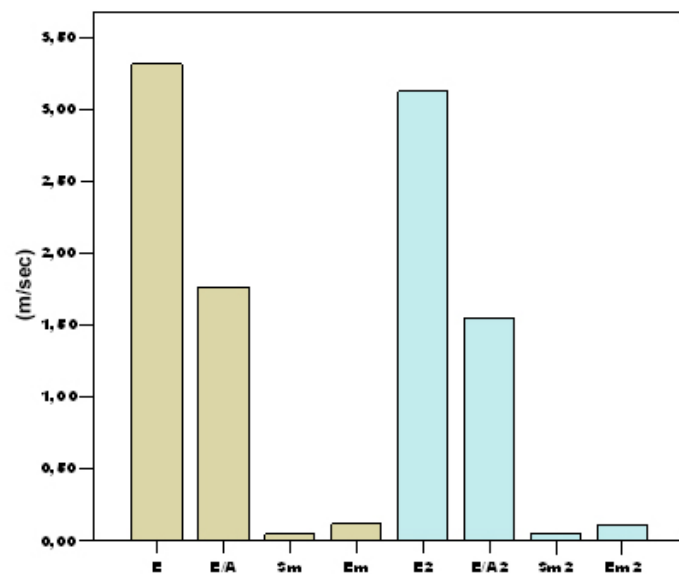


FIGURE 1. Comparison of the echocardiographic parameters between Day 0 and Day 5 in the study group (E, E/A, Sm, Em – Day 0, E2, E/A2, Sm2, Em2 – Day 5).

In the study group, comparison of echocardiographic parameters during acute allergy (Day 0) and after allergy treatment (Day 5) revealed significant differences in terms of mitral flow progression velocity (Vp), E velocity, E/A ratio, systolic (Sm) and early diastolic (Em) velocities and tricuspid peak gradient (TPG) ($p<0.05$) (Table 3). In the patient group, echocardiographic parameters including mitral flow progression velocity (Vp), E velocity, E/A ratio, systolic velocity (Sm), early diastolic velocity (Em) and tricuspid peak gradient (TPG) measured during acute allergic reaction (Day 0) were found to be significantly different than those measured after allergy treatment (Day 5) ($p<0.05$) (Table 3).

The comparison of echocardiographic parameters measured at Day 0 and Day 5 in the study group are presented in Figure 1. The comparison of echocardiographic color M mode flow progression velocities measured at Day 0 and Day 5 in the study group are presented in Figure 2.

Discussion

The incidence and prevalence of cardiovascular disorders have shown progressive increases over the years and have become the leading cause of mortality and morbidity worldwide. Advances in technology have facilitated the diagnosis, follow-up and treatment of cardiovascular disorders. Despite the significant progress, diagnosis and treatment remains still insufficient for most patients. A new perspective in cardiology is that of pre-

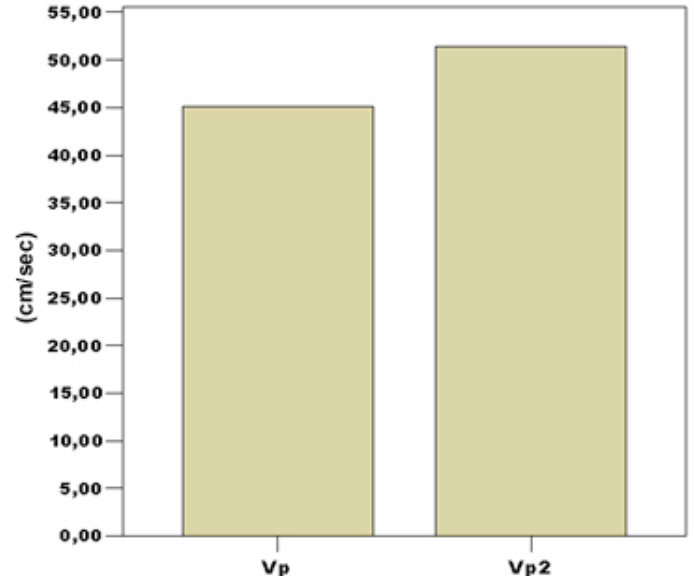


FIGURE 2. Comparison of echocardiographic color M mode flow progression velocities (Vp) in the study group between Day 0 and Day 5 (Vp – Day 0, Vp2 – Day 5).

TABLE 2. Inter-group comparisons of Day 0 measurements.

Variables	Group 0	Group 1	p*
IVRT (ms)	78.13 ± 14.11	73.74 ± 16.35	0.19
DT (ms)	215.90 ± 33.69	211.26 ± 34.74	0.58
Vp (cm/s)	54.93 ± 7.57	45.10 ± 11.03	0.001
E (m/s)	2.81 ± 0.71	3.31 ± 0.88	0.001
A (m/s)	1.8517 ± 0.87	2.16 ± 1.18	0.26
E/A	1.7080 ± 0.59	1.76 ± 0.56	0.65
Sm (m/s)	0.540 ± 0.22	0.04 ± 0.02	0.25
Em (m/s)	0.115 ± 0.05	0.11 ± 0.46	0.76
Am (m/s)	0.0557 ± 0.03	0.7 ± 0.10	0.65
E/Em	2.99 ± 1.48	3.56 ± 3.31	0.37
EF	61.40 ± 3.51	61.42 ± 3.04	0.75
IVS (mm)	8.77 ± 0.72	8.80 ± 0.99	0.80
VAD (mm)	7.53 ± 0.62	7.52 ± 0.73	0.69
TPG (mmHg)	18.1 ± 4.66	20.10 ± 4.91	0.08
Systole (mmHg)	25.97 ± 2.89	25.90 ± 2.03	0.84
Diastole (mmHg)	43.3 ± 2.69	44.30 ± 3.05	0.16

*:Mann-Whitney U test

Group 0: Control Group; Group 1: Study Group

ventive medicine, which has prompted cardiologists to address the risk factors of cardiac diseases. Along with traditional risk factors such as diabetes, hypertension, dyslipidemia, smoking and family history, numerous studies have recently addressed the question of whether or not allergy has an impact on the heart functions.

In 1991, Kounis and Zavras reported a patient who experienced chest pain following an allergic reaction, which was referred to as “allergic angina syndrome” [5]. Kounis and Zavras’s study focused on the effects of allergic reactions on systolic functions, and the effects of allergic reactions on diastolic functions have not been addressed. In contrast, the present study evaluated the effects of allergic reactions on diastolic function.

In 1995, Constantinides reported that allergic reactions could result in plaque rupture [6]. In one case, myocardial infarction was caused by allergy-induced plaque rupture. Diastolic function was not addressed.

In 1998, Braunwald noted that the release of histamine and leukotrienes in response to allergic reactions might affect smooth muscles, including coronary vessels [7]; however, diastolic function was not discussed. Urinary levels of inflammatory mediators, such as histamine, neutral protease, arachidonic acid metabolites and platelet activating factors, together with many other cytokines and chemokines, have been shown

to be elevated during allergic attacks and acute coronary syndrome. The release of these mediators has been shown to be associated with coronary artery spasm and the rupture of atheroma plaque [7]. Allergic reactions may affect diastolic heart function, either by the direct effects of the mediators or by inducing coronary artery spasm. In our study, mitral flow progression velocity (Vp) and early diastolic filling velocity (E) were significantly different between the control group and the study group (Vp in the Control Group: 54.93 ± 7.57 cm/sec, Vp in the Study Group: 45.10 ± 11.03 cm/sec; E in the Control Group: 2.81 ± 0.71 m/sec, E in the Study Group: 3.31 ± 0.88 m/sec, p<0.05) In addition, significant improvement was observed during early follow-up period in diastolic function of patients who experienced allergic diastolic dysfunction (Vp Day 0 – 45.10 ± 11.03 cm/sec, Vp Day 5 – 51.38 ± 6.86 cm/sec, E Day 0 – 3.31 ± 0.88 m/sec, E Day 5 – 3.12 ± 0.88 m/sec, E/A Day 0 – 1.76 ± 0.56, E/A Day 5 – 1.55 ± 0.49, Sm Day 0 – 0.04 ± 0.02 m/sec, Sm Day 5 – 0.05 ± 0.01 m/sec, Em Day 0 – 0.11 ± 0.46 m/sec, Em Day 5 – 0.10 ± 0.03 m/sec, p<0.05) (Table 3).

Although there was no significant difference between the study group and the control group in terms of diastolic function at Day 0, there was significant difference in terms of some parameters between Day 0 and Day 5 suggesting a develop-

TABLE 3. Intra-group comparisons of the measurements in Group 1.

Variables	Day 0	Day 5	p*
IVRT (ms)	73.74 ± 16.35	72.94 ± 10.77	0.93
DT (ms)	211.26 ± 34.74	208.90 ± 23.04	0.79
Vp (cm/s)	45.10 ± 11.03	51.38 ± 6.86	0.001
E (m/s)	3.31 ± 0.88	51.38 ± 6.86	0.001
A (m/s)	2.16 ± 1.18	2.20 ± 0.98	0.79
E/A	1.76 ± 0.56	1.55 ± 0.49	0.02
Sm (m/s)	0.04 ± 0.02	0.05 ± 0.01	0.02
Em (m/s)	0.11 ± 0.46	0.10 ± 0.03	0.02
Am (m/s)	0.7 ± 0.10	0.05 ± 0.01	0.38
E/Em	3.567 ± 3.31	3.561 ± 1.90	0.069
EF	61.42 ± 3.04	61.54 ± 2.87	0.38
IVS (mm)	9.10 ± 0.99	9.14 ± 0.92	0.07
VAD (mm)	7.86 ± 0.73	7.92 ± 0.66	0.082
TPG (mmHg)	20.10 ± 4.91	15.52 ± 4.69	0.001
Systole (mmHg)	25.90 ± 2.03	25.64 ± 1.46	0.08
Diastole (mmHg)	44.30 ± 3.05	44.28 ± 2.92	0.92

*:Mann-Whitney U test

Group 0: Control Group; Group 1: Study Group

ment of diastolic dysfunction. This is an important finding that suggests that allergic reactions may affect diastolic function in the acute period.

In studies on patients with allergic reactions, coronary spasm, plaque rupture and cytokines have been previously implicated in the impairment of systolic heart functions, [8, 9, 10, 11]. It is likely that similar mechanisms may impair diastolic heart function thorough similar pathways. Ours is the first study to provide data that supports this theory.

Cardiomyocytes are the local source of serotonin in the cardiac tissue. Serotonin, or 5- hydroxytryptamine, exerts positive chronotropic and positive inotropic effects on cardiomyocytes through its receptors, and has a mitogen effect on the myocytes [12]. Serotonin acts as either a vasodilator or vasoconstrictor on blood vessels, depending on the condition of the endothelial cell lining, and it augments the effects of other vasoconstrictive agents. Serotonin also exerts mitogenic effects on the vascular smooth muscle cells and endothelial cell [13]. Serotonin, as one of the mediators released during allergic reactions, affects both systolic and diastolic heart function.

Histamine causes coronary spasm through H1 activation, and tachycardia, vasodilation and increased myocardial contraction through H2 activation; therefore, it affects systolic heart function, either directly or indirectly,. In addition to se-

rotonin and histamine, many other mediators released during allergic reaction affect the cardiovascular system through similar mechanisms [14, 15 , 16].

The limitations of our study were the limited number of patients, lack of long-term follow-up after allergic reaction, non-compliance of patients to the allergy treatment and continuing exposure to the allergens, all of which should be addressed in future studies.

Conclusion

Allergy is a commonly encountered clinical condition and additional research is necessary to determine to what extend mediators released during allergic reaction affect cardiac function. Although mortality from diastolic heart failure is not as high as from systolic heart failure, it is an important cause of mortality and morbidity, significantly impairing the quality of life of affected patients. The present study demonstrated impaired left ventricular diastolic function in patients with acute allergic reactions. Comprehensive studies with larger samples are needed to elucidate the cardiac effects of this condition.

Acknowledgments

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