Medizinische Klinik mit Schwerpunkt Kardiologie, Campus Virchow Klinikum

der Medizinischen Fakultät Charité - Universitätsmedizin Berlin

DISSERTATION

Biatrial function and mechanics in cystic fibrosis patients

Biatriale Funktion und Mechanik bei Patienten mit zystischer Fibrose

zur Erlangung des akademischen Grades

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1. List of abbreviations

2Ch – 2-chamber

2D – 2 dimensional

4Ch – 4-chamber

χ^2 – Chi-squared

A (in E/A) – late diastolic mitral flow

AF – atrial fibrillation

ANOVA – analysis of variance

BMI – body mass index

BSA – body surface area

CRT – cardiac resynchronization therapy

CV - cardiovascular

E- early diastolic mitral flow

e'- the average early diastolic flow velocity across the septal and lateral segments of mitral annulus

EF – ejection fraction

EKG - electrocardiography

FAC – fractional area change

FEV1 – forced expiratory volume in first second

FVC – forced vital capacity

CF – Cystic Fibrosis

CFTR – cystic fibrosis transmembrane conductance regulator

LA – left atrium

LAV – left atrial volume

LAVi – left atrial volume, indexed

LSD – least significant difference

LV- left ventricle

LVEF – left ventricular ejection fraction

MEF 25 – maximal expiratory flow at 25% of forced vital capacity

n – sample size

PAH – pulmonary artery hypertension

PAP – pulmonary artery pressure

ΔPhe508 – Deletion of phenylalanine on 508 place in gene

RA – right atrium

RAVi – right atrial volume, indexed

RV- right ventricle

RWT- relative wall thickness

STE – speckle tracking echocardiography

s' - systolic flow velocity across the lateral segment of tricuspid annulus

TAPSE – tricuspid annular plane systolic excursion

TDI – tissue Doppler imaging

TTE – transthoracic echocardiography

2. Abstract (English)

Background: The Cystic fibrosis (CF) is an autosomal recessive inherited disease. The mutation of the transmembrane conductance regulator gene causes the mucous to be more viscous. Due to the respiratory organ complications, changes in heart structure and function often occur. The right ventricle (RV) is frequently affected, but the left ventricle (LV) can be impaired as well. There are no data on atrial function and structure in this group of patients.

Aim: We investigated the left and right atrial function and mechanics in CF patients, and their predictive value regarding the mortality.

Methods: A total of 82 CF patients (18 of them died until the June 2019, and 64 survived, 2 Groups) and 32 healthy subjects, who underwent TTE between the October 2012 and December 2016, were included in this retrospective study. Patients with heart, liver, kidney, lung or malignant disease were excluded, as well as those with inadequate images (n=15). All non-echocardiographic parameters were gained from the subjects' histories. The echo-images assessment was performed "offline" on an EchoPAC 201 Program by a single blinded examiner. Statistical analysis was done in IBM SPSS 25.0 Program by applying adequate tests.

Results: The three groups did not differ in age and sex. Non-survivors had lower body mass index (BMI) than the other two groups. The control group had greater LV diameters, but the relative wall thickness (RWT) was greater in CF groups. The diastolic dysfunction was more frequent in CF non-survivor group than in others, whereas systolic function did not differ. LA volume index (LAVi), E/e' and E/A had significantly greater values in non-survivors. RV parameters was similar between the groups. The values of tricuspid annular plane systolic excursion (TAPSE) was reduced significantly in CF patient groups. CF patients had greater RAVi and PAP than the controls. The global LA strain (total, positive and negative) did not show any differences among the groups. The global LA early diastolic strain rate was diminished significantly in CF patients. The total strain and positive strain values in 4-chamber view were significantly decreased in the groups with patients, as was the LA early diastolic strain rate also. Strain and strain rate was without significance between the groups in 2-chamber view. The RA strain and strain rate parameters showed no difference. Two parameters were predictors of mortality in CF patients: LAVi and RAVi.

Conclusion: CF patients had larger atria, especially the non-survivors, than the controls. CF patients had decreased conduit and reservoir function. RA function did not differ from the controls. LAVi and RAVi were predictors of a fatal outcome. This work highlights the importance of the atrial assessment in CF patients.

3. Abstrakt (German)

Hintergrund: Die zystische Fibrose ist eine autosomal-rezessive vererbte Erkrankung. Die Mutation des transmembrane conductance regulator Gens verursacht den dickflüssigen Mukus. Aufgrund der respiratorischen Komplikationen, kann es zu Veränderungen in der Funktion und Struktur des Herzens vorkommen. Die rechte Kammer ist oft betroffen, aber auch die linke Kammer kann Veränderungen aufweisen. Es liegen in der Literatur keine Daten zur atrialen Funktion und Struktur bei diesen Patienten vor.

Ziel: Das Ziel der Arbeit ist die Einschätzung der linken und der rechten atrialen Funktion und Mechanik bei CF Patienten und dessen Wertes bezüglich der Mortalität.

Methoden: 82 CF Patienten (18 bis June 2019 gestorben und 64 überlebt, 2 Gruppen) und 32 Probanden, die einer TTE Untersuchung in Zeitspanne von Oktober 2012 und Dezember 2016 unterzogen wurden, wurden in der retrospektiven Studie eingeschlossen. Patienten mit Herz-, Leber-, Nieren-, Lungen- und Krebserkrankungen sowie jene mit inadäquaten Aufnahmen (n=15) wurden ausgeschlossen. Alle nicht-echokardiographischen Parameter wurden aus den Patientenakten erhoben. Die Auswertung der echokardiographischen Aufnahmen erfolgte „offline“ mittels EchoPAC 201 Programm, von einem verblindeten Untersucher. Statistische Analyse erfolgte mittels IBM SPSS 25.0 Programms und der entsprechenden Tests.

Ergebnisse: Die 3 Gruppen ähnelten sich im Alter und Geschlecht. Die nicht-überlebende Gruppe wies einen niedrigeren BMI als die anderen Gruppen auf. LV Diameter war größer in der Kontrollgruppe, aber RWT war niedriger. Diastolische Dysfunktion war häufiger in CF nicht-überlebende Gruppe als in den anderen zwei, aber hinsichtlich der systolischen Dysfunktion gab es keinen Unterschied. LAVi, E/e‘ und E/A waren höher in der nicht-überlebende Gruppe. RV Parameter zeigten keinen Unterschied zwischen den Gruppen, bis auf TAPSE, das kleiner in CF Gruppen war. RAVi und PAP waren größer bei CF Patienten als bei Kontrollen. Die globale LA Strain (total, positiv und negativ) zeigte keinen Unterschied zwischen den Gruppen. Die globale LA früh-diastolische Strain Rate war niedriger bei CF Patienten. Die totale und positive LA Strain und LA früh-diastolische Strain Rate im 4-Kammer Blick waren niedriger in CF Gruppen. Wir fanden keinen Unterschied in Strain und Strain Rate zwischen den Gruppen im 2-Kammer Blick und für den rechten Vorhof. 2 Parameter stellen prognostische Faktoren für die Mortalität bei CF Patienten dar: LAVi und RAVi.

Schlussfolgerung: Beide Vorhöfe sind größer bei CF Patienten, besonders bei nicht-überlebende als bei Kontrollen. LA conduit and reservoir Funktionen sind niedriger bei CF Patienten. RA Funktion ist ähnlich zwischen den Gruppen. LAVi und RAVi sind Prädiktoren der Mortalität. Unsere Arbeit betont die Signifikanz der atrialen Bewertung bei CF Patienten.

4. Background

4.1. Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive inherited disorder that affects the CF transmembrane conductance regulator gene, which is responsible for a chloride and bicarbonate transport through the cell membranes. Consequently, the mucous in lungs, digestive and reproductive system is more viscous. The most frequent mutation is ΔPhe508 deletion, causing a missfolding of CFTR protein.[1,2] Cystic fibrosis is the most common in Europe and North America with the prevalence of 0,737/10,000 and 0,797/10,000 respectively.[3]

The natural history of the disease in the 1950-ies was infaust, with most of the patients dying only a couple of months after birth due to a meconial ileus or malnutrition, whereas on autopsy reports, 70% of children and infants had chronic cor pulmonale.[2,4] An improvement in therapy and an early diagnosis resulted in an increased life expectancy of these patients, with around 50% chance of reaching 40 years nowadays.[2,5]It is expected, that in the 2025, 70% of all patients will be adults.[2]

4.2. 2D speckle tracking echocardiography: atrial phasic function

2D speckle tracking is a novel method used in echocardiography for evaluation of the mechanical properties of the myocardium. Small parts of the myocardium are marked by capturing the backscatter of the ultrasound, which are called speckles. Groups of them are tracked throughout the cardiac cycle. Their displacement from the initial position in the reference to the heart apex is defined as a strain. A strain rate measures an instantaneous rate of this change.[6] During the contraction and relaxation of the heart muscle, the strain gets negative and positive values respectively.[7]

The atrial function is best described through its 3 phases: reservoir, conduit and the booster pump function. The reservoir function is the ability of atria to store blood when the mitral valve is closed (during the contraction and isovolumetric phase of ventricle). The conduit function represents the passive phase of blood passing into the LV and is impaired when filling pressures are elevated. The LA active booster pump function corresponds to the contraction of the atria and their active contribution to the LV filling.[8]

A variety of methods are being used together to assess atrial and consequently, LV diastolic function. The 2D STE could complement them for more precision, or even be used alone. Depending on the EKG reference point (P or R wave), two types of the strain

curves can be generated. However, the consensus is yet to be made on which one should be used preferably.[8,9] In the paper of Rimbas et al, the P-P and R-R methods were compared. The conduit and reservoir functions had significantly different values depending on the triggering methods being used. The author arguments that the P-P triggering should be preferred as it corresponds more closely to the physiological atrial cycle.[10] (Figure 1.) (*Figure 1. is an original created entirely by the first author for the purpose of this dissertation, and was never published before)

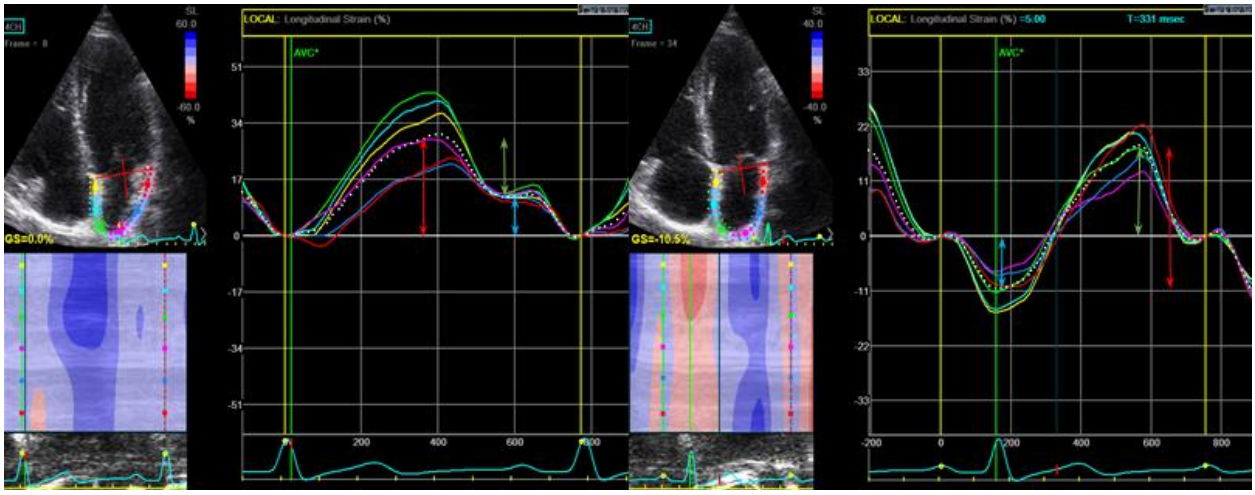

Figure 1. Left atrial strain analysis in the 4-chamber apical view after R-R triggering (left) and P-P triggering (right). Red arrows represent the reservoir atrial function. Green arrows represent the conduit function. Blue arrows show the atrial pump function

The advantage of the 2D STE is that it is angle independent, and less time-consuming in comparison to the TDI. On the other hand, a need for a high frame rate complicates the use of the 2D STE. Other challenges regarding the strain imaging are the complex atrial mechanics with regional differences and the need for a software adapted for atria.[7] Nonetheless, the first investigations of its utility in cardiovascular diseases have already commenced. Although still at the beginning, the research on predictive value of sinus rhythm maintenance after a cardioversion in AF patients [11] and a response to a CRT have already provided some positive results.[12]

4.3. Structure and function of RV and LV in patients with cystic fibrosis

The changes of structure and function in hearts of CF patients were already investigated, mostly in small studies, and on younger patients with a severe disease. The most common findings were an impaired RV systolic function and an elevated PAP. [13-16]

An increased anterior RV wall thickness was also reported.[17]A substantial number of CF patients with severe disease, used to die due to cardiac complications like acute cor pulmonale, before the advances in therapy have been made.[18]

On the other hand, LV function, expressed as LVEF, was usually preserved. Vizza et al reported that only 2% of the patients with an end-stage lung disease, due to CF, have impaired LVEF.[13,14,18]

4.4. 2D STE analysis in patients with cystic fibrosis

The evaluation of subclinical LV and RV dysfunction was made possible by implementation of the TDI and 2D STE in clinical practice. These methods are not as dependent as EF on the loading conditions.[19]

Subclinical RV dysfunction can be detected significantly earlier nowadays, even during the childhood.[17,19-21] Furthermore, a subclinical LV systolic dysfunction,[19,22,23] together with impaired LV diastolic parameters were reported.[22]

4.5. Atrial phasic function and volume as a prognostic factors

LA volume (LAV) is a well-known prognostic factor for mortality in patients with different CV diseases (ischemic heart disease, atrial fibrillation, pulmonary hypertension, heart failure)[10,24,25] Furthermore, LAV index (LAVi) is a prognostic factor for adverse CV events even in a general population.[10,26] Besides the fact that the atrial strain provides more information regarding the atrial function (reservoir, conduit and active) better than other methods, one should be aware of the fact that global longitudinal LA strain can be predictive of elevated LV filling pressure, which could be often seen in patients with LV diastolic dysfunction.[24]

The prognosis of patients with pulmonary artery hypertension, which is a common finding in CF patients[14] is shown to be worse in those patients with elevated RAVi, RA area or an impaired RA function determined by 2D STE.[27,28]

No data could be found on 2D STE in assessing LA and RA function in CF patients.

5. Aim

The aim of the doctoral thesis was to assess:

1. Differences in atrial phasic function between cystic fibrosis patients and healthy individuals.
2. Atrial phasic function among survivors and non-survivors CF patient, and compare it with healthy individuals
3. Predictors of an all-cause mortality in CF patients

6. Methods

6.1. Study design and population

The study was performed as a retrospective cross-sectional study, and was approved by the local Ethics Committee under the number (EA4/087/19). All subjects (n=114) enrolled into the study underwent transthoracic echocardiography as a clinically indicated examination in the period from October 2012 to December 2016. A total number of subjects consisted of 82 consecutive CF patients, and 32 healthy individuals.
After the initial examination, CF patients referred regularly for controls to a CF department.

The last update of our database, performed in June 2019, showed that 18 CF patients have died during this time, dividing the CF group into the two subgroups (survivors and non-survivors CF group).[29]

6.2. Inclusion and exclusion

In order to be involved into the study, CF patients had to have the diagnosis confirmed in their medical history, by either positive sweat chloride test or by a positive genetic testing on two known mutations typical for CF.

Healthy subjects in control group were individuals referred to an echocardiography examination for a regular check-up or for clarification of palpitations or a functional murmur. Subjects with known symptoms or signs of coronary artery disease, at least moderate valve heart disease, atrial fibrillation, congenital heart disease, liver or kidney failure, significant pulmonary disease or an active malignant disease were excluded from the study.

Due to inadequate images, 15 subjects were excluded.[29]

6.3. Anthropometric measures

Biometric parameters (height, weight) were obtained for the majority of the participants. Body mass index (BMI) and body surface area (BSA) were derived from them as well.[29]

6.4. Echocardiography measurements

Echocardiographic images of all of the subjects in the study were acquired on Vivid 7 (GE Vingmed, Horten, Norway) machine. Only one examiner performed the measurements, both standard and strain, in order to minimize inter-examiner variability.

They were done offline on the EchoPAC 201 (GE-Healthcare, Horten, Norway) software. Furthermore, the examiner was blinded to the origin of the images regarding the groups.[29]

6.5. LV ventricle

LV diameters, posterior wall, and septum thickness were measured, and the relative wall thickness was calculated using the formula recommended by American society of cardiology and the European association of cardiovascular imaging. Modified Simpson biplane method was used to determine the left ventricular ejection fraction. LV mass was calculated according to American Society for Echocardiography recommendations, and indexed for BSA.[29,30]

Transmitral LV flow was measured in 4-chamber view via pulsed-wave Doppler according to American Society for Echocardiography recommendations.[29,30]

LV myocardial velocities were obtained using Tissue Doppler imaging in the 4-chamber view, whereas sample volume was placed at the septal and lateral segments of the mitral annulus in an early diastole (e'). The mean value for the two velocities was derived and the E/e' ratio was calculated.[29]

6.6. Left atrial volume and function assessment

LA volumes (LAV) were obtained by using the biplane method in 4- and 2- chamber views, at the end-systole, after which it was indexed for BSA (LAVi).[29,30]

In our work, the P-P triggering was used to gain LA strain and LA strain rates.

They were measured in 4- and 2-chamber views.[31] After tracing LA endocardium manually, LA strains were acquired. LA peak strain rate was measured at the LV systolic phase, early LA strain rate during the early filling phase, and late LA strain rate in the late LV diastolic phase. A longitudinal strain curve, after P-P triggering consists of a negative deflection (negative strain) and a positive deflection (positive strain), whereas negative one represents an active contraction of LA, and positive one the conduit function. Total LA longitudinal strain was computed by adding the measured peaks of both deflections together, and represents the reservoir function. LA positive, negative and total strain were averaged from values obtained in 4-chamber and 2-chamber apical views to gain global positive, negative and total strain. (Figure 2.)[29] (*Figure 2. is an original created entirely by the first author for the purpose of this dissertation, and was never published before)

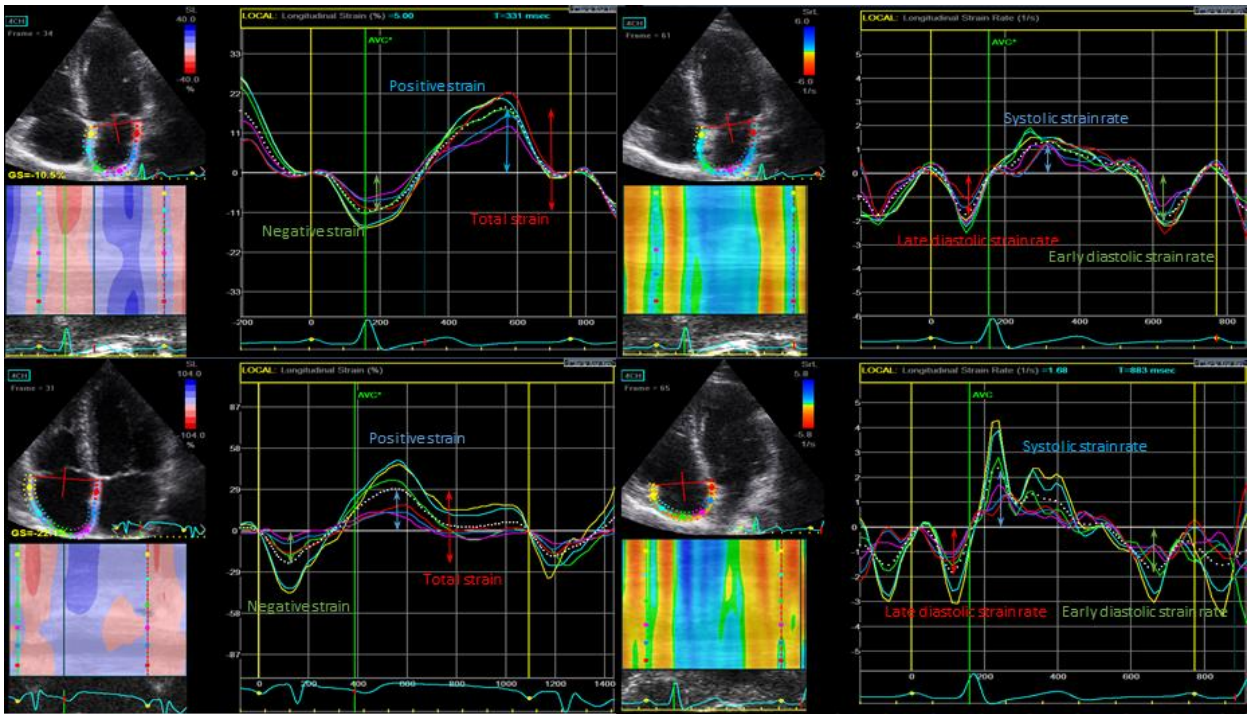

Figure 2. Left atrial strain analysis (upper left), Left atrial strain rate analysis (upper right), Right atrial strain analysis (lower left), Right atrial strain rate analysis (lower right)

6.7. Right ventricle

RV and atrium parameters were acquired in the apical 4-chamber view. RV global systolic function was measured in M-mode as the tricuspid annular plane systolic excursion (TAPSE). RV systolic blood pressure (PAPs) was measured indirectly in patients who had some degree of tricuspid regurgitation, by measuring the peak jet velocity.[29,32]

6.8. Right atrial volume and function assessment

RA volume was assessed similarly to LA volume, only in 4-chamber apical view, and latter indexed for BSA. RA strain and strain rates were measured by using the same methods as for the LA, after P-P triggering. (Figure 2.)[29]

6.10. Statistical analysis

Statistical analysis was done in IBM SPSS Statistics 25 program. All of the continuous variables, which had normal distribution, were presented as mean± standard deviation and were statistically tested with ANOVA. χ^2 test was used to compare counts and percentages. The groups were compared by using the LSD post-hoc analysis .In order to determine the predictors of mortality, a univariate and multivariate logistic regression analyses were applied. Variables that showed $p < 0.1$ in univariate logistic regression analysis, were analyzed with multivariate also, after which $p<0.05$ was considered significant.[29]

7. Results

7.1. Demographic parameters

No difference was found in age and sex among the groups (control, CF survivor and non-survivor group). Non- survivors had significantly lower BMI than the other groups. Diabetes mellitus was equally frequent in the CF groups. (Table 1.)[29]

Table 1. Demographic characteristics and clinical parameters of the study population.

	Controls (n=32)	**CF survivors (n=64)**	**CF non-survivors (n=18)**	**p**
Age (years)	36 ± 7	34 ± 11	34 ± 8	0.593
Female (%)	12 (38)	32 (50)	12 (67)	0.138
BMI (kg/m^2)	24.0 ± 3.3	19.9 ± 3.7 [b]	18.1 ± 2.1 [a,c]	<0.001
Diabetes (%)	0 (0)	27 (42)	9 (50)	0.372

BMI – body mass index, CF – cystic fibrosis,

a- p<0.01 for controls vs. CF non-survivors, b- p<0.01 for controls vs. CF survivors,

c – p<0.05 for CF survivors vs. CF non-survivors

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7.2. Left and Right ventricle dimensions and function

7.2.1. LV dimensions

The diameters of the left ventricle in the control group were significantly greater than in the groups with patients. Whereas, septal and posterior wall thickness showed no difference among the groups, the relative wall thickness was significantly higher in the both groups with patients than in the control group. However, LV mass index was without significant difference. (Table 2.)

7.2.2. Systolic and diastolic LV function

The groups did not differ in terms of ejection fraction.

LV diastolic dysfunction was more frequent in CF non-survivors than in the CF survivors and the controls. Specifically, E/e' and LAVi were significantly higher in non-

survivors, than in the other two groups, and E/A was higher in the CF patient groups than in the control group. On the other hand, mitral deceleration time was not different among the groups. (Table 2.)

7.2.3. RV structural and functional parameters

RV dimensions did not differ between the groups in terms of RV diameter and the RV areas. Only TAPSE showed the significantly lower values in the CF patient groups, whereas other RV systolic measures did not differ (FAC and systolic flow velocity of the lateral segment of tricuspid annulus).

CF patients had greater RAVi than the controls. No group had higher frequency of RA dilatation (RAVi> 25mL/m^2 for women and >26mL/m^2 for men).

PAP was higher in the groups with patients than the control group. Furthermore, pulmonary arterial hypertension was significantly more frequent in the non-survivor group, than in the other groups. (Table 3.)[29]

Table 2. Left ventricular echocardiographic parameters of the study population.

	Controls (n=32)	CF survivors (n=64)	CF non-survivors (n=18)	p
LV end-diastolic diameter (mm)	46.6 ± 0.5	41.2 ± 0.5 [b]	42.8 ± 0.6 [d]	<0.001
IVSd (mm)	9.0 ± 1.2	9.2 ± 1.6	9.3 ± 2.0	0.819
Posterior wall thickness (mm)	8.3 ± 1.9	8.9 ± 1.5	9.0 ± 2.0	0.300
Relative wall thickness	0.36 ± 0.08	0.43 ± 0.09 [b]	0.43 ± 0.1 [a]	<0.001
LV mass index (g/m^2)	71.7 ± 19.7	73.8 ± 21.5	84.1 ± 35.1	0.202
Ejection fraction (%)	64 ± 6	63 ± 8	60 ± 11	0.257
E/A ratio	1.7 ± 0.7	1.3 ± 0.4 [b]	1.2 ± 0.3 [a]	<0.001
Deceleration time (ms)	215 ± 74	198 ± 68	211 ± 65	0.543
E/e´	5.9 ± 1.4	7.0 ± 1.8	8.8 ± 3.1 [a,c]	<0.001
LV diastolic dysfunction (%)	3 (9)	7 (11)	8 (44) [a,e]	0.001
LA volume index (ml/m^2)	26.5 ± 5.3	26.6 ± 8.1	33.7 ± 10.5 [a,e]	0.004
LA dilatation (%)	1 (3)	9 (14)	10 (56) [a,e]	<0.001

A- late diastolic mitral flow (pulse Doppler), e´**-** the average early diastolic flow velocity across the septal and lateral segments of mitral annulus obtained by tissue Doppler, E- early diastolic mitral flow (pulse Doppler), LA-left atrial, LV – left ventricle, IVSd – Interventricular septum thickness in diastole, CF – cystic fibrosis

a- p<0.01 for controls vs. CF non-survivors, b- p<0.01 for controls vs. CF survivors, c – p<0.05 for CF survivors vs. CF non-survivors, d- p<0.05 for controls vs. CF survivors, e- p<0.01 for CF survivors vs. CF non-survivors, f- p<0.05 for controls vs. CF non- survivors

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Table 3. Right ventricular echocardiographic parameters of the study population.

	Controls (n=32)	CF survivors (n=64)	CF non-survivors (n=18)	p
RV basal diameter (mm)	32.0 ± 4.6	29.9 ± 4.9 [d]	29.6 ± 4.6	0.088
RV end-diastolic area (cm^2)	16 ± 4	14 ± 4 [d]	13 ± 3.5 [f]	0.048
RV end-systolic area (cm^2)	8.3 ± 2.5	7.6 ± 3.7	7.7 ± 3.6	0.686
Fractional area change (%)	48 ± 8	45 ± 10	47 ± 8	0.598
s' (cm/s)	12.6 ± 1.4	11.6 ± 2.7	11.0 ± 1.5	0.191
TAPSE (mm)	24 ± 4	20 ± 4 [b]	19 ± 3 [a]	<0.001
RA volume index (ml/m^2)	21.2 ± 5.5	23.1 ± 9.0 [d]	24.9 ± 11.8 [e]	0.010
RA dilatation (%)	5 (16)	11 (17)	7 (39)	0.096
PAPs (mmHg)	20 ± 7	31 ± 12 [b]	35 ± 10 [a]	<0.001
Pulmonary hypertension (%)	1 (3)	5 (8)	7 (39) [a,e]	<0.001

RA – right atrium, PAPs- systolic pulmonary pressure, RV- right ventricle, s'- systolic flow velocity across the lateral segment of tricuspid annulus, TAPSE-tricuspid annular plane systolic excursion, CF-cystic fibrosis.

a- p<0.01 for controls vs. CF non-survivors, b- p<0.01 for controls vs. CF survivors, c – p<0.05 for CF survivors vs. CF non-survivors, d- p<0.05 for controls vs. CF survivors, e- p<0.01 for CF survivors vs. CF non-survivors, f- p<0.05 for controls vs. CF non- survivors

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7.3. LA and RA strain parameters

The global values of LA strain (total, positive and negative) did not show any differences among the groups. When assessed for the global values of strain rate, the LA early diastolic strain rate was significantly lower in CF patients. (Table 4.)

However, total strain and positive strain in 4-chamber view were significantly lower in the groups with patients than in the control group, as well as the LA early diastolic strain rate. (Table 5.)

There was no difference in strain and strain rate parameters between the groups when they were assessed in 2-chamber view. (Table 5.)

The RA strain (total, positive and negative) and strain rate parameters were not different between the three groups. (Table 4.)[29]

Table 4. Global left and right atrial speckle tracking parameters.

	Controls (n=32)	CF survivors (n=64)	CF non-survivors (n=18)	p
Global LA speckle tracking parameters				
LA global strain (%)	38 ± 8	34 ± 9	33 ± 12	0.301
LA positive strain (%)	22 ± 8	19 ± 7	18 ± 8	0.228
LA negative strain (%)	15 ± 3	15 ± 5	15 ± 5	0.981
LA early diastolic strain rate (cm/s)	2.3 ± 0.7	1.9 ± 0.7 [d]	1.7 ± 0.9 [f]	0.047
LA late diastolic strain rate (cm/s)	2.3 ± 0.7	2.2 ± 0.9	2.0 ± 0.7	0.633
LA systolic strain rate (cm/s)	1.8 ± 0.4	1.9 ± 0.6	1.7 ± 0.5	0.638
Global RA speckle tracking parameters				
RA global strain (%)	38 ± 9	35 ± 13	35 ± 10	0.518
RA positive strain (%)	24 ± 8	21 ± 10	19 ± 7	0.251
RA negative strain (%)	14 ± 5	14 ± 6	16 ± 6	0.567
RA early diastolic strain rate (cm/s)	1.9 ± 0.6	1.7 ± 0.7	1.6 ± 0.7	0.528
RA late diastolic strain rate (cm/s)	2.1 ± 0.7	2.1 ± 0.9	2.6 ± 1.2	0.194
RA systolic strain rate (cm/s)	2.1 ± 0.6	2.1 ± 0.7	2.3 ± 0.9	0.672

LA –left atrium, RA – right atrium, CF – cystic fibrosis

a- $p<0.01$ for controls vs. CF non-survivors, b- $p<0.01$ for controls vs. CF survivors, d- $p<0.05$ for controls vs. CF survivors, f $p<0.05$ for controls vs. CF non- survivors

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Table 5. Left atrial speckle tracking parameters in 4-Chamber and 2-Chamber view.

	Controls (n=32)	CF survivors (n=64)	CF non-survivors (n=18)	p
4Ch LA speckle tracking parameters				
LA global strain (%)	38 ± 9	33 ± 10 [d]	30 ± 12 [f]	0.040
LA positive strain (%)	23 ± 9	19 ± 8 [d]	15 ± 7 [a]	0.014
LA negative strain (%)	15 ± 4	14 ± 6	15 ± 5	0.839
LA early diastolic strain rate (1/s)	2.5 ± 0.8	1.9 ± 0.8 [b]	1.6 ± 0.8 [a]	0.002
LA late diastolic strain rate (1/s)	2.1 ± 0.7	2.0 ± 0.9	1.9 ± 0.7	0.800
LA systolic strain rate (1/s)	1.7 ± 0.4	1.8 ± 0.8	1.6 ± 0.6	0.570
2Ch LA speckle tracking parameters				
LA global strain (%)	35 ± 7	34 ± 10	36 ± 12	0.544
LA positive strain (%)	20 ± 7	18 ± 8	21 ± 9.8	0.448
LA negative strain (%)	15 ± 4	16 ± 6	15 ± 5	0.998
LA early diastolic strain rate (1/s)	2.1 ± 0.7	1.8 ± 0.8	1.9 ± 0.9	0.398
LA late diastolic strain rate (1/s)	2.4 ± 0.9	2.4 ± 1.0	2.3 ± 0.8	0.876
LA systolic strain rate (1/s)	1.8 ± 0.5	1.9 ± 0.7	2.0 ± 0.6	0.831

2Ch- two chamber, 4Ch- four chamber, LA –left atrium, CF – cystic fibrosis

a- $p<0.01$ for controls vs. CF non-survivors, b- $p<0.01$ for controls vs. CF survivors, d- $p<0.05$ for controls vs. CF survivors, f $p<0.05$ for controls vs. CF non- survivors

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7.4. Predictors of mortality

Only two echocardiographic parameters, LAVI and RAVI, were recognized as predictors of mortality in CF patients. After adjusting for confounders, by multivariate analysis, their predictive value for mortality could not be shown. (Table 6.)[29]

Table 6. Predictors of mortality in patients with cystic fibrosis.

	Univariate		
	OR	**95% CI**	**p**
Age (years)	0.52	0.17 – 1.50	0.215
BMI (kg/m^2)	0.83	0.67 – 1.00	0.056
LV mass index (g/m^2)	1.01	0.99 – 1.03	0.153
LAVi (ml/m^2)	1.09	1.02 – 1.16	0.008
LA longitudinal strain in 4Ch (%)	0.97	0.92 – 1.03	0.362
LA early diastolic strain rate 4Ch (cm/s)	0.59	0.28 – 1.24	0.161
LA positive strain 4Ch (%)	0.95	0.88 – 1.02	0.149
TAPSE (mm)	0.94	0.80 – 1.09	0.400
PAPs (mmHg)	1.02	0.98 – 1.07	0.335
RAVi (ml/m^2)	1.10	1.02 – 1.18	0.020
RA longitudinal strain (%)	0.99	0.95 – 1.05	0.808

BMI – body mass index, LV – left ventricle, LA – left atrium, LAVI – left atrial volume index, RA – right atrium, RAVI - right atrial volume index, TAPSE-tricuspid annular plane systolic excursion, PAPs - systolic pulmonary pressure, 4Ch – four chamber view

Adapted with permission from Dordevic A, Genger M, Schwarz C, Cuspidi C, Tahirovic E, Pieske B, Düngen HD, Tadic M. Biatrial Remodeling in Patients with Cystic Fibrosis Running Title: Atrial Function in Cystic Fibrosis. J Clin Med 2019;8:e114.[29]

8. Discussion

The research on echocardiographic parameters in CF patients was focused mostly on RV for a long time, particularly on RV wall thickness, RV systolic function and PAP.[14,20,21,23] On the other hand, LV function and structure was rarely assessed and the authors mostly did not find any significant findings, regarding EF, and LV wall thickness.[14] Only recently, with the development of the novel echo techniques, LV changes, particularly diastolic dysfunction, were detectable.[22]

On the other hand, the importance of the LA and RA dimensions and function in CF patients is still not clear, as it was not investigated until now. Therefore, their assessment is usually being neglected in a routine clinical work. However, LA and RA dilatation and function were characterized as predictors of a worse outcome not only for patients with pulmonary hypertension, but in general population as well.[25,26,33]

As up to half of the CF patients have pulmonary hypertension diagnosed by catheter exam, it was rational to create the hypothesis of prognostic significance of the RA and LA assessment.[34,35]

8.1. RAVi and LAVi greater in CF, especially non-survivors

Our patients had a significantly larger RAVi than the controls. Nonetheless, non-survivors had significantly greater RAVi than the survivors did.[29]

Furthermore, the LAVi was significantly higher only in the non-survivor CF group when compared to CF survivor and to the control group. The LA dilatation was more frequent in the non-survivor than in the other two groups. The changes in LAVi, alongside with significantly increased parameters of diastolic dysfunction (E/e' and E/A ratios), could be an indicator of an increased LV filling pressure. An increased pulmonary pressures or an interventricular interdependence could cause these changes.[22,29]

Thus, a left heart should be a part of an echocardiographic evaluation of these patients, as it could provide information, which are important for the course of the disease.

8.2. LA conduit and reservoir function lower in CF

The CF patient groups had significantly lower LA conduit function (positive LA strain). Although, the groups were similar regarding the LA pump function (LA negative strains), the LA reservoir function (total LA strain) was significantly decreased in the groups with CF patients than the control group. This is most likely caused by the lower

conduit function. Despite the obvious drop of LA conduit and reservoir function towards the CF non-survivors, the statistical significance between the two CF patient groups was not reached, as the sample size was too low. The decreased LA conduit and reservoir functions in our patients could be an early indicator of the LV diastolic dysfunction, even when the traditional LV diastolic parameters were normal.[24,29,36]

However, the differences described above were noticed only in the 4-chamber view. Global values and values from the 2-chamber view were similar across the groups. This type of discrepancy in findings was described before in literature, where strain parameters of LV and RV were assessed. There, the significant differences in the strain values were found, when different ventricle segments were compared, although the global strains were similar between the groups.[20,37]

These results could be interpreted as the consequence of differences between the myocardial segments. However, it is more likely that it is due to a small sample size.

8.3. RA function in CF

We were not able to show that the right atrial function in the CF patients differs from the controls, even though the patients had significantly larger RA.[29] RA enlargement is, however, consistent with the findings of Sciatti et al.,[23] where it was expressed as an RA area. The enlargement occurs often in patients with pulmonary artery hypertension, as was the case with our groups, which can explain our findings of both elevated PAP and enlarged RA.[38]

8.4. Echocardiographic parameters as predictors of mortality

The research on predictive factors in patients with cystic fibrosis focused mostly on non-echocardiographic parameters, especially on lung function, which is directly affected by the disease. In literature, FVC and FEV1 are known predictors of a worse 3-year and 7 year prognosis, and are incorporated in some prognosis assessment scores for CF patients.[34,39]

In our study, the focus was on echocardiographic parameters, since there is only sparse data on the topic. LAVi and RAVi, but not the strain parameters were able to predict mortality in patients with CF, after the univariate analysis was done.[29] Interestingly, LAVi and RAVi were never investigated as prognostic factors in this group of patients, although they are shown to be prognostic factors of a worse prognosis in

patients with a variety of cardiovascular diseases, and even in the general population. [10,25]

Although we did not get a significant difference for PAP in our work, it was the most investigated echocardiographic prognostic factor of worse prognosis in literature. The data are however inconsistent, although the most of the authors reported positive results for prognosis. This holds true especially for the borderline values, which were the case in our study.[34,40] On the other hand, in the paper of Tonelli et al. no statistical significance was found for PAP as a predictor of mortality and a need for transplantation, although the trend existed.[35] The PAP in these studies was determined by both echocardiography and right side heart catheter.

Thus, the complete evaluation of heart by echocardiography, with more focus on atria, could be of importance for assessing the prognosis in these patients, but further studies on this topic are needed. One should at least perform a basic echocardiographic assessment of atrial volumina, which is easy and fast. If possible, strain assessment for better defining the atrial function is recommended.

9. Conclusions

1. CF patients have larger atria, than the controls, especially the non-survivors.
2. LA conduit and reservoir function in 4Ch view are decreased in CF patients.
3. RA phasic function do not differ from controls, despite the trend of worse function towards the non-survivors.
4. LAVi and RAVi are predictors of a fatal outcome, unlike the strain.

This work highlights the importance of biatrial function and mechanics assessment in the CF patients. However, larger studies are needed to elucidate the exact role of LA and RA function and mechanics, as well as strain parameters, regarding their prognostic value for mortality in patients with CF. These new prognostic factors (LAVi and RAVi) could be included into the novel risk score assessments of the CF patients who are at the higher risk for unfavorable outcome.

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11. Statutory Declaration

“I, Aleksandar Dordevic, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Biatrial function and mechanics in cystic fibrosis patients” and German “ Biatriale Funktion und Mechanik bei Patienten mit zystischer Fibrose”, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.
The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

12. Declaration of my own contribution to the publications

Aleksandar Dordevic contributed the following to the below listed publications:

Publication: Dordevic A, Genger M, Schwarz C, Cuspidi C, Tahirovic E, Pieske B, Düngen HD, Tadic M. Biatrial Remodeling in Patients with Cystic Fibrosis Running Title: Atrial Function in Cystic Fibrosis. J Clin Med 2019;8:e1141. doi: 10.33907jcm8081141

Contribution to the publication:
The literature search was done in Pubmed, where I was responsible for all the references that were included, besides the 3, 16, 21, 31-33. Data collection and the management of the database was done by me (Echo assessment of the images of all patients and gaining of their parameters from the medical history), after the tutoring and under supervision done by Ms. Tadic and Mr.Genger. Mr. Carsten Schwarz provided us with the list of potential subjects. Mentor (Marijana Tadic) did the statistical assessment, whereas we discussed it together along the way. Data interpretation was initially done by me, and was discussed with all other authors. The first draft was prepared by me and was being corrected along the way after the check-reading done by other authors. Figure 1 and Figure 2 were created by me, as well as the Table 1, Table 4 and 5.

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Signature, date and stamp of first supervising university professor / lecturer

_____
Signature of doctoral candidate

13. Journal Summary List (ISI Web of Knowledge SM)

15. Journal of Clinical Medicine, Impact Factor 2018: 5.688

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, GENERAL and INTERNAL"**
Selected Category Scheme: WoS
Gesamtanzahl: 160 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEW ENGLAND JOURNAL OF MEDICINE	344,581	70.670	0.686700
2	LANCET	247,292	59.102	0.427870
3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	156,350	51.273	0.300810
4	Nature Reviews Disease Primers	4,339	32.274	0.019740
5	BMJ-British Medical Journal	112,901	27.604	0.152760
6	JAMA Internal Medicine	15,215	20.768	0.095580
7	ANNALS OF INTERNAL MEDICINE	57,057	19.315	0.096020
8	PLOS MEDICINE	30,689	11.048	0.071200
9	Journal of Cachexia Sarcopenia and Muscle	2,799	10.754	0.005870
10	BMC Medicine	13,630	8.285	0.045220
11	Cochrane Database of Systematic Reviews	67,607	7.755	0.158690
12	MAYO CLINIC PROCEEDINGS	14,695	7.091	0.025750
13	CANADIAN MEDICAL ASSOCIATION JOURNAL	15,351	6.938	0.016500
14	JOURNAL OF INTERNAL MEDICINE	10,547	6.051	0.015700
15	Journal of Clinical Medicine	2,315	5.688	0.007210
16	MEDICAL JOURNAL OF AUSTRALIA	11,134	5.332	0.012600
17	PALLIATIVE MEDICINE	5,682	4.956	0.009860
18	AMYLOID-JOURNAL OF PROTEIN FOLDING DISORDERS	1,335	4.919	0.003270

14. Publication

Publication: Dordevic A, Genger M, Schwarz C, Cuspidi C, Tahirovic E, Pieske B, Düngen HD, Tadic M. Biatrial Remodeling in Patients with Cystic Fibrosis Running Title: Atrial Function in Cystic Fibrosis. J Clin Med 2019;8:e1141. doi: 10.33907jcm8081141
Impact Factor 2018: 5.688

Journal of
Clinical Medicine

MDPI

Article

Biatrial Remodeling in Patients with Cystic Fibrosis Running Title: Atrial Function in Cystic Fibrosis

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Abstract: Background: Previous studies have focused on left and right ventricular remodeling in cystic fibrosis (CF), whereas atrial function has not been assessed in detail so far. We sought to investigate left and right atrial (LA and RA) function in patients with CF. Methods: This retrospective investigation included 82 CF patients (64 survivors and 18 non-survivors) who were referred to CF department over the period of four years, as well as 32 control subjects matched by age and gender. All participants underwent an echocardiographic examination including a strain analysis, which was performed offline and blinded for groups. Results: LA and RA volume indexes were significantly higher in

CF patients than in controls and were particularly high in CF non-survivors. LA conduit and reservoir functions were significantly worse in CF survivors and non-survivors, compared with control subjects. RA phasic function was not different between controls, CF survivors and non-survivors. The parameters of lung function (forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1)) and the LA and RA volume indexes were predictors of mortality in CF patients. However, in a multivariate analysis, only FVC was an independent predictor of mortality in CF patients. Conclusions: Our results suggest that both atria are enlarged, but only LA function is impaired in CF patients. LA reservoir and conduit function is particularly deteriorated in CF patients. Though statistical significance was not reached due to our limited sample size, there was a trend of deterioration of LA and RA function from controls across CF survivors to CF non-survivors. LA and RA enlargement represented predictors of mortality in CF patients.

Keywords: cystic fibrosis; left atrium; right atrium; function; strain

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1. Introduction

Cystic fibrosis (CF) is the most frequent life-threatening autosomal recessive disease in the Caucasian race, occurring in 1 out of 2500 newborns. CF is caused by almost 2000 various mutations of the CF transmembrane conductance regulator gene, located on the seventh chromosome. Previously, chronic corpulmonale was present in 70% of infants and children dying from CF [1]. However, the natural history of CF has been dramatically changed in the last few decades, the prognosis of these patients has been significantly improved, and lifespan has been significantly prolonged.

Studies conducted in the CF population have reported significant heart remodeling and, particularly, right ventricular (RV) hypertrophy and dysfunction in the advanced stages of disease [2–6]. These changes are usually connected with increased pulmonary pressure that develops because of increased stiffness in pulmonary circulation, which is the result of hypertrophy and hyperplasia of the

arterial media [3,7–9]. The introduction of new echocardiographic methods such as tissue Doppler imaging improved the diagnosis of subclinical cardiac dysfunction even in

patients with mild CF [10]. Nevertheless, the adoption of strain in everyday clinical practice has enabled the detection of subtle cardiac changes in mechanics, which was not previously possible. Several studies have been published on this topic, and there has been no agreement regarding the influence of CF on left ventricular (LV) and RV mechanics [11–15]. These investigations have been mainly focused on the RV, but they have also demonstrated subtle LV strain changes [13,15]. However, there are still many inconsistencies that need to be resolved.

Atrial remodeling is usually underestimated and neglected in patients with various cardiovascular diseases. However, left atrial (LA) enlargement and dysfunction is related with both cardiovascular and overall mortality [16]. Right atrial (RA) function has been proven to be an important predictor of outcome in patients with pulmonary hypertension [17], which is common in the CF population. There are no data regarding atrial function in CF patients, and these data potentially could explain LV and RV diastolic dysfunction and the development of cardiac-related symptoms.

The aim of the present study was to evaluate LA and RA phasic function using the strain method in CF patients. Additionally, we sought to investigate if LA and RA function and volume represent predictors of lethal outcome in CF patients.

2. Methodology

This is a retrospective study that involved 82 consecutive CF patients who were referred to the CF department in the period between October 2012 and December 2016. The diagnosis of CF was confirmed via a documented positive sweat chloride test or by the identification of two genetic mutations known to cause CF. Controls were recruited from the echocardiography department among the patients who were referred to a regular check-up examination, palpitations or innocent heart murmur. Control subjects were matched with the CF group by age and gender. Patients with symptoms or signs of coronary artery disease, valve heart disease more than mild, atrial fibrillation, congenital heart disease, liver or kidney failure were excluded from this study. All study participants underwent an echocardiographic examination, and one researcher (AD) performed an offline strain analysis. This investigator was blinded to which group study participant belonged (control, CF survivors and CF non-survivors). All CF patients had spirometry before their echocardiographic examination. Patients
with inadequate echocardiographic images were excluded (n = 15).

All CF patients had regular follow-up examinations at the CF department. Our records showed that 64 CF were alive and 18 CF patients died until June 2019, when the last check-up of our database
was performed.
Anthropometric measures (height, weight) and laboratory analyses (level of fasting glucose, serum creatinine and urea) were obtained from all the participants. Body mass index (BMI) and body surface area (BSA) were calculated for each subject. The study was approved by the local ethics committee.

2.1. Echocardiography

Echocardiographic examinations were performed by a Vivid 7 (GE Vingmed, Horten, Norway) ultrasound machine. LV diameters, posterior wall and septum thickness were measured, and relative wall thickness was calculated according to the current recommendations [18]. The LV ejection fraction (EF) was calculated by using the modified Simpson biplane method. LV mass was calculated by using the American Society for Echocardiography formula [18] and indexed for BSA.

A pulsed-wave Doppler evaluation of transmitral LV was obtained in the apical 4-chamber view according to guidelines [19]. Tissue Doppler imaging was used to get LV myocardial velocities in the apical 4-chamber view, with a sample volume placed at the septal and lateral segments of the mitral annulus during early diastole (e'). The average of the peak early diastolic relaxation velocity (e') of the septal and lateral mitral annulus was obtained, and the E/e' ratio was computed.

2.2. Assessment of Left Atrial Volumes and Strain

LA volumes (LAVs) were measured just before the mitral valve opening. The LA volume was determined according to the biplane method in the 4-and 2-chamber views, and it was indexed for BSA (left atrial volume index—LAVI) [18].
2D LA strain imaging was performed in the apical 4- and 2-chamber views [20], and commercially available software Echo PAC 201 (GE-Healthcare, Horten, Norway) was used for the offline 2D strain analysis. LA strain and strain rates were calculated by P-P triggering (Figure 1). Namely, there are two methods for evaluation of LA strain: R-R and P-P triggering and we decided to use P-P triggering [20]. The LA endocardium was manually traced. LA peak strain rate was measured at the LV systolic phase, while early and late LA strain rates were measured during early LV filling and throughout the late LV diastolic phase, respectively. An average longitudinal strain curve was automatically

generated, and it included a negative deflection (LA negative longitudinal strain) representing LA active contraction, followed by a positive one during LA filling (LA positive longitudinal strain). Their summation represented the total LA longitudinal strain. LA strains (positive, negative and total) were calculated by averaging the values obtained in the 4-and 2-chamber apical views.

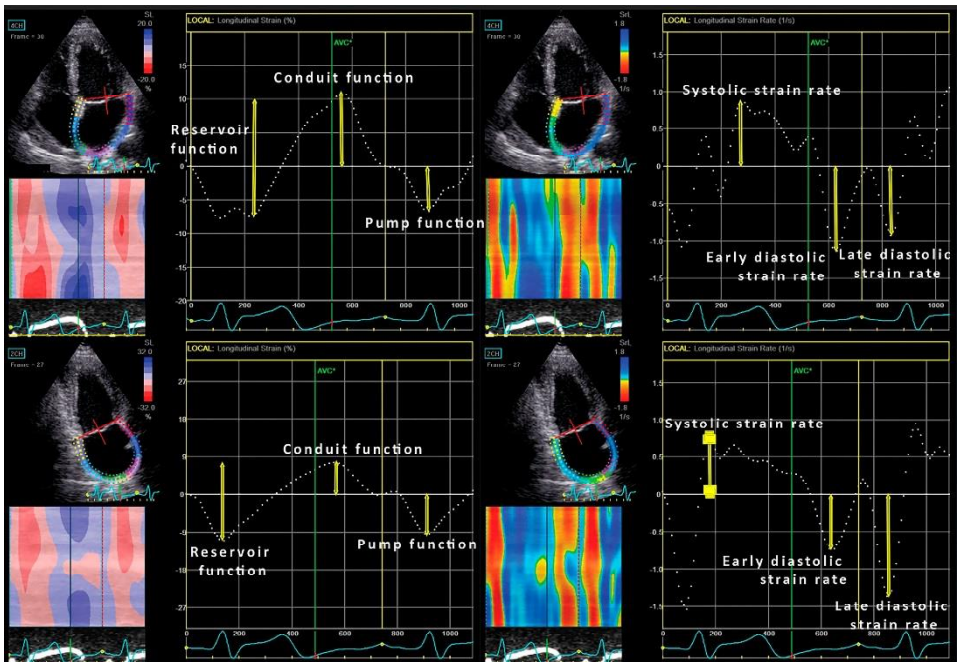

Figure 1. Left atrial strain and strain rate analysis in the four-chamber view (upper two plots, consequently) and in the two-chamber view (lower two plots, consequently).

2.3. Right Ventricle and Atrium

The RV internal diameter was measured in the apical four-chamber view [21]. RV global systolic function was assessed as the tricuspid annular plane systolic excursion (TAPSE) [21]. RV systolic blood pressure (PAPs) was assessed in patients with minimal/mild tricuspid regurgitation.

2.4. D Assessment of Right Atrial Volumes and Function

RA volume was evaluated just before the tricuspid valve opening and indexed for BSA [4]. RA strain and strain rates were calculated by P-P triggering using the same methods that were described in the section regarding LA strain assessment (Figure 2) [21].

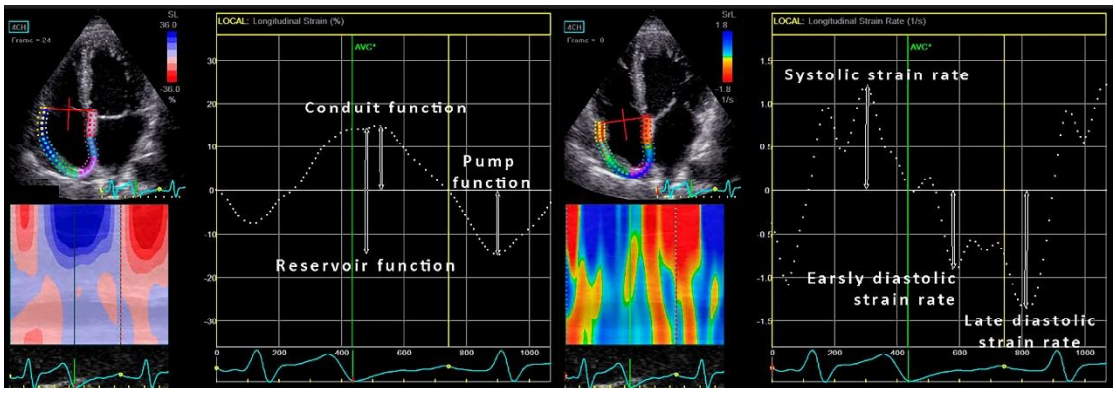

Figure 2. Right atrial strain and strain rate analysis in the four-chamber view.

2.5. Statistical Analysis

Continuous variables are presented as mean ± standard deviation, showed a normal distribution, and were compared by the analysis of equal variance (ANOVA). An LSD post hoc analysis was used for the comparison between different groups. Differences in proportions were compared by the χ^2 test. Univariate and multivariate logistic regression analyses were used for the determination of predictors of mortality in the CF patients. A multivariate logistic regression analysis included variables that showed p <0.1 in the univariate logistic regression analysis. The p-value <0.05 was considered statistically significant.

3. Results

There was no significant difference in age and sex distribution between controls, CF survivors and CF non-survivors (Table 1). BMI was significantly lower in non-survivors than in controls and CF survivors. There was no difference in the prevalence in diabetes between CF survivors and CF non-survivors (Table 1). Urea and serum creatinine levels were significantly higher in CF non-survivors than in the other two groups (Table 1). The fasting glucose level was higher in CF survivors and non-survivors than in controls (Table 1). Forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were significantly lower in CF non-survivors than CF survivors (Table 1).

Table 1. Demographic characteristics and clinical parameters of the study population.

	Controls (*n*= 32)	CF Survivors (*n*= 64)	CF Non-Survivors (*n*= 18)	*p*
Age (years)	36 ± 7	34 ± 11	34 ± 8	0.593
Female (%)	12 (38)	32 (50)	12 (67)	0.138
BMI (kg/m^2)	24.0 ± 3.3	19.9 ± 3.7 [b]	18.1 ± 2.1 [a,c]	<0.001

Plasma glucose (mg/dL)	87 ± 13	133 ± 28 [b]	146 ± 35 [d]	0.011
Diabetes (%)	0 (0)	27 (42)	9 (50)	0.372
Urea (mg/dL)	26 ± 6	30 ± 7	44 ± 8 [a,c]	0.007
Serum creatinine (mg/dL)	0.87 ± 0.18	0.87 ± 0.28	1.33 ± 0.54 [c,d]	0.066
FVC (%)	-	63 ± 21	43 ± 17	<0.001
FEV1 (%)	-	45 ± 21	33 ± 13	0.033
MEF 25 (%)	-	21 ± 11	14 ± 7	0.310

BMI—body mass index, CF—cystic fibrosis, FVC—forced vital capacity, FEV1—forced expiratory volume in the first second, MEF 25—mean expiratory flow at 25% of the vital capacity. a—*p* <0.01 for controls vs. CF non-survivors, b—*p* <0.01 for controls vs. CF survivors, c—*p* <0.05 for CF survivors vs. CF non-survivors, d—*p* <0.05 for controls vs. CF non-survivors.

3.1. Left and Right Ventricle

Left ventricular diameter was significantly higher in the control group than in the two CF groups

(Table 2). Interventricular and posterior wall thickness did not differ between the three observed groups (Table 2). Therefore, relative wall thickness was significantly higher in the CF groups than in controls (Table 2). There was no difference in the LV mass index and the ejection fraction between the three groups. The mitral E/A ratio was lower in CF patients than in controls. Mitral E/e' was higher in non-survivors than in controls and survivors (Table 2). Mitral deceleration time was similar between the groups (Table 2). The LA volume index was significantly higher in CF non-survivors than in controls and CF survivors (Table 2). LA dilatation (LAVI >34 mL/m^2) was significantly higher in CF non-survivors than in controls and CF survivors (Table 2). LV diastolic dysfunction prevalence was higher in CF non-survivors than in controls and CF survivors (Table 2).

Table 2. Echocardiographic parameters of the study population.

	Controls (*n*= 32)	**Cystic Fibrosis Survivors (*n*= 64)**	**Cystic Fibrosis Non-Survivors (*n*= 18)**	***p***
LV parameters				
LV end-diastolic diameter (mm)	46.6 ± 0.5	41.2 ± 0.5 [b]	42.8 ± 0.6 [d]	<0.001
Interventricularseptumthickness (mm)	9.0 ± 1.2	9.2 ± 1.6	9.3 ± 2.0	0.819
Posterior wall thickness (mm)	8.3 ± 1.9	8.9 ± 1.5	9.0 ± 2.0	0.300
Relative wall thickness	0.36 ± 0.08	0.43 ± 0.09 [b]	0.43 ± 0.1 [a]	<0.001

LV mass index (g/m^2)	71.7 ± 19.7	73.8 ± 21.5	84.1 ± 35.1	0.202
Ejectionfraction (%)	64 ± 6	63 ± 8	60 ± 11	0.257
E/A ratio	1.7 ± 0.7	1.3 ± 0.4 [b]	1.2 ± 0.3 [a]	<0.001
Deceleration time (ms)	215 ± 74	198 ± 68	211 ± 65	0.543
E/e'	5.9 ± 1.4	7.0 ± 1.8	8.8 ± 3.1 [a,c]	<0.001
LV diastolicdysfunction (%)	3 (9)	7 (11)	8 (44) [a,e]	0.001
LA volume index (mL/m^2)	26.5 ± 5.3	26.6 ± 8.1	33.7 ± 10.5 [a,e]	0.004
LA dilatation (%)	1 (3)	9 (14)	10 (56) [a,e]	<0.001
RV parameters				
RV basal diameter (mm)	32.0 ± 4.6	29.9 ± 4.9 [d]	29.6 ± 4.6	0.088
RV end-diastolic area (cm^2)	16 ± 4	14 ± 4 [d]	13 ± 3.5 [f]	0.048
RV end-systolic area (cm^2)	8.3 ± 2.5	7.6 ± 3.7	7.7 ± 3.6	0.686
Fractionalareachange (%)	48 ± 8	45 ± 10	47 ± 8	0.598
s' (cm/s)	12.6 ± 1.4	11.6 ± 2.7	11.0 ± 1.5	0.191
TAPSE (mm)	24 ± 4	20 ± 4 [b]	19 ± 3 [a]	<0.001
RA volume index (mL/m^2)	21.2 ± 5.5	23.1 ± 9.0 [d]	24.9 ± 11.8 [e]	0.010
RA dilatation (%)	5 (16)	11 (17)	7 (39)	0.096
PAPs (mmHg)	20 ± 7	31 ± 12 [b]	35 ± 10 [a]	<0.001
Pulmonaryhypertension (%)	1 (3)	5 (8)	7 (39) [a,e]	<0.001

A—late diastolic mitral flow (pulse Doppler), e'—the average early diastolic flow velocity across the septal and lateral segments of mitral annulus obtained by tissue Doppler, E—early diastolic mitral flow (pulse Doppler), LA—left atrial, LVEDD—left ventricle end-diastolic dimension, PAPs—systolic pulmonary pressure, RWT—relative wall thickness, LVMI—left ventricle mass index, RV—right ventricle, s'-systolic flow velocity across the lateral segment of tricuspid annulus, TAPSE—tricuspid annular plane systolic excursion. a—*p* <0.01 for controls vs. CF non-survivors, b—*p* <0.01 for controls vs. CF survivors, c—*p* <0.05 for CF survivors vs. CF non-survivors, d—*p* <0.05 for controls vs. CF survivors, e—*p* <0.01 for CF survivors vs. CF non-survivors, f—*p* <0.05 for. controls vs. CF non-survivors.

RV diameter and areas were similar between controls and CF patients (Table 2). The parameters of RV systolic function-FAC and systolic flow velocity across the lateral segment of tricuspid annulus (s') did not differ between CF patients and controls, whereas TAPSE was significantly lower in CF survivors and non-survivors (Table 2). The RA volume index was higher in CF patients than in controls (Table 2). There was no difference in the prevalence of RA dilatation (right atrial volume index (RAVI) >25 mL/m^2 for women and >26 mL/m^2) between controls and CF patients (Table 2). PAPs was also higher in survivors and non-survivors than in controls. Pulmonary hypertension was

significantly more prevalent in CF non-survivors than in CF survivors and controls (Table 2).

3.2. LA and RA Strain Parameters

There was no difference in LA speckle tracking parameters between groups when global values of LA strain (average of four chamber (4Ch) and two chamber (2Ch)) were evaluated (Table 3). Different results were obtained when the LA strain was separately assessed in the 4Ch and 2Ch views. The LA positive strain measured in 4Ch, which corresponds with LA conduit function, was significantly lower in CF survivors and non-survivors (Table 3). There was no difference in the LA negative strain, which corresponds with LA active pump function (Table 3). The total LA strain and early diastolic strain rate that represent LA reservoir function were also significantly lower in CF survivors and non-survivors than in controls (Table 3). Late diastolic strain and systolic strain rates were not different among the three groups (Table 3). There was no significant difference in LA speckle tracking parameters when they were analyzed—this difference was only present in 2Ch (Table 3).

Table 3. Left atrial speckle tracking parameters.

	Controls (*n*= 32)	Cystic Fibrosis Survivors (*n*= 64)	Cystic Fibrosis Non-Survivors (*n*= 18)	*p*
	Global LA speckle tracking parameters			
LA global strain (%)	38 ± 8	34 ± 9	33 ± 12	0.301
LA positive strain (%)	22 ± 8	19 ± 7	18 ± 8	0.228
LA negative strain (%)	15 ± 3	15 ± 5	15 ± 5	0.981
LA early diastolic strain rate (cm/s)	2.3 ± 0.7	1.9 ± 0.7 [d]	1.7 ± 0.9 [f]	0.047
LA late diastolic strain rate (cm/s)	2.3 ± 0.7	2.2 ± 0.9	2.0 ± 0.7	0.633
LA systolic strain rate (cm/s)	1.8 ± 0.4	1.9 ± 0.6	1.7 ± 0.5	0.638
	4Ch LA speckle tracking parameters			
LA global strain (%)	38 ± 9	33 ± 10 [d]	30 ± 12 [f]	0.040
LA positive strain (%)	23 ± 9	19 ± 8 [d]	15 ± 7 [a]	0.014
LA negative strain (%)	15 ± 4	14 ± 6	15 ± 5	0.839
LA early diastolic strain rate (1/s)	2.5 ± 0.8	1.9 ± 0.8 [b]	1.6 ± 0.8 [a]	0.002
LA late diastolic strain rate (1/s)	2.1 ± 0.7	2.0 ± 0.9	1.9 ± 0.7	0.800

LA systolic strain rate (1/s)	1.7 ± 0.4	1.8 ± 0.8	1.6 ± 0.6	0.570
2Ch LA speckle tracking parameters				
LA global strain (%)	35 ± 7	34 ± 10	36 ± 12	0.544
LA positive strain (%)	20 ± 7	18 ± 8	21 ± 9.8	0.448
LA negative strain (%)	15 ± 4	16 ± 6	15 ± 5	0.998
LA early diastolic strain rate (1/s)	2.1 ± 0.7	1.8 ± 0.8	1.9 ± 0.9	0.398
LA late diastolic strain rate (1/s)	2.4 ± 0.9	2.4 ± 1.0	2.3 ± 0.8	0.876
LA systolic strain rate (1/s)	1.8 ± 0.5	1.9 ± 0.7	2.0 ± 0.6	0.831

2Ch—two chamber, 4Ch—four chamber, LA—left atrium. a—p <0.01 for controls vs. CF non-survivors, b—p <0.01 for controls vs. CF survivors, d—p <0.05 for controls vs. CF survivors, f—p <0.05 for controls vs. CF non-survivors.

The RA strains (total, positive and negative) and strain rates were similar between controls, CF survivors and CF non-survivors (Table 4).

Table 4. Right atrial speckle tracking parameters.

	Controls (*n*= 32)	**CysticFibrosisSurvivors (*n*= 64)**	**Cystic Fibrosis Non-Survivors (*n*= 18)**	***p***
RA global strain (%)	38 ± 9	35 ± 13	35 ± 10	0.518
RA positive strain (%)	24 ± 8	21 ± 10	19 ± 7	0.251
RA negative strain (%)	14 ± 5	14 ± 6	16 ± 6	0.567
RA early diastolic strain rate (cm/s)	1.9 ± 0.6	1.7 ± 0.7	1.6 ± 0.7	0.528
RA late diastolic strain rate (cm/s)	2.1 ± 0.7	2.1 ± 0.9	2.6 ± 1.2	0.194
RA systolic strain rate (cm/s)	2.1 ± 0.6	2.1 ± 0.7	2.3 ± 0.9	0.672

CF—cystic fibrosis, RA—right atrium.

3.3. Predictors of Mortality

Parameters of lung function (FVC and FEV1), the LA and RA volume indexes were predictors of mortality in CF patients (Table 5). PAPs was not a predictor of mortality in CF patients. However, in the multivariate analysis that included BMI, FVC, LAVI and RAVI, only FVC was an independent predictor of mortality in CF patients (OR 0.94, 95%CI: 0.90–0.98, p = 0.004).

Table 5. Predictors of mortality in patients with cystic fibrosis.

	Univariate		
	OR	**95% CI**	***p***

Age (years)	0.52	0.17–1.50	0.215
BMI (kg/m^2)	0.83	0.67–1.00	0.056
FVC (%)	0.94	0.91–0.98	0.001
FEV1 (%)	0.96	0.93–0.99	0.042
LV mass index (g/m^2)	1.01	0.99–1.03	0.153
LAVI (mL/m^2)	1.09	1.02–1.16	0.008
LA longitudinal strain in 4Ch (%)	0.97	0.92–1.03	0.362
LA early diastolic strain rate 4Ch (cm/s)	0.59	0.28–1.24	0.161
LA positive strain 4Ch (%)	0.95	0.88–1.02	0.149
TAPSE (mm)	0.94	0.80–1.09	0.400
PAPs (mmHg)	1.02	0.98–1.07	0.335
RAVI (mL/m^2)	1.10	1.02–1.18	0.020
RA longitudinal strain (%)	0.99	0.95–1.05	0.808

BMI—body mass index, FVC—forced vital capacity, LA—left atrium, LAVI—left atrial volume index, RA—right atrium, RAVI—right atrial volume index, TAPSE—tricuspid annular plane systolic excursion.

4. Discussion

Our investigation provided several important findings: (i) Both atria were significantly enlarged in CF patients—particularly in CF non-survivors; (ii) LA conduit and reservoir functions were significantly lower in CF survivors and non-survivors than in controls; (iii) RA function was not impaired in CF patients; (iv) the atrial volume indexes (LAVI and RAVI) were predictors of mortality in CF patients.

Most investigations about CF performed in the last three decades have been focused on RV structure, RV function, and, more recently, RV mechanics [10,12,14]. LV remodeling became an interesting topic only when an echocardiographic technique developed enough to provide information other than the LV diameters and the ejection fraction. Nevertheless, LA and RA size and function have not been considered as important in CF patients. Considering the fact that bi-atrial enlargement and function are predictors of outcome in both the general population and in patients with pulmonary hypertension [16,17], it would be reasonable to hypothesize that LA and RA remodeling is also present in CF patients. A similar study has not been previously performed, and there are no data regarding atrial function and its influence on survival in CF patients.

Our findings revealed significant LA and RA enlargement in CF patients. Namely, LA and RA volumes gradually increased from controls, across CF survivors to CF non-survivors. Interestingly, LA dilatation was a bit more pronounced than RA dilatation, and in CF non-survivors, the LA volume index (33.7 ± 10.5 mL/m^2) was almost equal to the cut-off value for LA dilatation in the general population (≥ 34 mL/m^2). This shows that left heart must

not be forgotten in the assessment of CF patients, and this evaluation cannot be based solely on the calculation of the LV ejection fraction. LA dilatation in our CF patients was associated with a significant increase in the mitral E/e' ratio and a decrease in the mitral E/A ratio. Both parameters are associated with an increased LV filling pressure that could be explained by an increased LV preload, a low pulmonary blood flow, an increased pulmonary pressure, an impaired RV performance, and interventricular interdependence throughout interventricular septum [22].

Atrial phasic function is very important because it determines LV diastolic (dys)function [23]. There are three parts of the diastole which could be assessed with three different types of atrial function. LA reservoir function represents the ability of the LA to store pulmonary venous return during LV contraction and isovolumetric relaxation. Conduit LA function reflects the capability of transferring blood passively into the LV, whereas LA pump function means active contraction during the last phase of diastole and contributes to 15–30% of LV stroke volume. Similar refers to the RA and its phasic function. The only difference is that venous return comes from systemic and not pulmonary circulation.

LA conduit and reservoir functions assessed by strain were significantly lower in CF patients than in the control group. In fact, LA conduit function was impaired in CF patients, and LA booster pump function was similar between the observed groups. As the result, LA reservoir function was also impaired in CF patients comparing with controls. There was a trend of the gradual deterioration of the LA reservoir and conduit functions from controls across CF survivors to CF non-survivors. However, a statistical significance in LA function between CF survivors and non-survivors was not reached due to the limited sample size. The deterioration of LA conduit and reservoir functions in our study indicated the presence of LV diastolic dysfunction, even though parameters for LV diastolic dysfunction were still in normal range. However, it must be underlined that these differences in LA phasic function between CF patients and controls were obtained only in the four-chamber view and not in the two-chamber view, and, subsequently, they were also not observed in global values—obtained as the average between the four- and two-chamber views. These regional differences are not an exception because other authors also did not find a statistically significant difference in global LV and RV strains, but significant differences were found in some LV and RV segments [11,14]. This could be the result of segmental myocardial impairment in CF, but a more reasonable explanation is that this is the consequence of our small sample size.

RA phasic function was not significantly deteriorated in CF patients compared with controls. However, RA was significantly larger in CF patients than in controls. Sciatti et al. recently reported significantly larger RA area in CF patients than in controls [12]. RA volume was not analyzed in this study [12]. RA volume, similar to LA, gradually increased from controls to CF non-survivors. Our CF patients had significantly increased pulmonary pressure than controls, which could be one of the reasons for RA dilatation in this group.

The LA and RA volume indexes were significant predictors of mortality among our patients with CF. This showed the great importance of the evaluation of LA and RA volumes in the CF population. Besides the LA and RA volume indexes, the only predictors of mortality in the CF population were lung function parameters (FVC and FEV1). LA and RA strain parameters were not predictors of a lethal outcome in CF patients. The only independent predictor of mortality was lung function (FVC).

The most relevant clinical implication of the current study is underlined importance of a bi-atrial echocardiographic evaluation, which involves the assessment of the LA and RA volume indexes. This is not time-consuming and is widely available because an atrial volume assessment does not require any additional equipment besides a basic echocardiographic machine, which makes it favorable from a cost-effectiveness perspective. An additional evaluation of LA and RA strains would be beneficial and also recommended, because it provides better insight in atrial function and remodeling.

5. Limitations

Our study has several limitations. First, our sample size was limited and a statistical significance was not reached in many comparisons where obvious trend existed. Second, this was a retrospective study, and the echocardiographic exam was not optimized for the research, which resulted in the exclusion of some patients due to a lack of adequate images. Third, diabetes was very prevalent in CF patients and could contribute to atrial remodeling. However, CF induces diabetes in more than 50% of adult patients, and it also represents a characteristic of CF in a certain age group. Fourth, biomarkers related to RV or LV dysfunction were not available for this study, and these would have been helpful to reach a conclusion.

6. Conclusions

LA and RA were enlarged in CF patients. The dilatation was more remarkable in CF non-survivors than in CF survivors and controls. LA conduit and reservoir functions, evaluated

by strain, were deteriorated in CF patients in comparison with controls. RA phasic function in CF patients was not significantly different from controls, even though there was an obvious trend of RA function impairment from controls to CF non-survivors. The LA and RA volume indexes, but not strain, were predictors of mortality in CF patients. This study underlines the importance of a bi-atrial assessment in CF patients, which involves the evaluation of, at least, LA global strain, as well as atrial volume indexes whenever is feasible. Further follow-up studies with larger numbers of patients are necessary to determine the predictive value of LA and RA phasic function and strain on the outcome in CF patients.

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Conflicts of Interest: The authors declare no conflict of interest.

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15. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

My CV is not published in the electronic version of my work for data protection reasons.

16. Publication List

1. **Dordevic A**, Genger M, Schwarz C, Cuspidi C, Tahirovic E, Pieske B, Düngen HD, Tadic M. Biatrial Remodeling in Patients with Cystic Fibrosis Running Title: Atrial Function in Cystic Fibrosis. J Clin Med 22019;8.e1141.
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5. Djordjevic DB, Tasic IS, Kostic SI, Stamenkovic BN, **Djordjevic AD**, Lovic DB. QTc dispersion and Cornell duration product can predict 10-year outcomes in hypertensive patients with left ventricular hypertrophy. ClinCardiol 2017;40:1236-1241.
   doi: 10.1002/clc.22815
6. Jarkovska D, Bludovska M, Mistrova E Krizkova V, Kotyzova D, Kubikova T, Slavikova J, Erek SN**, Djordjevic A**, ChottovaDvorakova M. Espression of classical mediators in hearts of rats with hepatic dysfunction. Can J PhysiolPharmacol 2017;95:1351-1359.
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