



Dynamic Left Ventricular Outflow Tract Obstruction: Clinical and Echocardiographic Risk Factor Association in Critically Ill Patients

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Abstract

Background: Dynamic left ventricular outflow tract obstruction (LVOTO) is increasingly recognized in critically ill patients and is a cause of significant morbidity and mortality.

Objectives: To identify clinical risk predictors that may identify patient at high-risk of developing LVOTO based on their echocardiographic features.

Methods: Clinical and demographic data of all patients diagnosed with acute LVOTO were matched with a randomly derived control group to develop a clinical scoring model (development cohort). Subsequently, a cross sectional study was conducted to validate the scoring model using 143 consecutive patients admitted to intensive care units who underwent echocardiography (validation cohort). A blinded observer classified all patients as either high or low echocardiographic risk for developing LVOTO.

Results: The retrospective cross sectional study (of validation cohort) could not validate the clinical score (developed from the development cohort) because it did not differentiate between different LVOTO risk groups ($P = 0.54$). Univariate analysis suggested female gender (high vs low risk, 64% vs 32%; $P = 0.009$), age > 60 years (74.8 ± 14.1 vs 57.8 ± 18.4 ; $P = 0.0004$) and lack of inotrope use (35% vs 61%; $P = 0.03$) to be significantly associated with high-risk LVOTO group. All other variables were statistically non-significant. Based on the multiple logistic regression analysis, age > 60 ($P = 0.003$) was found to be the only independent predictor of high risk for developing LVOTO, with the estimated area under the ROC curve being 0.81.

Conclusions: Elderly patients are at high risk of developing dynamic LVOTO. Other clinical and demographic parameters did not reliably predict risk in our study. Further studies are warranted to improve risk prediction and identification of this, rare but potentially life threatening, cardiac condition before its clinical manifestation.

Keywords: Dynamic LV Outflow Tract Obstruction, Critical Care, Clinical Risk Prediction, Echocardiography, Cardiology

1. Background

In critically ill patients, hypotension is a common occurrence and is a cause of concern for both families and providers. An under-recognized but potentially lethal cause of hypotension in this population is dynamic left ventricular outflow tract obstruction (LVOTO) which if not identified correctly and treated appropriately can lead to adverse outcomes (1).

LVOTO was first described in 1964 by Tafur et al. (2). Since then LVOTO has been described with multiple cardiovascular disorders such as hypertrophic cardiomyopathy, amyloidosis, hypertension, myocardial infarction and Takotsubo syndrome (3-7). Some studies show that about 20% - 25% of patients suffering from stress cardiomyopathy may develop LVOTO (6, 8). Evidence is accumulating

that LVOTO is an important clinical condition, which poses diagnostic, and management dilemmas for clinicians. Importantly, this may occur spontaneously in critical care settings in the absence of any underlying cardiac disease (1, 8). Yet there seems to be paucity of organized clinical research efforts towards understanding clinical presentation and outcomes of LVOTO.

2. Objectives

The aim of this study is to identify clinical risk predictors that may identify critically ill patients who are at high risk of developing LVOTO based on clinical and echocardiographic features. To identify these factors, we first performed a case-control study (development cohort) to identify high-risk clinical and demographic variables.

Subsequently, we carried out a systematic, retrospective cross sectional investigation (validation cohort) to correlate if these clinical predictors can identify patients with echocardiographic features high risk of developing LVOTO.

3. Methods

3.1. Development Cohort

Clinical and demographic data of all patients diagnosed with acute LVOTO at the University of Missouri Hospitals and Clinics between December 2006 and March 2008 were collected. A board certified echocardiographer with special interest in this area reviewed the echocardiograms at the time of acute LVOTO. Peak LVOTO gradients were measured in twenty-four patients. Various echocardiographic parameters that might increase the likelihood of LVOTO were collected from older (pre-LVOTO) echocardiogram or subsequent echocardiogram performed after the acute LVOTO had resolved.

A control group was derived from patients admitted to the intensive care units (ICUs) and who had clinically indicated echocardiograms during their ICU stay. A second group designated as 'high risk' for LVOTO was also derived from the echocardiography laboratory database where overt LVOTO or anterior mitral leaflet systolic anterior motion (SAM) were absent but believed to be high risk for developing LVOTO with further cardiac and hemodynamic stress.

3.2. High Risk for LVOTO: Echocardiographic Features

Echocardiographic features such as sigmoid shaped septum or basal septal bulge, chordal SAM, hypercontractile left ventricle (LV) as well as small LV chamber size with crowding at the LV outflow level factored in the determination of high risk for LVOTO (9).

3.3. High Risk for LVOTO: Clinical Features

A clinical scoring model was developed from the development cohort to screen ICU patients for "high" risk of dynamic LVOTO during critical illness. We identified the following 8 high-risk clinical variables associated with dynamic LVOTO: female sex, age > 60 years, presence of chest pain, systolic blood pressure < 90 mmHg, documented intravascular volume loss, diuretic administration, inotrope infusion (use of dopamine, dobutamine or norepinephrine), presence of new murmur on cardiac auscultation. Intravascular Volume loss was defined as any negative fluid balance documented in medical records on the day of admission. For each clinical variable (dichotomized-Yes/No), the odds ratio was calculated between the two

groups (High vs. Low echocardiographic risk for developing LVOTO). The odds ratios were expressed as percentages of the total odds ratio. The estimated odds ratios of the eight clinical predictors with P values and the weight of each predictor for clinical scores developed from development cohort are shown in [Table 1](#).

3.4. Validation Cohort

Consecutive patients admitted to the various ICUs at the University of Missouri Hospital between July 2007 and Nov 2009 and underwent clinically indicated echocardiography were identified. A retrospective review of chart was performed for 143 patients who met study inclusion criteria. Our exclusion criteria included significant valve disease, prior established LVOTO or hypertrophic obstructive cardiomyopathy. We conducted a cross-sectional study to identify the above high risk clinical variables at ICU admission that would differentiate high risk vs low risk patients for developing LVOTO. Based on the pre-determined echocardiographic criteria (described previously), an echocardiographer blinded to the clinical condition classified all patients as either high (n = 17) or low risk (n = 126) for developing LVOTO. To test the significance of identified clinical predictors a logistic regression and multivariate logistic model was used. The study was approved by the institutional review board of the University of Missouri.

3.5. Statistical Analysis

Eight clinical variables that were considered in the pilot study were examined. For univariate analyses, a Chi-square test or a Fisher's exact was used for nominal clinical variable. For continuous clinical variable, a two sample t-test was used. For multivariate analysis, a multiple logistic model was used. A 'p' value of less than 0.05 was considered significant. All statistical analysis was performed using SAS 9.2 (Cary, NC). The results are expressed as mean +/- Standard Deviation (SD) as described in the text.

4. Results

Demographic, clinical and echocardiographic characteristics of the overall population included in the validation study are shown in [Table 2](#). The cross sectional study of the validation cohort could not validate the clinical score developed during the pilot study because the eight point scoring system did not differentiate between the high and low risk LVOTO groups (37 ± 13 vs 34.6 ± 16.1 ; $P = 0.54$) ([Figure 1](#)). Univariate analysis suggested female gender (high risk vs low risk, 64% vs 32%; $P = 0.009$), age > 60 years (74.8 ± 14.1 vs 57.8 ± 18.4 ; $P = 0.0004$) and lack of inotrope use

Table 1. The Estimated Odds Ratios of the 8 Clinical Predictors with P Values and the Weight of Each Predictor for Clinical Score that Was Developed from the Development Cohort

Clinical Factor	N	Odds Ratio	P Value ^a	Clinical Score
Sex				
Female	14	14.0	0.009	16
Male	10			
Age in years				
> 60	14	5.5	0.07	6
≤ 60	10			
Chest pain				
Yes	6	13.0	0.04	15
No	18			
Systolic BP mmHg				
< 90	18	10	0.07	11
> 90	6			
Intravascular Volume loss				
Yes	5	2.9	0.4	3
No	19			
Diuretics				
Yes	5	10	0.07	12
No	19			
Inotrope infusion				
Yes	5	10	0.07	12
No	19			
New murmur				
Yes	8	21.5	0.009	25
No	16			
Total	24	87		100

^aP values are based on the Fisher's exact test (Two-side). Each clinical variable was dichotomized (Yes/No) and the odds ratio was calculated between two groups (High vs. Low echocardiographic risk for developing LVOTO). The odds ratios of these eight variables were expressed as percentages of the total odds ratio. The estimated odds ratios of the eight clinical predictors with P values and the weight of each predictor for clinical scores are shown here.

(35% vs 61%; $P = 0.03$) to be significantly associated with high risk LVOTO group identified by echocardiographic criteria (Table 3). All other variables in the clinical scoring system were not significantly different in the high risk and low risk groups.

Based on the multiple logistic regression analysis, age (odds ratio [OR]: 1.1 [95% confidence interval (CI): 1.02 to 1.1], $P = 0.003$) was found to be the only independent predictor of high risk for developing LVOTO. The area under the receiver operating characteristic (ROC) curve (AUC) based on the multiple logistic regression analysis using age, gender, and inotropes use as predictors was 0.81 (Figure 2). Although female gender was associated with an increased

risk (OR: 2.8 [95% CI: 0.9, 8.9], $P = 0.07$) to develop LVOTO, it was not statistically significant. The absence of inotrope use (OR: 2.6 [95% CI: 0.8 to 8], $P = 0.1$), was associated with high risk LVOTO in univariate analysis, was not significant on multivariate analysis (Figure 3).

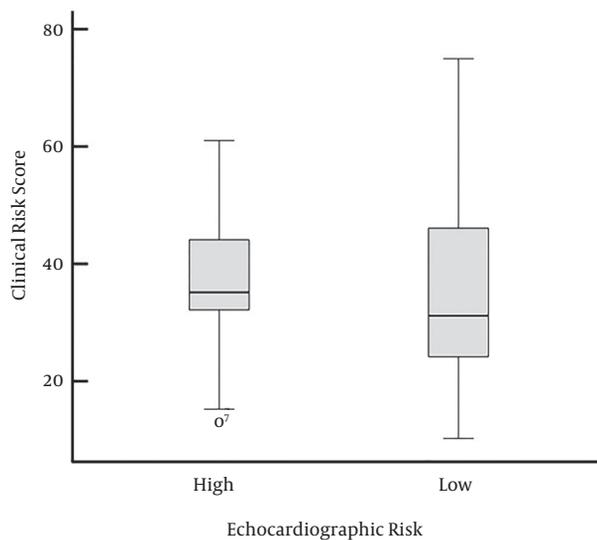
There were no differences between groups regarding the use of common cardiac medications including beta-blocker, angiotensin converting enzyme inhibitor and anti-platelet therapy prior to admission.

5. Discussion

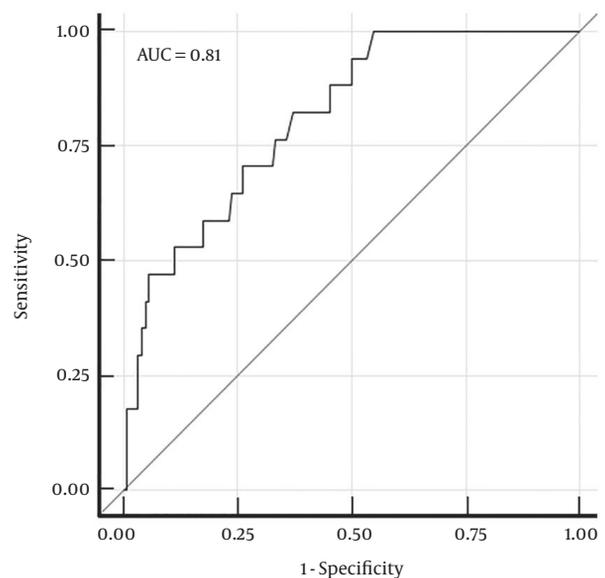
Our study is the first to our knowledge, to evaluate causative relationship of clinical and demographic factors

Table 2. Baseline demographic, clinical and echocardiographic characteristics of the overall population included in the cross sectional study of the validation cohort (n = 143 patients)

Valuable	Value
Age (years)	58 ± 18
Female (%)	36.4
Caucasian (%)	89.5
Hypertension (%), on medications	41.9
Heart rate (beats/minute)	101.1 ± 26.4
Systolic blood pressure (mmHg)	102.7 ± 28.8
Diastolic blood pressure (mmHg)	58.8 ± 14.7
Baseline hemoglobin (g/dL)	11.2 ± 2.3
Baseline creatinine (g/dL)	1.5 ± 1.6
Hospital length of stay (days)	8 ± 7.7
ICU length of stay (days)	2.7 ± 4.7
IVSd (mm)	11.7 ± 1.6
Ejection fraction (%)	53.5 ± 13.1
Angle between basal septum and aortic root (degrees)	134 ± 17.3

**Figure 1.** A box-whisker plot of the clinical scores of validation cohort (n = 143) between two groups (High risk vs. Low risk of LVOTO). The box indicates 25th and 75th percentiles, the center line in the box indicates the median, and the stretched lines indicate the minimum and the maximum. Abbreviation; CS, clinical scoring. (P value = 0.54)

and echocardiographic risk of developing LVOTO in critically ill patients without prior history of hypertrophic cardiomyopathy or established LVOTO. Using clinical and echocardiographic features observed in LVOTO cases (developmental cohort), we were able to design a 8-point clin-

**Figure 2.** A Plot of the Area Under the ROC Curve Based on the Multiple Logistic Regression Using Age, Sex, and Inotropic Drug Use as Predictors

ical scoring system (Table 1) to identify patients at high risk of developing LVOTO. However, in the cross sectional study (validation cohort) of 143 critically ill patients admitted to the ICU this clinical scoring system failed to differentiate between high and low-risk patients using echocardiography. In our study, the univariate analysis indicated that elderly females not receiving inotropes are at high risk of possibly developing LVOTO. While the association of advanced age (age > 60 years) and female gender is consistent with prior reported data (1), it is interesting to note that patients who did not receive inotropic drugs would have a higher risk ([OR]: 2.6 [95%CI: 0.8 to 8.0], P = 0.03) of possibly developing LVOTO since this is contrary to previously published reports (1, 10).

Our results are intriguing and challenges the current paradigm of hemodynamic and echocardiographic changes associated with dynamic LVOTO, especially in critically ill patients (9). Since our cohort consisted of patients that are high risk of developing LVOTO and did not have a diagnosis of LVOTO and were on inotropic agents, it is conceivable that there was a selection bias in our cohort and analysis. Since age, gender and use of inotropic drugs are not entirely independent variables (8-10), we evaluated this relationship using multivariate analysis. From the fitted model, age continued to be a significant predictor, with higher age related to higher risk of LVOTO ([OR]: 1.1 [95% CI: 1.02 to 1.1], P = 0.003) but gender and inotropic drug use were not statistically significant. The area under the ROC

Table 3. Results of Univariate Analysis^a

	Low Echocardiographic Risk (n = 126), (Mean ± SD)	High Echocardiographic Risk (n = 17), (Mean ± SD)	P Value
Age (years)	57.8 ± 18.4	74.8 ± 14.1	0.0004 ^b
Female sex	41 (32%)	11(64%)	0.009 ^c
Inotrope use	78 (61%)	6(35%)	0.03 ^c
Volume loss (on admission)	47 (37.3%)	4(23.5%)	0.2 ^c
Presence of chest pain on admission	26 (20%)	4 (23%)	0.7 ^d
Oral diuretic use	32 (25.4%)	3 (17.6%)	0.76 ^d
New murmur (on admission)	9 (7.1%)	0	0.36 ^d
Length of stay (days)	8 ± 6.6	8.2 ± 4.9	0.91 ^b
Systolic blood pressure (on admission)	101.7 ± 27.9	110.4 ± 34.4	0.24 ^b

Abbreviation: SD, Standard Deviation.

^aBased on the univariate analysis of the data from the validation cohort, female sex ($P = 0.009$), age > 60 years ($P = 0.0004$) and lack of inotrope use ($P = 0.03$) were significantly associated with Echocardiographic "high risk" LVOTO group. All other variables in the clinical scoring system were not significant. The statistical test used for the analysis are identified in superscripts next to P value.

^bTwo sample t-test.

^cChi-Square test.

^dFisher's Exact test.

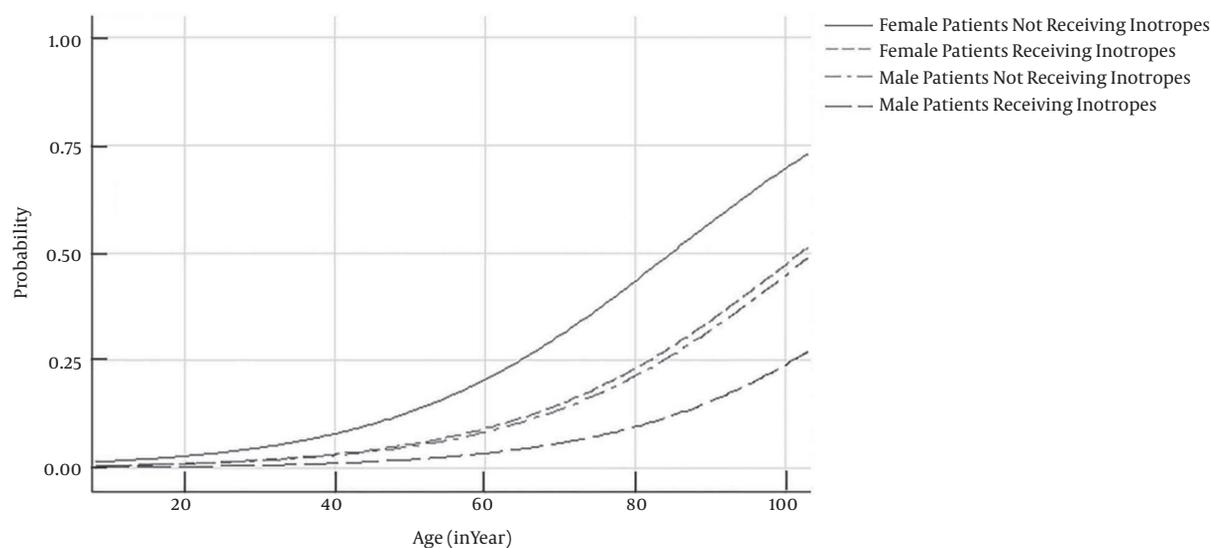


Figure 3. the predicted probability of developing LVOTO based on the multiple logistic regression using age, sex and use of inotropic agents. Female patient who did not receive inotropes were at the highest risk of developing LVOTO, and this risk increased with age.

curve (AUC) based on the multiple logistic regression using age, gender, and use of inotropic drugs as predictors was 0.81 (Figure 2). Although not significant, the plot assessing the echocardiographic risk based on gender and inotropic use (Figure 3) revealed that women not receiving inotropes had a higher risk of developing LVOTO than men who received inotropes. We expect inotrope use to increase LVOTO irrespective of sex. Our contrarian finding probably results from our small sample size. Literature

suggests several anatomic and hemodynamic alterations that could predispose to dynamic LVOTO such as uncoiled aorta in elderly patients leading to obtuse angulation between the basal septum and aortic root, hypertensive patients with hyper-dynamic LV and small LVOT, decreased preload and afterload, and presence of underlying hypertrophic cardiomyopathy (HCM).

The number of patients in our study is small (high-risk group $n = 17$) which is consistent with previously pub-

lished reports highlighting that LVOTO remains an underdiagnosed clinical syndrome. There is no study to date that analyzed eight-high risk clinical risk predictors and risk of developing LVOTO before its apparent manifestation. The strength of our study is that this is the first study highlighting an 8-point clinical scoring system of which there was a reported trend that elderly women admitted with critical illness are at increased risk of possibly developing LVOTO. This study has the limitations of a single center, observational, retrospective analysis and lack of data regarding which patients subsequently developed LVOTO. We excluded patients with underlying HCM and did not quantify LV hypertrophy, LVOTO diameter, length of anterior mitral leaflet or mitral regurgitation. Our study might have been underpowered to confirm our pilot work. Thus, we were unable to determine if the factors that are appearing to be non-contributory towards the development of LVOTO are due to underpowered study or if they are truly not significant. Further, the identification of new LVOTO cases may be limited at our institution due to the heightened awareness of LVOTO, which may have led to altered management decision, thereby avoiding the development and/or progression of LVOTO. These altered management strategies along with the limited number of high risk cases and retrospective design of study prevented us from demonstrating what percentage of high risk patient went on to develop actual LVOTO.

5.1. Conclusion

Elderly patients are at high risk of developing dynamic LVOTO. Other clinical and demographic parameters did not reliably predict risk in our study. Further studies are warranted to improve risk prediction and identification of LVOTO, a rare but potentially life threatening, cardiac condition before its clinical manifestation.

Footnotes

Authors' Contribution: All authors participated in study design, data collection and analysis and writing the

manuscript; all authors agree with the contents of the manuscript.

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