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The Structure of Left Ventricular Relaxation in Case of Ventriculography

Aim	To study the relaxation structure of the left ventricle (LV) in patients who underwent ventriculography.
Material and methods	LV ventriculography was performed in 37 patients. Before catheterization, echocardiography was performed in each patient. In 6 patients, the LV ejection fraction (EF) was below 40%; these patients with systolic dysfunction were not included in the study. In 31 patients, the LV EF was higher than 50%. In this group, 13 patients had NYHA functional class (FC) 2–3 chronic heart failure (CHF); the rest of the patients had FC 1 CHF. Eighteen of 31 patients had stable ischemic heart disease; 50% of these patients had a history of myocardial infarction; the rest of the patients had hypertension and atrial and ventricular arrhythmias. The dynamics of the LV pressure decrease was analyzed from the moment of the maximum rate of pressure drop, which usually coincides with the closure of the aortic valves. The pressure drop curve was logarithmized with natural logarithms and divided into 4–5 sections with different degrees of curve slope. The relaxation time constant was calculated for each section. Its inverse value characterizes the relaxation time constant (tau).
Results	In 31 patients with LV EF 52–60%, three types of the dynamics of the relaxation rate constant were identified during the pressure decrease in the isovolumic phase: in 9 patients, the isovolumic relaxation constant (IRC) steadily increased as the pressure decreased; in 13 patients, it continuously decreased; and in 9 patients, the dynamics of IRC change was intermediate, with an initial increase followed by a decrease.
Conclusion	In diastolic dysfunction, one group of patients had an adaptation type associated with an increase in the LV wall elasticity, while the other group had a different type of adaptation associated with its decrease. Each type has advantages and disadvantages. This is probably due to changes in the structure of the sarcomeric protein connectin (titin).

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Introduction

Diastolic dysfunction represents the most prevalent form of chronic heart failure (CHF) [1]. CHF is distinguished by prolonged relaxation, elevated filling pressure, diminished contraction velocity, and a reduction in cardiac output [2]. Myocardial relaxation impairment related to CHF represents a significant clinical challenge, affecting the majority of patients with end-stage CHF [3, 4]. Moreover, it serves as a primary indicator of diastolic dysfunction. In the clinical setting, delayed relaxation serves as an independent diagnostic criterion for CHF with preserved left ventricular ejection fraction (LVEF) [5].

The relaxation commences during the isovolumic phase and is based on the removal of Ca^{2}+ ions from actomyosin bonds. The active relaxation phase requires the expenditure of up to 30% of the total energy per cardiac cycle [6]. However, this component of relaxation does not characterize its final part, in which the rate of pressure decline is typically faster than the rate of Ca^{2}+ removal [3], indicating the inclusion of an additional component. The passive component facilitates a gradual restoration of the initial length of sarcomeres and is determined by the properties of contractile proteins [7].

The analysis of the relaxation process in patients is typically confined to the determination of the relaxation time constant (tau) in the isovolumic phase [8]. The passive component of relaxation has only been the subject of study in animal models. Upon logarithmizing the LV pressure curve in guinea pig and canine models, it was observed that the final stage of relaxation occurs at a faster rate than in the isovolumic phase [9, 10]. This phenomenon is based on the suction phenomenon, which was observed in the experiment on the turtle heart [11]. Despite the onset of LV filling, the pressure within the LV continues to decrease due to this suction phenomenon. In recent study on rat hearts [12], a gradual

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acceleration of LV pressure decline during the transition from the isovolumic phase to the auxovolumic phase was established. The LV pressure decline continues despite the opening of mitral valves. Furthermore, accelerated end-phase relaxation was observed in isolated trabeculae, which is believed to reflect the rapid opening of cross-bridges [13]. In healthy hearts, echocardiography and magnetic resonance imaging revealed slight elongation or unwinding at end-systole [14–16].

Objective

The objective of the study was to conduct a comprehensive examination of myocardial relaxation patterns in patients who underwent left ventricular ventriculography.

Material and Methods

The study was conducted in accordance with the requirements of the Ethics Committee of the Academician Chasov National Medical Research Center for Cardiology (minutes No. 232, dated December 25, 2017) and the ethical principles set forth in the Declaration of Helsinki of the World Medical Association. All patients signed the informed consent to be included in the trial.

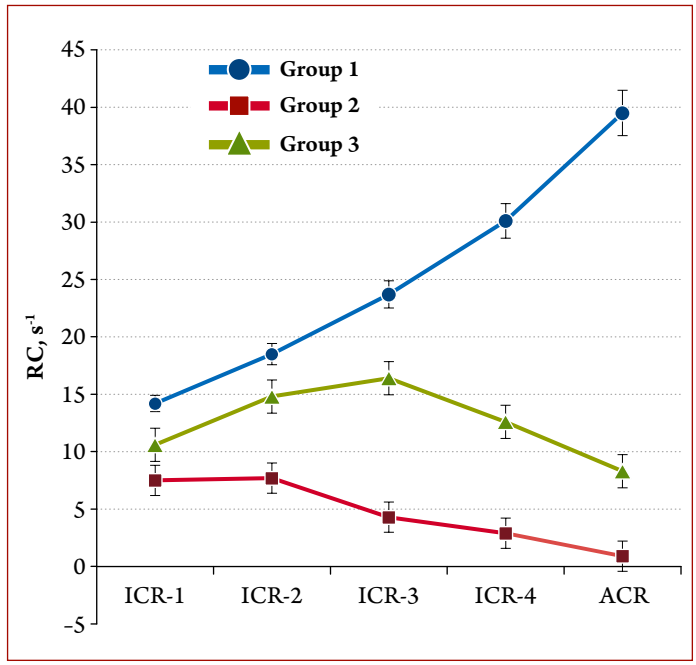
Inclusion criteria. The study was conducted on 37 patients with a range of different diagnoses. The most prevalent diagnosis was CHD (n = 22), with 50% of patients with CHD having a history of infarction. Other diagnoses included hypertensive heart disease and atrial and ventricular arrhythmias. In the cohort of patients with LVEF above 50% (n = 31), NYHA class II was observed in 6 patients, NYHA class III in 7 patients (all diagnosed with CHD), and the remainder had NYHA class I. There are no explicit indications for routine LV ventriculography in the current clinical guidelines. Therefore, diastolic dysfunction with preserved LVEF was the criterion for patient selection.

LV ventriculography was conducted on patients selected from the cohort of patients who were indicated for coronary angiography with stenting or ballooning. Patients of both sexes aged 18 years or over, with a variety of CHD manifestations, including a history of myocardial infarction and heart failure with LV systolic and diastolic dysfunction, who provided voluntary informed consent to participate in the study were eligible for inclusion in the study.

Exclusion criteria. Critical aortic valve (AV) stenosis, AV insufficiency stages III–IV, the presence of LV thrombi, mechanical or biological AV prostheses, and the presence of life-threatening ventricular arrhythmias. Patients with a LVEF of less than 50% (n = 6) were excluded.

LV ventriculography was conducted using the conventional method. Once arterial access had been established (via the radial artery) and the 6F introducer had been inserted into the LV cavity, a PigTail 6F diagnostic catheter was then placed through a 0.035-inch diagnostic guide. Subsequently, the catheter was connected to the system for invasive pressure monitoring, and the LV pressure curve was recorded.

Central illustration. Changes in relaxation rate constants (RC, s^{-1}) in three groups



ICR-1–4, different phases of isovolumic relaxation; ACR, auxovolumic relaxation; RC, LV relaxation rate constant (s^{-1}).

Echocardiogram

Echocardiogram was performed using a Vivid E9 ultrasound system (GE Healthcare, USA) with the use of a M5S sector matrix transducer. The study was conducted with the patient lying on the left side and in a supine position in order to assess central venous pressure. The images were registered from both the parasternal and apical views. The apical four-, three-, and two-chamber sections were recorded to ascertain global longitudinal strain and LV myocardial performance. Simultaneously, electrocardiogram synchronization was performed to determine the phase of the cardiac cycle. Three to five cycles were recorded while the patient was instructed to hold their breath.

The echocardiographic protocol included the standard positions in B, M, PW, and CW modes, as well as color Doppler mapping and myocardial tissue Doppler at a rate exceeding 140–150 frames per second. LV and left atrial systolic and diastolic volumes were calculated in B-mode from apical four- and two-chamber views using the modified Simpson disk method. Subsequently, the LVEF was calculated based on the values of end-diastolic volume (EDV) and end-systolic volume (ESV) using the following formula:

$$LVEF = (EDV - ESV)/EDV.$$

The stroke volume was calculated as the product of the LV outflow tract (LVOT) cross-sectional area and the LVOT linear velocity integral. The LVOT cross-sectional area was calculated using the following formula:

$$S = \pi r^2$$

using the LV diameter measured from the parasternal view along the LV long axis in the ZOOM mode at a distance of 1 cm from the AV at mid-systole. The integral of linear blood flow velocity was calculated by tracing the spectrum obtained from the apical five chamber view in the pulsed-wave Doppler mode.

Calculation of relaxation constants

The analysis was conducted using the LV pressure segment, commencing at the point of peak pressure decline rate, which precisely coincides with the moment of AV closure. The natural logarithms revealed four to five distinct segments, characterized by varying degrees of slope. In each segment, a trend line was selected, and the value of approximation reliability R2 was calculated to be at least 0.999. The inverse value (1000/slope constant) characterizes the relaxation time constant (tau). The methodology is described in more detail in the article by V. I. Kapelko et al. [12].

The statistical processing of the obtained data was conducted using the SPSS Statistica v. 26 (IBM, USA) and JMP Pro 17 (SAS, USA) software programs. The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. The initial comparison between the groups was conducted using an analysis of variance (ANOVA). Subsequently, post hoc tests were performed using the Holm corrections for multiple comparisons. The results were deemed statistically significant at a level of $p < 0.05$.

Results

Detailed analysis of the LV relaxation phase in 31 patients with diastolic dysfunction revealed 3 types of response. In Group 1 (n = 9), the relaxation rate constant demonstrated a consistent increase with decreasing pressure in the isovolumic phase. In contrast, Group 2 (n = 13) exhibited a gradual decline in this parameter. Group 3 (n = 9) consisted of patients with moderate dynamics, displaying an initial acceleration of relaxation followed by deceleration (Central figure).

The LV curves differed in shape in these three groups (Figure 1). In Group 1, patients were characterized by a predominance of the rate of LV pressure decline over the rate of LV pressure rise. In the other two groups, these values were approximately the same. They also differed from Group 1 in terms of end-diastolic pressure.

Group 1 exhibited lower LV diastolic pressure and shorter cycle duration compared to the other groups. Group 2 was distinguished by elevated LV diastolic pressure and a prolonged cycle duration. Group 3 occupied an intermediate position closer to Group 2.

A more detailed overview of the cardiohemodynamic characteristics of these groups is provided in Table 1. Group 2 exhibited notable differences from Group 1, with a markedly elevated diastolic pressure and a reduction in the rate of pressure rise and decline. Group 3 occupied an intermediate position.

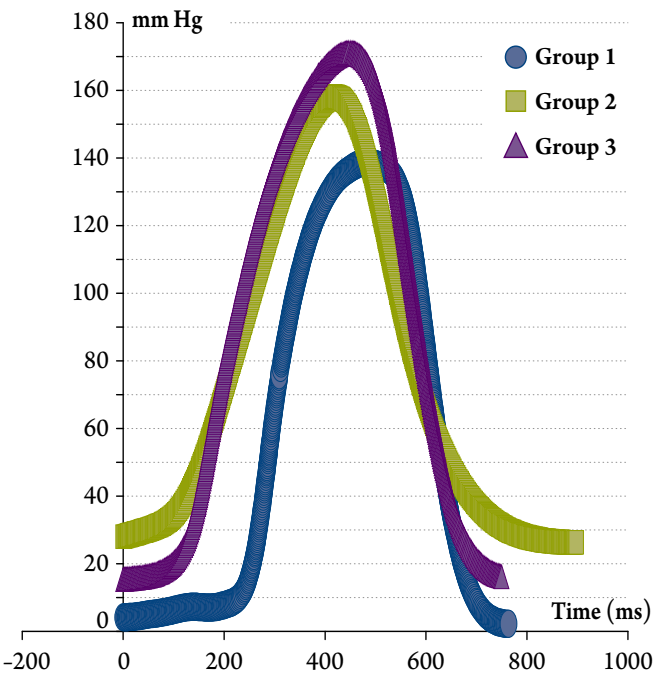
Our findings demonstrated a considerable degree of variability in the relaxation patterns observed in the study group. Patients in Group 1 exhibited the highest relaxation rates and the lowest minimum LV diastolic pressure. In general, there is a strong negative correlation between these values in the general sample ($r = -0.71$). It is evident because faster relaxation is able to reduce LV pressure to a greater extent within the same time interval.

The echocardiographic findings were found to be largely similar across all groups: E is 75, 55, and 66 in Groups 1, 2, and 3, respectively; the E/m ratio is 10.5 ± 2.3, 8.8 ± 0.7, and 10.8 ± 2.4, respectively. In Group 1, 2 (22%) of 9 patients had CHF class II, while the remaining patients had CHF class I, with a mean value of 1.2 ± 0.1. In Group 2, 6 (46%) of 13 patients had CHF class II–III, with the mean value of 1.8 ± 0.3 ($p = 0.07$).

Discussion

A recent study has demonstrated that in the hearts of normal rats, the logarithmization of the LV pressure

Figure 1. Typical cardiac cycles in patients of the three groups



Horizontal axis – time (ms), vertical axis – LV pressure (mm Hg).

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Table 1. Cardiodynamics in three patient groups based on ventriculography data

Parameter	Group 1 (n = 9)	Group 2 (n = 13)	Group 3 (n = 9)
Heart rate, bpm	65 ± 1	66 ± 2	60 ± 6
LV systolic pressure, mm Hg	137 ± 7	130 ± 7	141 ± 8
Minimum LV diastolic pressure, mm Hg	–0.2 ± 0.4	20 ± 2**	7.8 ± 1.1**,#
LV end-diastolic pressure, mm Hg	11 ± 2	24 ± 2**	15.8 ± 1.6*
Maximum rate of LV pressure rise, mm Hg/sec	910 ± 89	650 ± 73*	890 ± 66
Maximum rate of LV pressure decline, mm Hg/sec	1190 ± 169	670 ± 85	930 ± 61

* $p < 0.05$; ** $p < 0.001$ compared to Group 1; # $p < 0.001$ compared to Group 2. CHD, coronary heart disease; LV, left ventricle.

curve reveals a steady increase in the rate of pressure drop constant during the isovolumic phase until the auxovolumic phase [12]. This phenomenon can be attributed to the gradual involvement of the passive component of relaxation, which facilitates a gradual restoration of the initial sarcomere length. This function is fulfilled by the sarcomeric protein connectin, which was first identified in 1976 [17], but is more commonly referred to as titin. The spring-like structure undergoes contraction when the sarcomeres contract and relaxation when they relax, thereby returning the ends of the myosin filaments to their original position [7, 18]. This function is carried out by the more elastic isoform N2B, whereas the more pliable isoform N2BA provides some resistance when myocardial fibers are stretched during diastole. The greater the elasticity of the spring, the more rapidly the initial length of the sarcomeres is restored prior to contraction, due to the accelerated rupture of actomyosin bonds [19]. Computer modeling replicates this behavior, indicating that rapid elongation accelerates relaxation by accelerating the detachment of cross-bridges [20]. A correlation has been observed between the rate of relaxation in the isovolumic phase and that of elongation in the auxovolumic phase [21, 22].

Permanent increase in the relaxation rate constant in Group 1 was demonstrated in earlier experiments on control rats [12]. However, the magnitude of the increase in the ACR/ICR1 ratio, which is indicative of the extent of LV relaxation acceleration, was markedly greater in human patients. In rats, the ratio was determined to be equal to 1.8, whereas in humans, as illustrated in the Central figure, it was 2.8. This discrepancy is presumably attributable to the differing ratios of N2BA/N2B in the rat and human myocardium. In the rat myocardium, the N2B isoform constitutes approximately 80% [23, 24], whereas in humans and other large mammals, the N2B isoform represents a variable ranging from 20% to 40% of the connectin structure [23]. Accordingly, the low initial fraction of N2B in human myocardium provides a notable increase of this isoform during the aforementioned adaptation.

The discrepancy in the ratio of N2BA and N2B isoforms is naturally attributable not only to the differing sizes of hearts, but primarily to the frequency of contractions. In large animals, the primary component of the cardiac output is stroke volume, which is formed on the basis of increased sarcomere stretching in diastole. Consequently, the less elastic and more complaint N2BA isoform is predominant. In small animals, the primary component of the cardiac output is the high frequency of contractions, and the duration of the diastolic pause is relatively brief. This necessitates the rapid completion of relaxation, which should involve the participation of the elastic isoform N2B.

In Group 2, there was no increase in the relaxation rate constant. This suggests that there was a relative increase in the fraction of the N2BA isoform in the myocardium of patients in this group. As this isoform of connectin is responsible for determining the degree of wall resistance during LV filling, it was identified in patients with various pathological conditions. In patients with CHD and dilated cardiomyopathy, a relative increase in the N2BA fraction was observed, accompanied by elevated LV diastolic pressure [25]. A comparable effect was documented in cases of aortic regurgitation accompanied by LV dilation [26, 27]. Conversely, an increase in the N2B isoform was observed in patients with aortic stenosis [26, 28]. Furthermore, it is crucial to acknowledge that the reduction in myocardial elasticity observed in dilated cardiomyopathy does not necessarily signify alterations in the elasticity of connectin. Additionally, it may be a consequence of mutations in contractile proteins. [29].

The presented data suggest that there are two distinct forms of myocardial adaptation to conditions of impaired contractility. A reduction in the elasticity of connectin results in an enhanced filling, which consequently leads to a stronger contraction. An augmentation in connective tissue elasticity impedes the filling process but facilitates the development of contraction force. It is evident that alterations in connectin elasticity inevitably impact the process of myocardial relaxation. However, this phenomenon has not been subjected to rigorous scrutiny.

The accelerated relaxation observed in the terminal phase has the potential to significantly reduce the minimum LV diastolic pressure. This results in an augmented gradient between the atrium and ventricle, thereby facilitating its filling and allowing for the maintenance of normal pressure within the pulmonary circulation. Group 1 patients are also characterized by the prevalence of the maximum rate of pressure decline relative to the maximum rate of pressure development. This ratio is atypical for a normal heart, in which the opposite ratio is observed. It is proposed that this deviation is attributable to a reduction in myocardial contractility in diastolic dysfunction. At the same time, increased myocardial elasticity may confer increased resistance during the diastolic phase, as evidenced by the substantial pressure gradient between the end-diastole and early diastole (see Table 1). This evidence further supports the proposed hypothesis that myocardial diastolic elasticity is increased in Group 1 patients.

In group 2 patients, the opposite relationship is observed. As relaxation is completed, the contribution of the passive component of relaxation decreases, while the minimum diastolic pressure remains high and undergoes minimal change as LV filling progresses. This complicates LV filling, which requires an elevation in pressure within the pulmonary circulation and an increase in the load on the right ventricle.

Conclusion

The findings of the present study demonstrated the existence of two discrete forms of cardiac adaptation to conditions of reduced myocardial contractility in diastolic dysfunction in humans. The first type is associated with increased elasticity, and the second type is associated with reduced elasticity. Each type possesses both advantages and disadvantages. An increase in myocardial elasticity, coupled with accelerated relaxation and a reduction in minimum diastolic pressure, results in enhanced resistance to LV filling [30]. This may limit the increase in cardiac output during exercise unless the myocardium is able to reduce its elasticity, thereby facilitating LV filling. A reduction in myocardial elasticity significantly enhances LV filling, enabling greater myofibrillar stretching and consequently an augmented force of contraction [31]. However, at the same time, delayed relaxation is coupled with augmented minimum diastolic pressure, which requires a compensatory elevation of pressure within the minor circuit. This consequently imposes an augmented load on the right ventricle.

It can be proposed that the performance of moderate exercise may serve as an indirect indicator of myocardial diastolic elasticity. The higher heart rate increase may serve as an indicator of enhanced relaxation and increased diastolic elasticity. In patients with reduced diastolic elasticity, a lower increase in heart rate and higher mobilization of stroke volume should be anticipated.

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