In vivo relationship between human left atrial load and contractility

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ABSTRACT

Objectives: The aim of the study was to elicit the relation between the left atrial load and its contractile function.

Methods: 33 patients, 56.9±6.7 y.o., were enrolled in the study. All of them underwent transesophageal echocardiography due to different clinical indications. The Doppler spectrum of transmitral and pulmonary vein flow, left atrial dimensions and volumes were estimated.

Results: The links between left atrial contractility indices, its pressure and filling were determined. This supports the hypothesis of the Frank-Starling law validity for the human left atrium *in vivo*.

Conclusion: In the human heart in vivo there is an inverse exponential relationship between the left atrial volume (preload) and pressure (afterload) load and its active contractility, as well as a positive linear relationship between the afterload and contractility.

KEY WORDS: Frank-Starling law
Atrial contractility
Echocardiography

Introduction

The adequate function of the circulatory system primarily depends on cardiac output. Meanwhile, the obligatory condition of the normal heart function is the equality of the blood flow in the veins and its release into the arteries. The solution to this objective is provided mainly by the properties of the heart muscle itself. The development of these mechanisms is called myogenic autoregulation of the heart function: the strength of each heart beat depends on the venous inflow and is determined by the end-diastolic myocardial fiber length [1]. This relationship is called geterometrical regulation of the heart and is also known as the Frank-Starling law: "The strength of ventricular contraction of the heart measured by any means is a function of the length of the muscle fibers just before contraction" [2], i.e., the more the filling of the heart chambers, the greater the cardiac output. The preload growth is accompanied by cardiac index (CI) increase only up to a certain level of pulmonary artery wedge pressure (12-15 mm Hg), followed by a plateau, and further preload growth is not accompanied by an increase in CI. With a further preload increase CI begins to decline [3].

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It is established that the ultrastructural fundamental of this law is based on the fact that the number of actomyosin bridges is the maximum at the length of each sarcomere of about 2.2 microns. Less or more sarcomere tension leads to the decrease in the contraction force because of the smaller number of actomyosin bridges [4, 5, 6]. Until now, it remains unknown whether the Frank-Starling law is valid for the human left atrium (LA) *in vivo*.

The aim of the study was to elicit the relation between the left atrial load and its contractile function.

The essence of the hypothesis is shown in Figure 1. It is assumed that the relationship between the degree of the left atrial stretching and contractility fits the shape of an inverted parabola like the Frank-Starling curve. The normal type of left ventricular (LV) filling and transmitral flow corresponds to the region of the ascending limb of the curve. In this condition, the LA during its contraction develops small strength and wall tension due to the insufficient degree of sarcomere stretching and actomyosin

bridge density in order to create the maximum power needed. Therefore, the velocity of the peak A of transmitral flow and its integral is less than that of peak E. The maximum extension of sarcomeres, the density of actomyosin bridges and, therefore, myocardial contractility is observed in hypertrophic left ventricular filing type, which corresponds to the top of the curve, where the velocity and the integral of transmitral peak A flow are the highest. The further deterioration of LV diastolic function as well as progressive deterioration of LA contractility occur since there is a progressive hyperextension of sarcomeres and reduced density of actomyosin bridges. In this case a decrease in peak A velocity and integral is observed, first, during pseudonormal and then – to the maximum of the E/A ratio – during the restrictive pattern. The rising part of the curve (more left than normal) corresponds to a state often observed in young physically fit people. Small sizes of the left chambers and a very low level of LV end diastolic pressure in these individuals exclude the presence of diastolic dysfunction. However, recent studies suggest that these patients commonly have transmitral flow similar to the restrictive pattern. If the hypothesis is true, then the comparison of indexes characterizing the LA load and its contractile properties, will identify the described relationship.

Materials and methods

The study included 33 patients at the age of 56.9±6.7 years with different disease entities (Table 1), who underwent transthoracic and transesophageal echocardiography evaluation for various clinical indications.

Table 1. Clinical characteristics of the study patients

Age, years	56.9±6.7
Gender, M/F	24/9 (73/27%)
Healthy subjects	3 (9%)
Arterial hypertension	4 (12%)
Idiopathic paroxysmal arrhythmias	5 (15%)
Ischemic cardiomyopathy	5 (15%)
Dilated cardiomyopathy	7 (21%)
Myocarditis in healed stage	4 (12%)
Myocardial infarction in healed stage	5 (15%)

The spectral parameters of transmitral flow, blood flow in the pulmonary veins (PVs), the LA size and volume (Table 2) were assessed.

Table 2. Echocardiographic indices under study

Indices	Interpretation
LA AP	Left atrial anteroposterior size, mm
V LA	LA volume, ml
LA EF	Left atrial ejection fraction
Peak E	Peak velocity of transmitral blood flow during passive left ventricular filling
Peak A	Peak velocity of transmitral blood flow during active left atrial contraction
E/A	Ratio of the forenamed velocities
IVRT	Isovolumetric relaxation time
VTI A	Velocity-time integral of transmitral blood flow during active left atrial contraction
VTI	Velocity-time integral of total transmitral blood flow
AFF	Atrial filling fraction (VTI A / VTI)
Peak S	Peak velocity of pulmonary vein blood flow during left ventricular systole
Peak D	Peak velocity of pulmonary vein blood flow during passive left ventricular filling
Peak Ar	Peak velocity of pulmonary vein blood flow during active left atrial contraction (retrograde phase)
T Ar	Duration of pulmonary vein blood flow during active left atrial contraction (retrograde phase)
VTI PV	Velocity-time integral of pulmonary vein during total cardiac cycle

Statistical Analysis

The statistical data processing was carried out in the Statistica 10.0 software package (StatSoft, USA). The Spearman's R-test was used to assess the correlation between all the parameters in the entire study group, and the scatterplots with superimposed curves of the linear or exponential fit were built. The groups were also divided by the type of LV filling pattern, and for each group the median and quartiles were presented in the range plots.

Results

Table 3 shows the correlation between all the parameters assessed by the Spearman's R-test. Some relations are evident, such as a positive correlation between the peak A of transmitral flow and the E/A ratio, etc. Such types of correlations are gray-shaded in Table 3

Table 3. Correlations between the studied indices

Index	LA AP	V LA	LA EF	VTI	VTI A	AFF	Peak S	Peak D	Peak Ar	T Ar	VTI PV	Peak E	Peak A	E/A
V LA	**0.59**													
LA EF	-0.22	**-0.35**												
VTI	0.10	0.06	-0.03											
VTI A	-0.06	-0.15	0.05	**0.31**										
AFF	-0.15	**-0.26**	0.00	-0.16	**0.57**									
Peak S	**-0.35**	**-0.25**	0.08	0.04	-0.03	-0.03								
Peak D	**0.27**	0.15	0.02	0.07	-0.04	-0.13	-0.04							
Peak Ar	**-0.28**	-0.21	0.09	-0.01	-0.06	-0.06	**0.47**	-0.17						
T Ar	0.07	0.01	0.02	-0.10	**-0.24**	-0.15	0.04	-0.03	**0.28**					
VTI PV	0.02	0.07	0.03	0.11	-0.08	-0.21	**0.39**	**0.34**	0.19	0.06				
Peak E	0.11	0.23	-0.13	**0.42**	-0.19	**-0.55**	0.08	0.08	0.09	0.01	0.19			
Peak A	-0.04	-0.19	0.13	-0.02	**0.48**	**0.54**	-0.02	-0.19	0.03	-0.04	-0.11	**-0.35**		
E/A	0.10	0.23	-0.16	**0.28**	**-0.36**	**-0.66**	0.10	0.15	0.06	0.05	0.22	**0.71**	**-0.65**	
IVRT	-0.15	-0.21	0.02	-0.21	**0.31**	**0.50**	-0.01	-0.14	0.11	-0.08	-0.22	**-0.44**	**0.50**	**-0.56**

Significant correlations ($p<0.05$) are in bold.

Among the less obvious correlations the most interesting characterized the relationship between the LA contractility and its volume (preload) or pressure (afterload) load:

- the greater the LA volume load, the lower its ejection fraction, atrial filling fraction and passive stretching (the filling velocity of the pulmonary veins).
- the more LA anteroposterior size, the worse its passive stretch and active contractile function (velocity of retrograde flow in the pulmonary veins).
- there is a positive correlation between the passive stretch (peak S) and active LA contractile function (peak Ar).
- the greater the LA pressure load (IVRT), the higher the atrial filling fraction, as well as the integral and the velocity of LA active contraction (peak A).

Figures 2-4 demonstrates the diagrams characterizing the relationship between the most important variables. Of note is that these functional correlations, confirming the hypothesis put forward, are not always linear.

Figure 1. Diagram describing the hypothesis. Explanation on the diagram

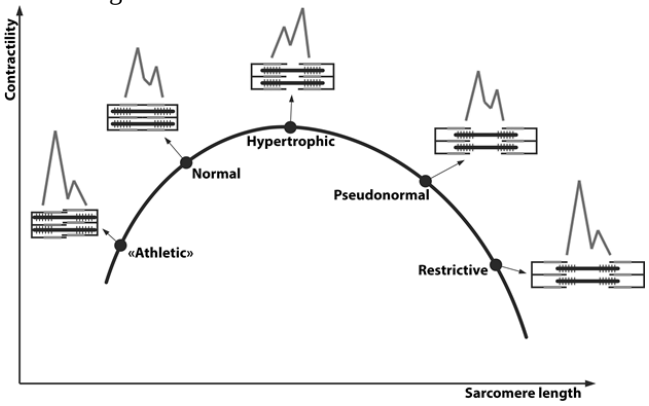


Figure 2. Diagram describing the negative exponential relationship between the LV filling patterns and atrial filling fraction

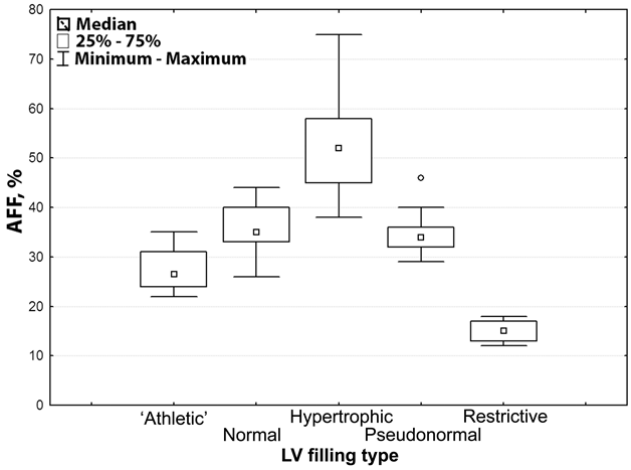


Figure 3. Scatterplot of the positive linear relationship between peaks S and Ar of the pulmonary venous blood flow

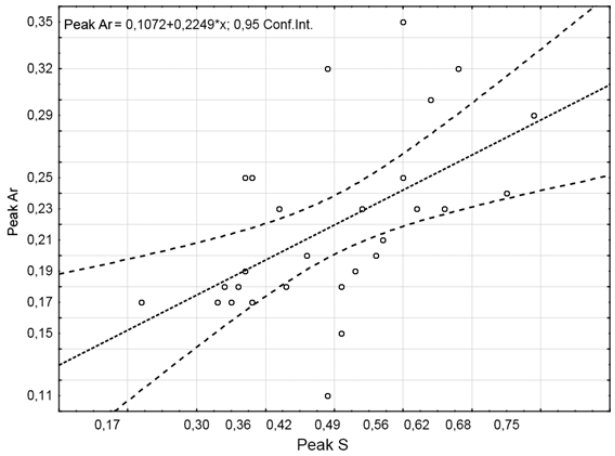
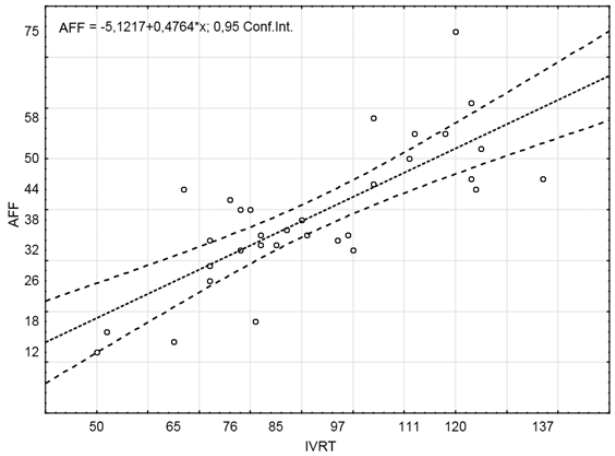


Figure 4. Scatterplot of the positive linear relationship between the isovolumetric relaxation time and atrial filling fraction



Discussion

Traditionally the LA mechanical function implies three different mechanisms [9]:

- LA actively contracts just before the LV systole.
- LA has a reservoir function, filling from the pulmonary veins during LV diastole and isovolumic relaxation period.
- LA passively expulses blood to the LV due to the pressure gradient after the mitral valve opening.

The myogenic atoregulation mechanisms, namely the Frank-Starling law, can influence the first of the forenamed components of the LA mechanical function. This pattern was established in the early 20th century on the ventricular specimens taken from animal experiments [2], and in 1987 was also demonstrated for the atria [10], again, only in vitro. This paper attempts to identify whether there is a similar relationship in vivo. Another contentious issue which the authors set out to answer is if such a relationship exists, whether the downslope segment of the Starling curve exists in the LA of the living human, which is proved to be absent in the entire heart [11]. Both of these questions could be answered positively by comparing the relationships between echocardiographic indicators of the LA filling and pressure load, and the indicators of active contractile function. Interesting was the fact that the relationship between LA filling (peak S) and the peak phase of PV retrograde blood flow (Ar) was linear, rather than negative exponential. Also, there was a linear relationship between the pressure load (IVRT) and LA contractility. This suggests some non-myogenic mechanisms (possibly the active contractile function of PVs) and the mechanisms associated with the afterload to participate in the regulation of LA contractility. The molecular mechanism of the Frank-Starling phenomenon remains an open question as more data on the infidelity of the 'actomyosin' theory and the impact of contractile protein sensitivity to calcium on this relationship were accumulated recently [12, 13]. However, there is no doubt that specific correlations between the LA load and its contractility do exist.

In the human heart in vivo there is an inverse exponential relationship between the LA volume (preload) and pressure (afterload) load and its active contractility, as well as a positive linear relationship between the afterload and contractility.

Conflict of Interest

We declare that we have no conflict of interest.

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