Original Article

Left Atrial Volumetric and Functional Properties in Hemophilia – Insights from a Three-Dimensional Speckle-Tracking Echocardiographic MAGYAR-Path Study

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Abstract

Introduction: Hemophilia is an inherited disorder due to deficiencies in factor VIII (type A) and factor IX (type B). Abnormalities in myocardial mechanics could be theorized due to hemophilia-associated hypocoagubility and related quantitative and qualitative changes of the blood. The present study aimed a detailed assessment of left atrial (LA) volumetric and functional properties in patients with hemophilia using three-dimensional speckle-tracking echocardiography (3DSTE). **Materials and Methods:** The study consisted of 12 subjects with hemophilia type A and 2 cases with hemophilia type B (mean age: 40.8 ± 19.1 years, all males). Results of hemophilia patients were compared to that of 23 age-, gender- and risk factor-matched controls (42.4 ± 9.0 years, all males). Routine two-dimensional Doppler echocardiography and 3DSTE were performed in all subjects. **Results:** LA volumes respecting cardiac cycle did not differ between controls and hemophilia patients. From LA volume-based functional properties, LA stroke volumes were similar between the groups examined in all phases of LA function. While total atrial emptying fraction featuring LA reservoir function was reduced in patients with hemophilia compared to that of controls, passive and active atrial emptying fraction characterizing LA conduit and booster pump functions were similar between the groups. From LA strains, peak mean segmental circumferential and longitudinal LA strains were impaired in patients with hemophilia, other peak LA strains were similar between the groups. LA strains at atrial contraction did not differ between groups of hemophilia patients and controls. **Conclusions:** Hemophilia is not associated with LA volumetric changes, but mild LA functional abnormalities are present.

Keywords: Echocardiography, hemophilia, left atrium, speckle-tracking, three-dimensional

Introduction

Hemophilia is a rare inherited disorder caused by gene mutations located on X chromosome. There are two main forms with deficiencies in factor VIII (type A) and factor IX (type B).[1,2] Approximately 85% of hemophiliacs have type A disease.[1,2] Adaptation in myocardial mechanics could be theorized due to hemophilia-associated hypocoagubility and related qualitative changes of the blood. The left atrium (LA) plays a significant role in maintaining circulation with systolic reservoir and diastolic conduit and booster pump functions.[3] Three-dimensional speckle-tracking echocardiography (3DSTE) is capable of simultaneous detailed volumetric and strain evaluation of the LA at the same time using the same acquired 3D-echocardiographic dataset.[4,5] In earlier studies different patterns of LA function could be demonstrated in different disorders.[6] Therefore, the present study aimed a detailed assessment of LA volumetric and functional properties in patients with hemophilia using 3DSTE.

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Materials and Methods

Patient population

The study comprised a group of 16 hemophilia patients from which 2 subjects were excluded due to insufficient image quality.

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All of them participated in the study as volunteers. Patients are cared at the Division of Hematology, Department of Medicine, University of Szeged, Hungary serving as a tertiary center. The remaining group of patients consisted of 12 subjects with hemophilia type A and 2 cases with hemophilia type B (mean age: 40.8 ± 19.1 years, all males) in which diagnosis was established in infant age. None of the hemophilia patients and controls were obese, but 2 cases were smoker. The known cardiovascular disease was not present in any subject, HCV positivity was present in 10 patients with hemophilia and hemophilic arthropathy in 7. Mild symptoms were present in 7 patients and severe symptoms were present in 7 cases. Factor level was below 1% in 9 patients with hemophilia, 4% in 2 cases, 6% in 1 case, and 9% in the remaining cases, respectively. Therapy was based in demand in 9 patients and profilactic in 5 cases. The mean dose of factor VIII or IX was between 2000-6000 U/week for each patient. Results of the hemophilic group were compared to that of 23 age-, gender-and risk factor-matched controls (42.4 ± 9.0 years, all males). Controls had no electrocardiographic or echocardiographic abnormalities, acute or chronic diseases or other states, which could affect results. Routine 2D Doppler echocardiography and 3DSTE were performed in all subjects. A large-scale clinical study was organized in our department called Motion Analysis of the heart and Great vessels bY three-dimensionAl speckle-tRacking echocardiography in Pathological cases (MAGYAR-Path) Study to analyze diagnostic and prognostic value of 3DSTE-derived parameters in several disorders including hemophilia ("Magyar" means "Hungarian" in Hungarian language). The clinical study was approved by the Institutional and Regional Human Biomedical Research Committee at the University of Szeged (registration no. 71/2011 and updated versions). The study complied with the ethical guidelines set in the 1975 Declaration of Helsinki (and updated versions). All healthy controls and hemophilia patients gave an informed consent.

Two-dimensional Doppler echocardiography

2D Doppler echocardiographic examination was performed using a Toshiba Artida echocardiographic tool (Toshiba Medical Systems, Tokyo, Japan) with a broadband 1-5 MHz PST-30BT phased-array transducer positioned in the left lateral position. International guidelines were used during chamber quantifications.[7] Doppler echocardiography was performed for grading valvular regurgitations and excluding valvular stenoses.

Three-dimensional speckle-tracking echocardiography

3D-echocardiographic data acquisitions were performed immediately after the 2D-echocardiographic study. The same Toshiba Artida echocardiographic machine (Toshiba Medical Systems, Tokyo, Japan) was used with a fully sampled PST-25SX matrix-array transducer (Toshiba Medical Systems, Tokyo, Japan) positioned on the apical window. During data acquisitions, six wedge-shaped subvolumes were acquired in each consecutive cardiac cycle within a single breath-hold. 3D Wall Motion Tracking software version 2.5 (Toshiba Medical Systems, Tokyo, Japan) was used for analysis of 3D echocardiographic datasets. Several views (apical four- and two-chamber long-axis and short-axis views at the level of basal, midatrial, and superior LA regions) were automatically selected from these datasets. In long-axis views, the border of the LA was manually traced by setting multiple reference points from the lateral left ventricle-mitral annulus edge through the LA apex to the septal left ventricle-mitral annulus edge. LA appendage and pulmonary veins were excluded from the evaluations. Following detection of LA boundaries at end-diastole 3D-endocardial surface was reconstructed and tracked in the 3D space during the cardiac cycle. Using the virtual 3D LA model, the following LA volumes were calculated:[3,5,6,8]

- V_{max} = maximum LA volume (the largest LA volume at end-systole just before mitral valve opening)
- V_{min} = minimum LA volume (the smallest LA volume at end-diastole before mitral valve closure)
- V_{preA} = LA volume before atrial contraction (the last frame before mitral valve reopening or at the time of *P* wave on electrocardiography at early diastole).

Using V_{max}, $V_{min,}$ and V_{preA}, several LA volume-based functional properties were assessed featuring a systolic reservoir, early diastolic conduit, and late diastolic active contraction phases of LA function as demonstrated in Table 1.

Left atrial three-dimensional speckle-tracking echocardiography-derived strain measurements

To quantify LA contractility objective features of LA strains were defined using the same 3D cast of the LA:[3,5,6,8]

- Unidimensional/unidirectional radial (RS), longitudinal (LS), and circumferential (CS) LA strains
- Multidimensional/multidirectional/complex area (AS) and 3D (3DS) LA strains

LA strains featuring end-systolic reservoir and late diastolic active contraction phases of the LA function were determined with global and mean segmental peak strains and strains at atrial contraction using a twin-peak curve [Figure 1]. Moreover, regional apical, midatrial and basal strains were also assessed from segmental strains from a segmentation model created for LV but used for LA.

Statistical analysis

Continuous and categorical data were presented as mean ± standard deviation and as frequencies and percentages (%), respectively. Student's *t*-test, X^2 test, and Fisher's exact test was used for group comparisons. Two-tailed $P < 0.05$ was considered to be statistically significant. For statistical analyses, MedCalc software package was used (MedCalc, Inc., Mariakerke, Belgium).

Results

Demographic data

Demographic data are presented in Table 2. None of the cardiovascular risk factors differed between hemophilic patients and matched controls.

Table 1: The way to calculate left atrial stroke volumes and emptying fractions in each phases of left atrial function

	Reservoir	Conduit function	Active contraction
SV (ml)	Total SV=V_{max}–V_{min}	Passive SV=V_{max}–V_{preA}	Active SV=V_{preA}–V_{min}
EF (%)	Total EF=Total SV/V_{max}	Passive EF=Passive SV/V_{max}	Active EF=Active SV/V_{preA}

EF=Emptying fraction, SV=Stroke volume, V_{max}=Maximum left atrial volume, V_{min}=Minimum left atrial volume, V_{preA}=Left atrial volume before left atrial contraction

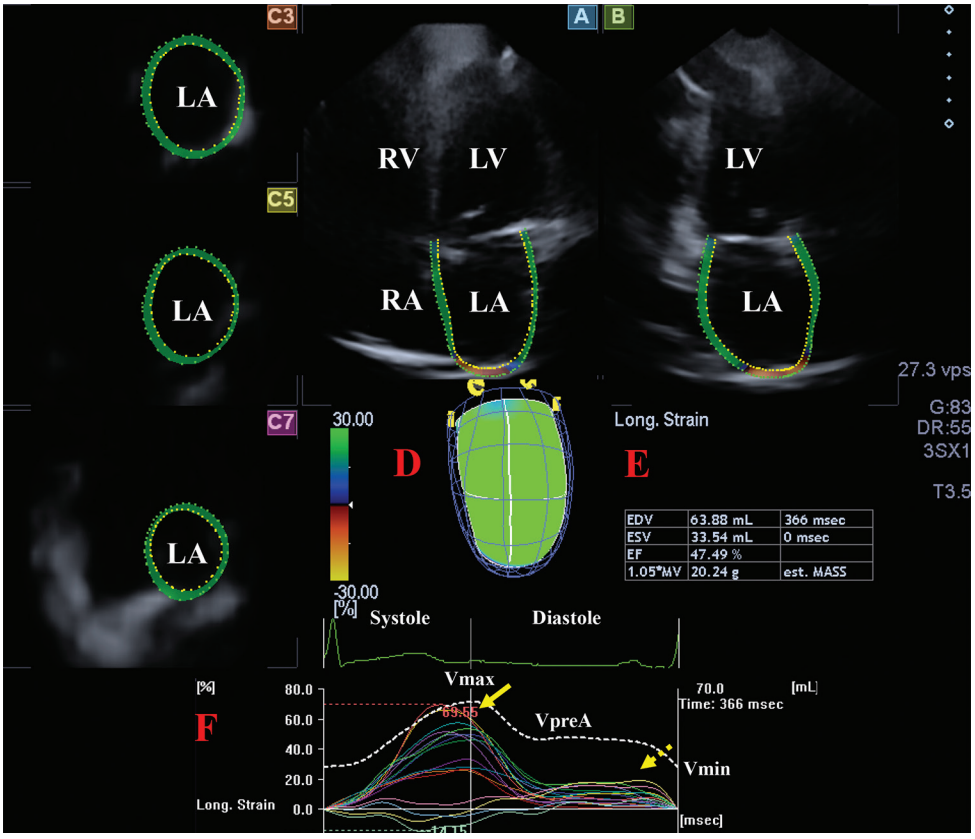

Figure 1: Three-dimensional speckle tracking echocardiographic left atrial (LA) analysis using a full-volume dataset in a healthy subject is demonstrated: (A) Apical four-chamber and (B) two-chamber views, short-axis views (C3) at basal, (C5) midatrial and (C7) superior LA levels are demonstrated with (D) a three-dimensional LA cast. (F) Time – global LA volume change (dashed line) and time – segmental LA longitudinal strain curves (coloured lines) with (E) calculated volumetric LA data are presented. Yellow arrow represents peak LA strains, while yellow dotted arrow represents LA strains at atrial contraction. LA= Left atrium, LV = Left ventricle, RA = Right atrium, RV = Right ventricle, EDV = End-diastolic volume, ESV = End-systolic volume, EF = Ejection fraction, V_{max} = Maximum LA volume, V_{preA} = Preatrial contraction LA volume, V_{min} = Minimum LA volume

Two-dimensional Doppler echocardiography

None of the routine 2D echocardiographic data differ between patients with hemophilia and controls [Table 2]. None of the patients and controls showed ≥grade 1 valvular regurgitations and had valvular stenoses.

Three-dimensional speckle-tracking echocardiography

LA volumes respecting cardiac cycle did not differ between controls and hemophilia patients. From LA volume-based functional properties, LA stroke volumes were similar between the groups examined in all phases of LA function. While total atrial emptying fraction featuring LA reservoir function was reduced in patients with hemophilia compared to that of controls, passive and active atrial emptying fraction characterizing LA conduit and booster pump functions were similar between the groups [Table 3]. From LA strains, peak mean segmental circumferential and longitudinal LA strains were impaired in patients with hemophilia, other peak LA strains were similar between the groups [Table 4]. From regional LA strains, only basal and midatrial LA-CSs were different between the groups [Table 5]. Global, mean segmental and regional LA strains at atrial contraction did not differ between groups of hemophilia patients and controls [Tables 6 and 7].

Discussion

The LA has a complex job during the cardiac cycle: works as a reservoir in systole, transitions blood from pulmonary veins into the LV as a conduit in early diastole, while behaves like a booster pump with active contraction in late

Table 2: Demographic and two-dimensional echocardiographic parameters of hemophilia patients and controls

	Controls (*n*=23)	Hemophilia patients (*n*=14)	*P*
Risk factors			
Age (years)	42.4±9.0	40.8±19.1	0.73
Male gender (%)	23 (100)	14 (100)	1.00
Hypertension (%)	1 (4)	2 (14)	0.54
Hyperlipidemia (%)	1 (4)	4 (29)	0.06
Diabetes mellitus (%)	1 (4)	3 (21)	0.14
2D echocardiography			
LA diameter (mm)	38.8±4.0	38.1±2.9	0.55
LV end-diastolic diameter (mm)	48.6±4.6	50.8±2.9	0.17
LV end-diastolic volume (ml)	106.8±27.0	121.7±18.1	0.06
LV end-systolic diameter (mm)	32.6±4.7	31.1±4.0	0.71
LV end-systolic volume (ml)	40.0±8.7	41.2±9.3	0.77
Interventricular septum (mm)	10.0±1.4	9.8±1.1	0.62
LV posterior wall (mm)	9.9±1.2	9.6±1.0	0.58
LV ejection fraction (%)	64.1±3.7	66.8±4.2	0.06

2D=Two-dimensional, LA=Left atrium, LV=Left ventricle

Table 3: Comparison of three-dimensional speckle-tracking echocardiography-derived volumetric left atrial parameters of hemophilia patients and controls

	Controls (*n*=23)	Hemophilia patients (*n*=14)
Left atrial volumes (ml)		
V_{max}	45.2±16.5	43.6±19.0
V_{min}	23.8±11.1	25.6±11.6
V_{preA}	33.8±15.2	35.0±16.9
Left atrial stroke volumes (ml)		
TASV	21.3±8.7	17.9±8.5
PASV	11.4±4.8	8.6±5.6
AASV	10.0±7.1	9.4±6.0
Left atrial emptying fractions (%)		
TAEF	47.9±12.7	41.1±8.8*
PAEF	26.5±11.4	20.3±13.1
AAEF	29.2±10.8	25.7±7.8

*P<0.05 versus controls. V_{max}=Maximum left atrial volume, V_{min}=Minimum left atrial volume, V_{preA}=Left atrial volume before atrial contraction, TASV=Total atrial stroke volume, PASV=Passive atrial stroke volume, AASV=Active atrial stroke volume, TAEF=Total atrial emptying fraction, PAEF=Passive atrial emptying fraction, AAEF=Active atrial emptying fraction

Table 4: Comparison of three-dimensional speckle-tracking echocardiography-derived peak global and mean segmental left atrial strain parameters in patients with hemophilia and controls

	Controls (*n*=23)	Hemophilia patients (*n*=14)
Global strains (%)		
Radial	−14.5±9.0	−11.5±11.5
Circumferential	28.3±13.5	21.2±9.6
Longitudinal	22.2±8.5	21.4±8.2
3D	−6.2±6.7	−6.4±6.2
Area	52.2±20.8	46.8±20.7
Mean segmental strains (%)		
Radial	−17.6±5.4	−12.1±10.2
Circumferential	32.6±12.5	23.9±9.4*
Longitudinal	26.1±7.2	21.4±5.7*
3D	−10.8±3.7	−7.7±8.8
Area	58.8±19.1	47.4±19.0

*P<0.05 versus controls. 3D=Three-dimensional

Table 5: Comparison of three-dimensional speckle-tracking echocardiography-derived peak regional left atrial strain parameters in patients with hemophilia and controls

Regional strains (%)	Controls (*n*=23)	Hemophilia patients (*n*=14)
RS_{basal}	−18.8±9.0	−19.1±10.3
$RS_{midatrial}$	−20.3±9.0	−16.9±8.7
$RS_{superior}$	−18.5±12.7	−16.8±12.0
CS_{basal}	39.6±16.3	26.3±6.9*
$CS_{midatrial}$	38.1±17.0	22.0±7.8*
$CS_{superior}$	33.2±20.6	32.5±22.4
LS_{basal}	16.5±7.3	19.0±8.6
$LS_{midatrial}$	36.5±13.3	31.0±12.7
$LS_{superior}$	25.6±14.7	18.5±9.6
$3DS_{basal}$	−13.0±8.4	−13.5±8.4
$3DS_{midatrial}$	−11.2±6.1	−10.0±5.8
$3DS_{superior}$	−10.4±7.9	−11.9±9.0
AS_{basal}	50.3±18.1	45.8±16.9
$AS_{midatrial}$	68.7±27.3	55.4±21.5
$AS_{superior}$	68.8±46.7	60.7±45.4

*P<0.05 versus controls. RS=Radial strain, CS=Circumferential strain, LS=Longitudinal strain, 3DS=Three-dimensional strain, AS=Area strain

diastole.[3,6,8] LA volumes and function have been shown to improve diagnostic accuracy and prognosis.[9] Thanks for recent improvements in non-invasive cardiovascular imaging, there is an opportunity of a detailed assessment of volumetric and functional abnormalities of the LA.[3,5,6,8] In recent studies, disease-related alterations of the LA have been suggested[6] ranging from mild abnormalities detected in young patients with type 1 diabetes mellitus[10] to severe abnormalities found in cardiac amyloidosis.[11] Most of the diseases show simultaneous dilation of LA volumes respecting cardiac cycle, which is accompanied with functional deteriorations up to all phases of LA function.[6] However, in some clinical scenarios (for instance in acromegaly), increased LA functions could be detected theoretically as a compensatory effect.[12] Due to missing clinical data of hemophilia-related changes in myocardial mechanics, to the best of the authors' knowledge, this is the first study to analyze LA volumetric and functional properties in a series of patients with hemophilia.

Table 6: Comparison of three-dimensional speckle-tracking echocardiography-derived global and segmental left atrial strain parameters at atrial contraction in patients with hemophilia and controls

	Controls (n=23)	Hemophilia patients (n=14)
Global strains (%)		
Radial	−4.2±4.5	−5.5±6.4.
Circumferential	12.7±8.6	13.1±5.8
Longitudinal	8.6±5.8	8.1±4.9
3D	−2.4±3.2	−2.9±7.1
Area	22.3±13.6	23.9±10.6
Mean segmental strains (%)		
Radial	−7.5±4.0	−6.3±7.6
Circumferential	13.8±7.6	11.8±5.4
Longitudinal	9.5±4.6	9.6±3.2
3D	−4.1±3.2	−3.7±6.5
Area	25.5±14.5	21.2±9.0

3D=Three-dimensional

Table 7: Comparison of three-dimensional speckle-tracking echocardiography-derived regional left atrial strain parameters at atrial contraction in patients with hemophilia and controls

Regional strains (%)	Controls (n=23)	Hemophilia patients (n=14)
RS_{basal}	−7.9±5.7	−10.5±6.2
$RS_{midatrial}$	−7.8±4.9	−10.1±5.0
$RS_{superior}$	−6.5±5.9	−7.9±9.3
CS_{basal}	16.2±8.0	13.6±6.4
$CS_{midatrial}$	12.0±8.1	10.7±5.3
$CS_{superior}$	13.3±11.3	15.2±10.4
LS_{basal}	7.4±2.9	8.3±3.6
$LS_{midatrial}$	11.0±7.2	12.6±5.9
$LS_{superior}$	10.3±8.5	9.5±6.2
$3DS_{basal}$	−4.7±4.9	−6.9±6.4
$3DS_{midatrial}$	−3.9±3.9	−6.1±4.5
$3DS_{superior}$	−3.4±5.5	−5.8±9.4
AS_{basal}	24.5±13.3	19.1±10.2
$AS_{midatrial}$	26.7±16.8	23.6±7.2
$AS_{superior}$	25.7±24.9	28.4±16.0

RS=Radial strain, CS=Circumferential strain, LS=Longitudinal strain, 3DS=Three-dimensional strain, AS=Area strain

The most important finding of the present study is that hemophilia is not associated with LA volumetric changes, but some mild LA functional abnormalities affecting LA reservoir function are present. The correct explanation of the above-mentioned LA abnormalities is not clear. These alterations were found to be present even though significant valvular regurgitation or stenosis could not be detected. It is known that the risk for coronary artery disease (CAD) is high and increasing.[13] Although patients in the present study did not undergo coronary angiography to exclude CAD, none of them showed any symptoms suspicious of CAD. Other explanations could be changes of LV mechanics and its effects on LA, which requires further detailed analysis. Moreover, aortic stiffness was found to be increased in hemophilia,[14] which shows a strong relationship with LV and LA mechanics even in healthy controls.[15,16] The role of cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and smoking) could also not be excluded. However, further studies are warranted to confirm our findings and to examine whether any prognostic impact exists.

Limitation section

Several important limitations have arisen during the study, which are listed below:

- The present study was designed to assess hemophilia-associated LA volumetric and functional abnormalities. It was not aimed to analyze similar parameters of other heart chambers, although 3DSTE is capable for detailed analysis of other chambers, as well[5]
- Low temporal and spatial resolutions are known technical limitations related to 3DSTE, which could also affect measurements[4,5]
- Mixed population of adult patients with hemophilia A and B with classic cardiovascular risk factors were involved in the study. It would have been better to study only hemophilia A or B separately, but it is considered to be a relatively rare disease[1,2]
- Standard therapy of factor replacement was anamnestically used in all cases.

Conclusions

Hemophilia is not associated with LA volumetric changes, but mild LA functional abnormalities are present.

Author contributions

Conceptualization, A. N.; Methodology, Á. K.; Software, Á. K.; Investigation, Á. K; Resources, I. M., K. V., Z. B.; Data Curation, Á. K.; Writing – Original Draft Preparation, A. N.; Writing – Review and Editing, A. N., Z. B.

Ethical clearance

The clinical study was approved by the Institutional and Regional Human Biomedical Research Committee at the University of Szeged (registration no. 71/2011 and updated versions).

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Conflicts of interest

There are no conflicts of interest.

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