Implications of Indeterminate and Determined Etiologies Leading to Small Left Atria

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ABSTRACT **Background:** Small left atria (LA) is associated with an increased risk of mortality.

Objectives: To determine whether the attributed risk of mortality is influenced by the underlying etiologies leading to decreased volumes.

Methods: We retrospectively evaluated patients with an available LA volume index (LAVI) as measured by echocardiography who came to our institution between 2011 and 2016. Individuals with small LA (LAVI < 16 ml/m^2) were included and divided according to the etiology of the small LA (determined or indeterminate) and investigated according to the specific etiology.

Results: The cohort consisted of 288 patients with a mean age of 56 ± 18 years. An etiology for small LA was determined in 84% (n=242). The 1-year mortality rate of the entire cohort was 20.5%. Patients with indeterminate etiology (n=46) demonstrated a lower mortality rate compared with determined etiologies (8.7% vs. 22.7%, *P* = 0.031). However, following propensity score adjustments for baseline characteristics, there was no significant difference between the groups (*P* = 0.149). The only specific etiology independently associated with 1-year mortality was the presence of space occupying lesions (odds ratio 3.26, 95% confidence interval 1.02–10.39, *P* = 0.045).

Conclusions: Small LA serve as a marker for negative outcomes, and even in cases of undetected etiology, the prognosis remains poor. The presence of small LA should alert the physician to a high risk of mortality, regardless of the underlying disease.

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Low left atrial volumes are associated with adverse outcomes [1,2]. While decreased volumes have been attributed to several different etiologies [3-12], none of these specific entities were shown to meaningfully impact the prognosis in this patient setting. Instead, the presence of small left atria (LA) is an independent marker heralding detrimental sequalae [1].

Previous studies have grouped individuals with small LA into one heterogenous population [1,2]. While small LA were present among patients in these cohorts, the specific etiologies that led to the condition varied in both source and timing, as some were found to be acute while others were found to be chronic. Moreover, in certain examples, such as bleeding and dehydration, the underlying process was potentially reversible. The reasons behind the increased risk associated with reduced LA volumes remained uncertain. It is unclear whether this increased risk stems from a highly variable characteristic influenced by the underlying etiology or if it signifies a transitional hemodynamic phase characterized by shared features, leading to a severely compromised patient state independent of the specific pathophysiology.

In the present study, we investigated whether the mortality risk attributed to small LA was influenced by the identifiable underlying etiologies that lead to decreased volumes. In addition, we investigated the predictive value of small LA to reveal an obscure underlying pathology during follow-up in patients with an initially indeterminate etiology.

PATIENTS AND METHODS

STUDY POPULATION

Our study was a single-center retrospective analysis of hospitalized patients who underwent echocardiography between 2011 and 2016 at Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (n=23,271) and had an available LA volume index (LAVI) measurement (n=17,343). In the case of multiple echocardiogram tests for the same patient, the first examination was selected. Individuals with LAVI under 16 ml/m^2 [13] were included and divided according to the etiology of small LA [1]. Discharge documentation was reviewed by an internal medicine specialist and echocardiograms were reviewed by a trained cardiologist with a specialization in advanced echocardiography. Laboratory results, including hemoglobin, electrolytes, and sepsis markers were assessed in addition to diagnoses

and additional available workup. The echocardiography images were blinded to the clinical outcome and clinical background of the patients. The study was reviewed and approved by the Tel Aviv Medical Center institutional review board (Helsinki Committee; 2 February 2018) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, with a waiver of informed consent.

ECHOCARDIOGRAPHY

Echocardiography was performed in a standardized manner, using the same equipment (iE33, Philips Medical Systems, Bothell, WA, USA). The echocardiographic parameters that were used to evaluate intravascular volume status were trans-mitral E/e', left atrial size, inferior vena cava size and collapsibility, left ventricle (LV) and right ventricle (RV) chamber size and function, and systolic pulmonary artery pressure. LA volume was calculated using the biplane area length method at end systole [13] and divided by body surface area (reported as LAVI, ml/m^2). Hemodynamic measurements and anatomical dimensions were acquired as recommended [13-15]. Pulmonary hypertension was divided into category II versus other categories, according to the presence and extent of left heart disease, and volume and pressure overload. An estimated systolic pulmonary artery pressure of 50 mmHg or higher was regarded as having significance, with higher values having increased impact. Pericardial effusion was considered significant when higher than moderate effusion was present or echocardiographic signs of tamponade were present (diastolic right ventricular collapse, systolic right atrial collapse, mitral inflow variation, engorged inferior vena cava). As shown in the tables, certain patients had a small pericardial effusion, and echocardiographic signs of tamponade were present. RV dysfunction was determined both clinically and echocardiography, using parameters such as s', tricuspid annular plane systolic excursion (TAPSE), RV fractional area change for function, and RV diameters for size. Decreased intravascular volume was evaluated by reviewing patient charts, clinical scenarios, and the echocardiography.

Table 1. Baseline characteristics according to etiology of small left atria

	Indeterminate etiology (n=46)	Determined etiology (n=242)	*P*-value
Age, years ± SD	49.6 (16.5)	57.3 (18.8)	0.010
Female sex, % (n)	43.5 (20)	49.2 (119)	0.479
Congestive heart failure, % (n)	6.5 (3)	2.1 (5)	0.119
Chronic lung disease, % (n)	4.3 (2)	9.5 (23)	0.392
Ischemic heart disease, % (n)	8.7 (4)	11.2 (27)	0.797
Pacemaker/implantable cardioverter defibrillator, % (n)	0 (0)	1.7 (4)	> 0.999
Valvulopathy ≥ moderate, % (n)	2.2 (1)	0.4 (1)	0.294
Atrial flutter/fibrillation, % (n)	0 (0)	2.5 (6)	0.594
Diabetes mellitus, % (n)	10.9 (5)	16.9 (41)	0.303
Hypertension, % (n)	23.9 (11)	35.1 (85)	0.139
Hyperlipidemia, % (n)	13 (6)	27.3 (66)	0.041
Renal dysfunction, % (n)	4.3 (2)	6.6 (16)	0.747
Malignancy, % (n)	10.9 (5)	19.0 (46)	0.185
Cerebrovascular accident/ transient ischemic attack, % (n)	2.2 (1)	0.4 (1)	0.294
Etiology for small left atria, % (n)			
Space occupying lesion		6.6 (16)	
Pericardial effusion		4.1 (10)	
Right ventricular failure		12.4 (30)	
Pulmonary hypertension with presumably underfilling		16.1 (39)	
Decreased intravascular volume		71.9 (174)	
Left to right shunt		0.4 (1)	
Sepsis		13.6 (33)	
Third spacing		2.9 (7)	
Multiple etiologies		25.6 (62)	

OUTCOMES

All-cause mortality data and readmissions were extracted from electronic health records. The date of mortality (if relevant) is automatically updated in the hospital records from social security via the Ministry of Health and retrieved by identification number.

STATISTICAL METHODS

Categorical variables were reported as numbers and percentages, and continuous variables were reported as means and standard deviations or medians and interquartile ranges (IQRs), as appropriate. Continuous variables were tested for normal distribution using histograms and Q-Q plots. Patients were divided according to etiology of the small LA, determined and indeterminate, and investigated according to the specific etiology. Continuous variables were compared between groups using independent samples *t*-test or Mann-Whitney test and categorical variables were compared using chi-square test or Fisher's exact test. Logistic regressions were used to evaluate the crude associations between etiologies of small LA and 1-year mortality. A propensity score consisting of baseline characteristics was then used to adjust for each association. A propensity score was devised from the parameters: age, sex, congestive heart failure, chronic lung disease, ischemic heart disease, pacemaker/implantable cardioverter defibrillator, valvulopathy, atrial flutter/fibrillation, diabetes mellitus, hyperlipidemia, renal dysfunction, malignancy, and

Table 2. Echocardiographic characteristics according to etiology of small left atria

	Indeterminate etiology (n=46)	Determined etiology (n=242)	*P*-value
Left atrial volume index, ml/m² (IQR)	15 (2.2)	14.2 (2.6)	0.020
Left ventricle end diastolic diameter, mm (IQR)	44.5 (5)	42 (8)	0.025
Left ventricle end systolic diameter, mm (IQR)	27 (3)	26 (5)	0.102
Left ventricle posterior wall width, mm (IQR)	8 (3)	8 (2)	0.493
Interventricular septum, mm (IQR)	9 (2)	9 (4)	0.223
Cardiac output index, l/min/m² ± SD	2.7 (0.6)	2.7 (0.8)	0.879
Deceleration time, ms ± SD	196 (93)	199 (79)	0.881
e' average, cm/s (IQR)	9 (5)	7 (4)	0.005
E/e' ratio (IQR)	7 (3)	7 (4)	0.359
Right atrial pressure, mmHg (IQR)	5 (0)	5 (0)	0.709
Systolic pulmonary artery pressure, mmHg (IQR)	24 (10)	27 (11)	0.061
Left ventricle ejection fraction, % (±)	60 (1)	56 (10)	0.002
Right ventricle dilatation ≥ moderate, % (n)	0 (0)	8.7% (21)	0.032
Right ventricle dysfunction ≥ moderate, % (n)	0 (0)	7.9% (19)	0.051
Pericardial effusion ⩾ 10 mm, % (n)	0 (0)	0.8% (2)	> 0.999

IQR = interquartile range, SD = standard deviation

Table 3. Etiologies of small left atria as associates of 1-year mortality

	Univariable		Propensity score adjusted*	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Etiology determined	3.09 (1.06–8.99)	0.039	2.26 (0.75–6.82)	0.149
Multiple etiologies	2.06 (1.09–3.89)	0.027	1.93 (0.96–3.89)	0.065
Space occupying lesion	4.33 (1.55–12.1)	0.005	3.26 (1.02–10.39)	0.045
Pericardial effusion	0.97 (0.20–4.69)	0.969	0.72 (0.12–4.42)	0.723
Right ventricular failure	1.48 (0.62–3.51)	0.378	1.81 (0.70–4.68)	0.219
Pulmonary hypertension	1.65 (0.77–3.54)	0.202	1.12 (0.57–2.68)	0.796
Decreased intravascular volume	1.13 (063–2.04)	0.686	0.99 (0.52–1.89)	0.978
Left to right shunt	N/A	> 0.999	N/A	
Sepsis/infection	1.83 (0.82–4.09)	0.142	1.70 (0.70–4.13)	0.240
Third spacing	1.57 (0.30–8.31)	0.595	1.83 (0.32–10.49)	0.498

*Parameters included in the propensity score: age, sex, congestive heart failure, chronic lung disease, ischemic heart disease, pacemaker/implantable cardioverter defibrillator, valvulopathy, atrial flutter/fibrillation, diabetes mellitus, hyperlipidemia, renal dysfunction, malignancy, cerebrovascular accident/transient ischemic attack

95%CI = 95% confidence interval, N/A = not applicable, OR = odds ratio

cerebrovascular accident/transient ischemic attack. Thereafter each patient was assigned the appropriate score and an adjusted analysis was performed. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were reported. A univariable cox regression was used to demonstrate (in a survival plot) the difference between determined and indeterminate cases. Hazard ratio (HR) and 95%CIs were reported. A two-tailed *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

RESULTS

PATIENT CHARACTERISTICS

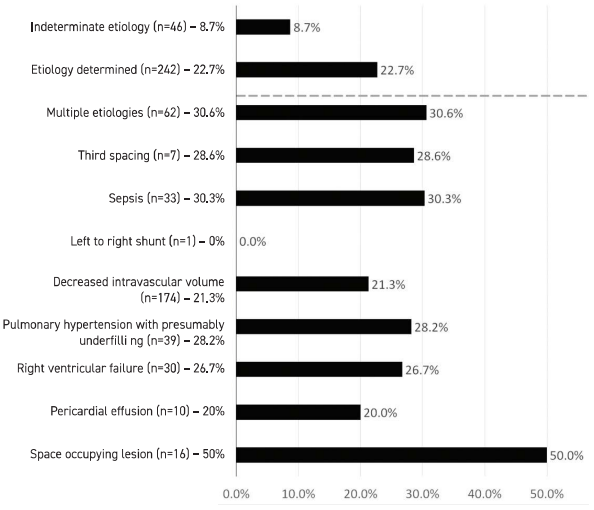
Our cohort consisted of 288 patients with small LA. The overall mean age was 56 ± 18 years and 48.3% were female. An evaluation of clinical data and echocardiography yielded an etiology for small LA in 84% of the study population. The list of etiologies for small LA included a space occupying lesion directly compressing the LA in 6.6% (n=16) of patients, a pericardial effusion limiting filling of the LA in 4.1% (n=10), RV failure limiting filling of the LA in 12.4% (n=30), pulmonary hypertension with presumably underfilling of the atrium in 16.1% (n=39), decreased intravascular volume (due to anemia, bleeding, or dehydration) in 71.9% (n=174), left to right shunt in 0.4% (n=1), sepsis with afterload reduction in 13.6% (n=33), and third spacing with afterload reduction in 2.9% (n=7). In 16% (n=46) of the cohort the etiology was indeterminate. One-fourth (25.6%; n=62) of the patients had more than one etiology for small LA. Of note, 9 patients were intubated and supported by a ventilator during the echocardiography.

Patients with indeterminate etiologies were younger (49.6 vs. 57.3 years, $P = 0.01$) and with less occurrences of hyperlipidemia compared with patients with determinate etiologies (13% vs. 27.3%, $P = 0.041$). Additional clinical characteristics did not differ significantly between the two groups [Table 1].

ECHOCARDIOGRAPHY

Median LAVIs were slightly, yet significantly higher in patients with an indeterminate etiology (15 vs. 14.2 ml/m^2, $P = 0.02$). LV end-diastolic diameter (44.5 vs. 42 mm, $P = 0.025$) and average mitral annulus e' (9 vs. 7 cm/s, $P = 0.005$) were also higher in patients with an indeterminate etiology. The remaining echocardiographic parameters did not differ between the groups [Table 2].

Figure 1. Mortality rates at 1-year according to etiology of small left atria



ETIOLOGY OF SMALL LEFT ATRIA AND MORTALITY

Mortality rate for the entire cohort at 1-year was 20.5%. Patients with indeterminate etiology demonstrated a lower rate of 1-year mortality compared with a determined etiology (8.7% vs. 22.7%, $P = 0.031$). Excluding left to right shunt, identified in a single patient, all etiologies demonstrated higher 1-year mortality rates compared to patients with indeterminate etiology [Figure 1]. The highest mortality rate was seen in patients with space occupying lesions (50%).

A determined etiology was associated with a risk over 3-times higher for 1-year mortality compared to an indeterminate etiology (OR 3.09, 95%CI 1.06–8.99, $P = 0.039$). Space occupying lesion was associated with an over 4-times higher risk for 1-year mortality (OR 4.33, 95%CI 1.55–12.1, $P = 0.005$). Patients with multiple etiologies for small LA had an over 2-times higher risk for 1-year mortality (OR 2.06, 95%CI 1.09–3.89, $P = 0.027$). The remaining etiologies were not associated with 1-year mortality [Table 3]. After propensity score adjustments were made, the only etiology associated with 1-year mortality was space occupying lesion (OR 3.26, 95%CI 1.02–10.39, $P = 0.045$). An indeterminate etiology was not associated with a lower risk for 1-year mortality when adjusted by the propensity score compared with a determined etiology ($P = 0.149$).

DISCUSSION

The current data suggest that the dismal outcomes marked by small LA pertain even when an apparent etiology for small LA is not detected. Nonetheless, an etiology should be evaluated and treated when possible. Therefore, small LA should be mentioned in the report of any echocardiography study in which it is identified.

These data clearly showed that small LA is an essential finding that should not go unnoticed. It should not only be part of the hemodynamic assessment for the echocardiographer but reveal essential prognostic information to the clinician. Moreover, none of the specific etiologies, excluding a space occupying lesion that presages poorer outcomes are pertinent in the prediction of mortality among this population. Obviously, in cases of small LA when the cause is irreversible (such as intra-atrial tumors and extracardiac tumors compressing the LA), the prognosis depends entirely on the gravity of the extra-cardiac lesion. At other times, the clinician should be encouraged to re-evaluate the patient's condition when the small LA is related to a reversible cause, namely intravascular volume depletion or decreased LA preload. The greatest benefit of identifying the presence of small LA size is when a reversible cause is present. In that case, the reversibility and not the etiology is important. Small LA indicates severe condition. While co-morbidities such as heart failure and atrial fibrillation, and echo pa-

rameters such as low e' are linked to large LA, these patients had small LA. The independent and strong association of small LA to adverse outcomes highlights the significance of this pathological state. Patients had small LA despite the predispositions for an opposing process, thus demonstrating the pathophysiological importance of this finding. Last, this is the first study to provide data on mortality rates of patients with specific pathologies and small LA. These results contribute to the understanding of prognostic significance and applicability of the entity in clinical practice.

Small LA was recently found to be associated with a high risk of mortality [1,2]. While the underlying entities leading to decreased LA volumes have previously been discussed [1,2,6,7,10-12,16-18], outcomes for this heterogenous group of pathologies have yet to be compared. The high 1-year mortality rates in the present study exceeded 20% consistently across the various etiologies, excluding left to right shunt, which was identified in a single patient. A lower 1-year mortality rate was observed among patients with an indeterminate etiology. Despite the lower risk in a crude assessment [Supplemental Figure 1, in the online version only], specific etiologies did not independently portend adverse outcomes, excluding a space occupying lesion that was associated with a particularly elevated mortality risk. We therefore conclude that not only do small LA represent a specific biomarker for a high-risk population, but that the prognostic significances of pathologies which lead to small LA seemingly lose relevance. Of note, the standard deviation of the left atrial volume indices in Table 2 of the current study are larger than the mean difference between the two groups. This diminishes the importance of a small numerical difference that perhaps results from the limitations of estimating left atrial size. Indeed, the difference in atrial size did not translate to outcome in the multivariable analysis.

STUDY LIMITATIONS

First, the retrospective nature of the study may introduce bias. Second, since the indeterminate etiology group consisted only of 46 patients, the predictive value of small LA could not be fully explored. We believe this finding should be regarded as hypothesis generating and be further investigated. Third, calculating left atrial volumes from 2-dimensional (2-D) echo is less accurate than other available methods such as 3-D echo or cardiac MRI. However cardiac MRI is not performed as often as echo, and 3-D echo for evaluating left atrial volume is more time consuming than 2-D echo, and therefore not performed regularly in most labs. Last, part of the suggested etiologies for small LA are theoretical since there is paucity of data on small LA. Until further studies evaluate the pathophysiology of small LA this entity remains speculative in certain instances.

CONCLUSIONS

Small LA are markers for a grave outcome conferred by the etiologies that lead to the decreased volumes, and even in cases of undetected etiology prognosis remains poor. Therefore, the presence of small LA should alert the physician to a high-risk of mortality, regardless of the underlying disease. Accordingly, this entity should be stated as a pathologic echocardiography finding and not be overlooked.

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