Differentiating Constriction from Restriction (from the Mayo Clinic Echocardiographic Criteria)

Salima Qamruddin, MD[a], Saqer Khaled Alkharabsheh, MD[b], Kimi Sato, MD[b], Arnav Kumar, MD[c], Paul C. Cremer, MD[b], Michael Chetrit, MD[b], Douglas R. Johnston, MD[d], and Allan L. Klein, MD[b,*]

Constrictive Pericarditis (CP) is a curable and reversible form of severe diastolic heart failure. We aimed to investigate the diagnostic accuracy of published echocardiographic Mayo Clinic Criteria in differentiating 107 patients with surgically proven CP from 30 patients with restrictive cardiomyopathy due to cardiac Amyloidosis. Five principal echocardiographic and Doppler variables were remeasured on preoperative transthoracic echocardiogram namely (1) respiration-related ventricular septal shift; (2) respiratory variation in mitral inflow E pulsed Doppler velocity; 3) tissue Doppler medial mitral annular e' velocity; (4) ratio of medial mitral annular e' to lateral mitral annular e' velocity; and 5) hepatic vein (HV) pulsed Doppler diastolic flow reversal ratio. Etiology of CP included viral/idiopathic or autoimmune (75%), postcardiac surgery (13%) and postradiation (7%). Univariate logistic regression analysis showed that (1) respiration related ventricular septal shift, (2) percentage change in Mitral E velocity, (3) medial e' velocity ≥9 cm/sec, (4) medial e'/lateral e' ratio ≥0.91, (5) HV diastolic reversal ratio ≥0.79 were associated with the diagnosis of CP. Multivariable logistic regression analyses showed that medial e' velocity ≥9 cm/s was independently associated with the diagnosis of CP. Respiration related ventricular septal shift had the highest sensitivity, whereas medial e' velocity ≥9 cm/s has the highest specificity to diagnose CP (Areas under curves 0.99, p 0.001). Combining respiration related ventricular septal shift with medial e' velocity ≥9 cm/s gave a desirable sensitivity (80%) and specificity (92%). Adding reversal ratio to this combination further increased the specificity (97%) but dropped the sensitivity (70%) to diagnose CP. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:932−938)

Constrictive pericarditis (CP) is a reversible form of diastolic heart failure secondary to a noncompliant pericardium,[1−3] that carries low perioperative mortality[4] in surgical centers with expertise. Echocardiography is the firstline tool for evaluation of CP.[6−10] Mayo Clinic evaluated the diagnostic accuracy of the following 5 echocardiographic and Doppler variables[11]: (1) respiration-related ventricular septal shift; (2) variation in mitral inflow E velocity (defined as [E Expiration − E Inspiration]/E Inspiration × 100); (3) medial mitral annular e' velocity; (4) ratio of medial mitral annular e' to lateral mitral annular e' velocity, and (5) hepatic vein (HV) expiratory diastolic reversal ratio in 133 patients with surgically confirmed CP and 36 patients with restrictive cardiomyopathy (RCM) or severe tricuspid regurgitation (TR). The results showed that the presence of respirophasic septal shift in association with either medial e′ velocity ≥9 cm/sec or HV expiratory diastolic reversal/forward flow velocity ratio ≥0.79 had a sensitivity of 87% and a specificity of 91% for the diagnosis of CP.[5] The aim of this study was to evaluate the diagnostic accuracy of the aforementioned 5 echocardiographic variables in distinguishing CP from patients with RCM at another large volume pericardial center.

Methods

Consecutive patients with surgically proven CP at the Cleveland Clinic from 2010 to 2014 were extracted from the Cardiothoracic Surgery database (n = 126). Patients with history of severe mitral regurgitation, mitral valve prosthesis and severe TR at the time of diagnosis of CP were excluded (n = 19). Patients with atrial fibrillation were included (n = 11). A total of 107 patients were included (Figure 1). In the restrictive cardiomyopathy (RCM) group (n = 30), the diagnosis was made by cardiac biopsy to rule in cardiac amyloidosis. Echocardiograms performed preoperatively within 6 months of the pericardiectomy in the CP group and within 6 months of cardiac biopsy in the RCM group were remeasured by 2 echocardiographers who were blinded to the diagnosis. The study was approved by the Institutional Review Board, informed consent was waived and data were deidentified.

All transthoracic studies were performed on Syngodynamics (Siemens Healthcare, Erlangen, Germany) per American Society of Echocardiography guidelines.[12] Parasternal and apical windows were used to detect ventricular septal shift with simultaneous respirogram. Pulsed-wave (PW) Doppler recordings at the level of the mitral leaflet tips were used to measure early (E) and atrial (A) diastolic inflow velocities. Respiration-related percent change in mitral E velocity was

aDivision of Cardiovascular Disease, John Ochsner Heart and Vascular Institute, New Orleans, Louisiana; bCenter for the Diagnosis and Treatment of Pericardial Diseases, Heart and Vascular Institute, Cardiovascular Section, Cleveland Clinic, Cleveland, Ohio; cDepartment of Cardiovascular Medicine, Andreas Gruentzig Cardiovascular Center, Emory University School of Medicine, Atlanta, Georgia; and dDivision of Cardiothoracic Surgery, Cleveland Clinic Foundation, Cleveland, Ohio. Manuscript received February 7, 2019; revised manuscript received and accepted June 20, 2019.

See page 938 for disclosure information.

*Corresponding author: Tel: (216) 444-3932; fax: (216) 445-6145.

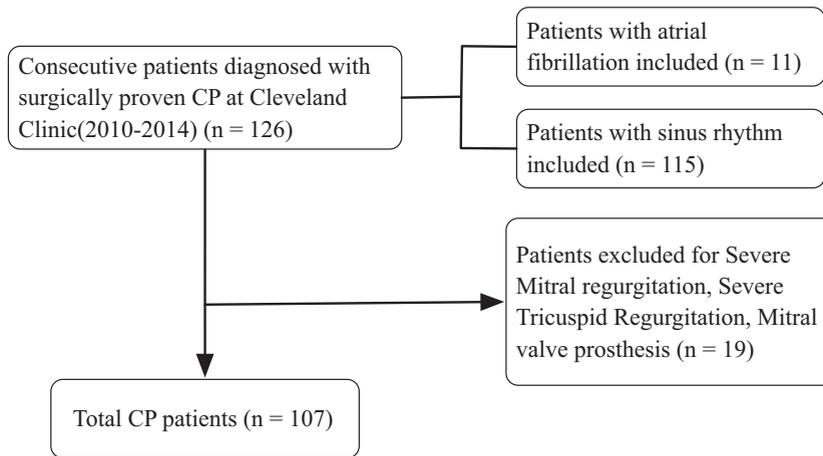*E-mail address:* kleina@ccf.org (A.L. Klein).

Figure 1. Flow diagram for inclusion of patients with constrictive pericarditis.

calculated as: (E Expiration − E Inspiration)/E Inspiration × 100) as per the Mayo criteria (Figure 2).[11] PW tissue Doppler velocity of mitral annulus was recorded at the medial (medial e') and lateral (lateral e') annulus in early diastole. From the subcostal window, PW Doppler recordings of HV forward and reversed velocities were obtained with simultaneous respirography. The HV expiratory diastolic reversal ratio (defined as diastolic reversal velocity/forward velocity in expiration) was recorded.

Differences in variables were assessed using a Student's *t* Test for continuous data and a Chi-square test for categorical data. Univariate and multivariate logistic regression was performed. Area under receiver operating curves (AUC) were generated for each of the above mentioned 5 variables. Sensitivity, specificity, positive predictive value, and negative predictive value were then estimated. All analyses were performed using the SPSS statistical software package (IBM, Chicago, Illinois, version 20).
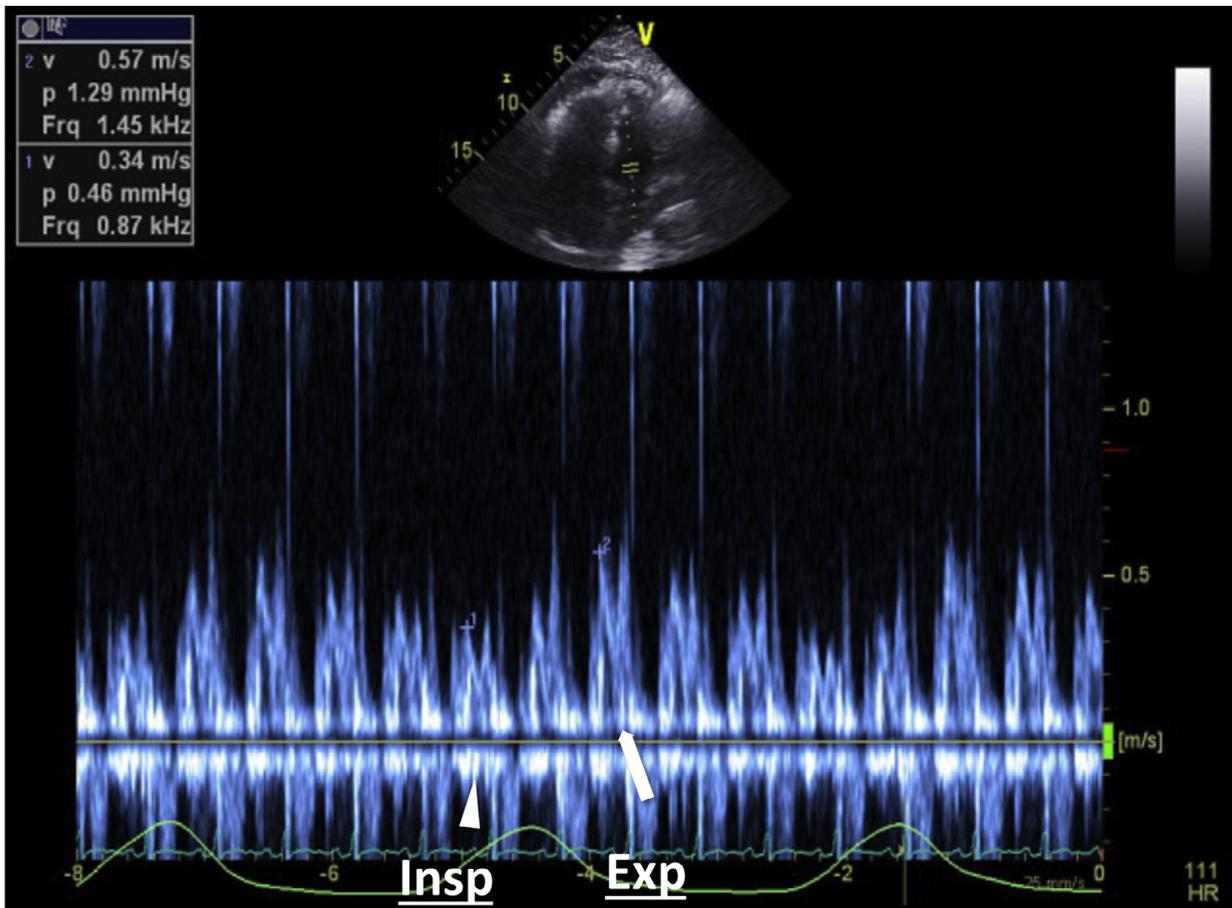

Figure 2. Pulsed-wave (PW) Doppler recording (*apical window*) at the level of the open mitral leaflet tips in CP. Note inspiratory decrease (*arrowhead marked Insp*) and expiratory increase (*arrow marked Exp*) in early Mitral E inflow velocity.

Table 1
Baseline echocardiographic characteristics of patient with CP and RCM

Echocardiographic variables	CP (n = 107)	RCM (n = 30)	p Value
EF %	57.9 ± 7.7	48.2 ± 11.7	0.14
Ventricular septal shift (%)	92	27	0.001
Mitral E inspiration cm/sec	74 ± 27	87 ± 26	0.007
Mitral E expiration cm/sec	92 ± 30	96 ± 26	0.3004
Respiration related percent change in Mitral E %	27 ± 18	12 ± 11	0.001
Medial mitral e' cm/sec	11 ± 3	4 ± 1	0.001
Lateral mitral e' cm/sec	10 ± 3	5 ± 2	0.001
Medial e'/lateral e'	1 ± 0.3	0.8 ± 0.2	0.001
HV diastolic reversal expiration cm/sec	24 ± 10	25 ± 7	0.34
HV diastolic forward flow expiration cm/sec	24 ± 10	35 ± 15	0.001
HV ratio in expiration	1 ± 0.5	0.7 ± 0.3	0.0004

EF, ejection fraction; HV diastolic reversal expiration cm/s, hepatic vein pulsed wave diastolic reversal flow velocity in expiration; HV diastolic forward flow expiration, hepatic vein pulsed wave diastolic forward velocity in expiration; HV ratio, ratio of pulsed wave hepatic vein diastolic reversal to forward velocity in expiration; Mitral E inspiration, mitral early diastolic E wave velocity in inspiration; Mitral E Expiration, mitral early diastolic E wave velocity in expiration; Medial mitral e', medial mitral annular early diastolic tissue Doppler (e') velocity; Lateral mitral e' cm/s, lateral mitral annular early diastolic tissue Doppler (e') velocity; Medial e'/lateral e', ratio of medial to lateral mitral annular early diastolic tissue Doppler (e') velocity.

Results

There were 107 patients in the CP group and 30 patients in RCM group. Etiology of CP (n = 107) included viral/idiopathic/rheumatologic (75%), postcardiac surgery (13%), and postradiation (7%). Eighty two percent of the patients were males in CP group, and were younger than those in the RCM group (58.9 ± 13.8 vs 69.7 ± 9.9 years, p <0.001).

A significantly higher percentage of patients with CP demonstrated respiration related ventricular septal shift and percent change in Mitral E velocity with inspiration (Table 1). Figure 2 demonstrates a patient with CP that had lower Mitral E velocity with inspiration. Difference in Mitral E velocity was not seen on expiration between the groups (Table 1). Medial e' velocity was higher than lateral e' velocity in patients with CP (Table 1). Figure 3 shows an example of a patient with CP who has higher mitral medial e' velocity (A) compared with the lateral e' velocity (B). Medial e', lateral e' velocity, and ratio of medial to lateral mitral annular e' velocity were significantly higher in the CP group (Table 1). There was significantly lower diastolic HV forward flow in expiration in the CP group. Figure 4 is an example of a patient with CP who has decreased diastolic forward flow and larger diastolic flow reversal in expiration. The HV reversal ratio (calculated as diastolic
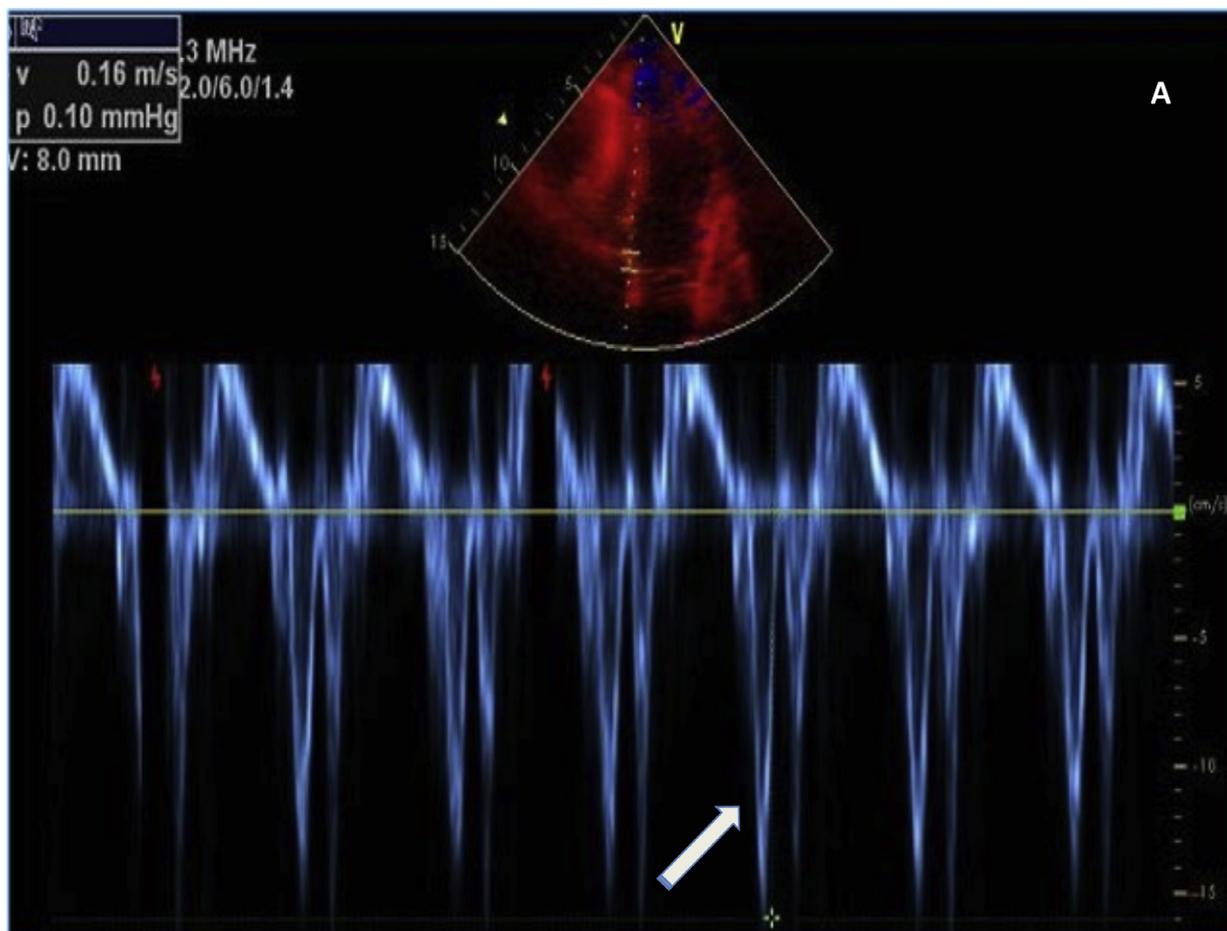

Figure 3. Pulsed-wave (PW) tissue Doppler recording in apical 4 chamber view. Medial mitral annular (Medial e') velocity (A) is larger (16 cm/sec) than lateral mitral annular (Lateral e) velocity (B) (14 cm/sec). This phenomenon is termed "annulus reversus," (reverse of the normal mitral anuular tissue Doppler configuration).
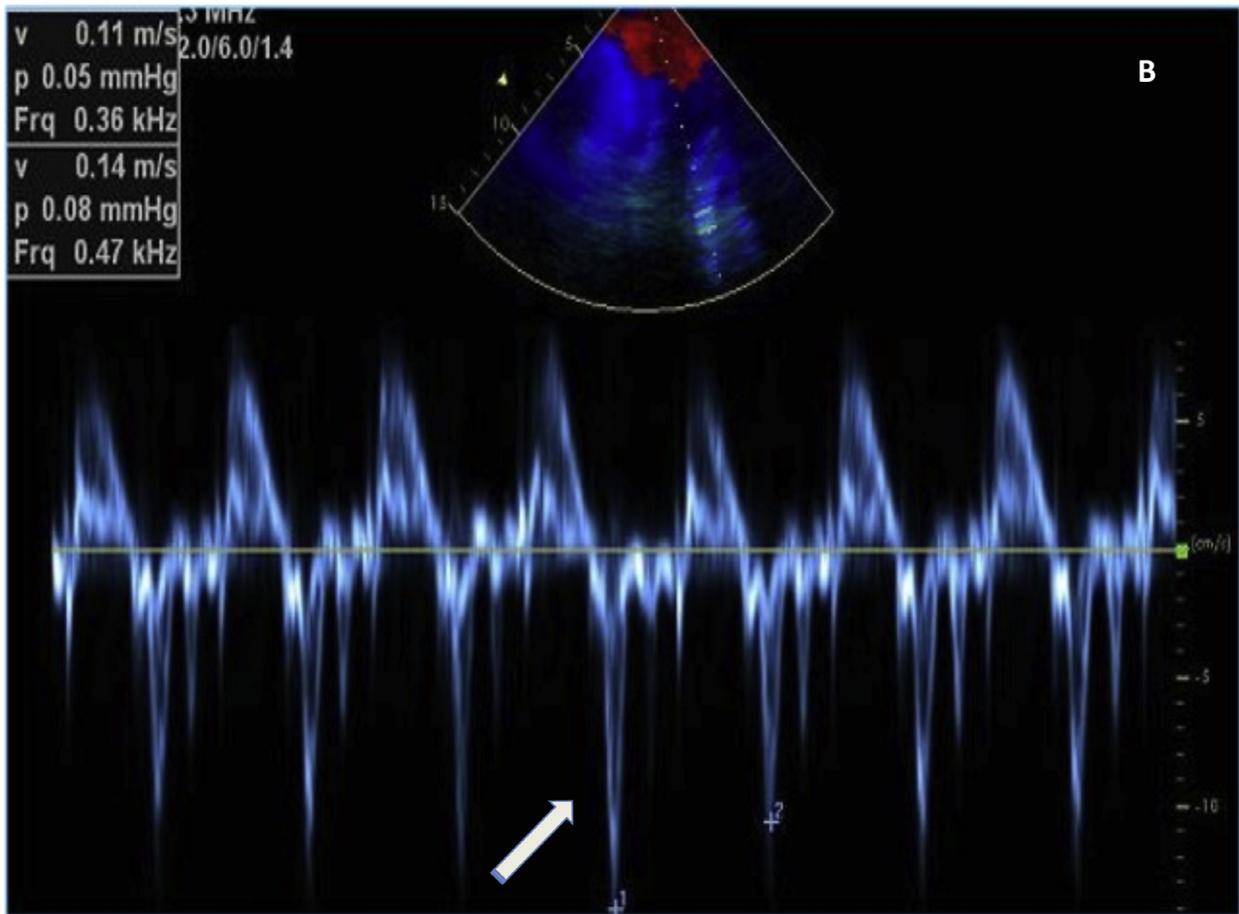
Figure 3. Continued

reversal velocity/forward velocity in expiration) was significantly higher in the CP group (Table 1).

Univariate logistic regression analysis showed that: (1) respiration related ventricular septal shift, (2) percentage change in Mitral E velocity, (3) medial e' velocity ≥9 cm/sec, (4) medial e'/lateral e' ratio ≥0.91, and (5) HV ratio ≥0.79 were associated with the diagnosis of CP. The optimal threshold for percentage change in Mitral E velocity to diagnose CP was found to be 13.5% with 80% sensitivity and 76% specificity (AUC 0.82, p 0.001; Figure 5). The optimal cutoff for medial e' was ≥7 cm/sec with 99% sensitivity and 99% specificity (AUC 0.99; Figure 5). The optimal cutoff for ratio of medial e'/lateral e' was 0.86 that was 83% sensitive and 73% specific (AUC 0.78, p 0.001; Figure 5). The optimal cutoff for HV ratio (calculated as HV diastolic reversal velocity/forward HVvelocity in expiration) was 0.77 (sensitivity 85%, specificity 53%, AUC 0.76, p 0.0001; Figure 5). At HV ratio ≥0.79, the sensitivity and specificity both dropped (70 and 43%, respectively; Table 2).

From a stepwise-selected multivariable model of the 5 echocardiographic variables, only increased levels of medial e' velocity ≥9 cm/sec (odds ratio = 8, expressed per 1 cm/sec; 95% confidence interval 2.4 to 28; p = 0.001) was independently associated with the diagnosis of CP. A combination variable of ventricular septal shift and medial e'

velocity ≥9 cm/sec was 80% sensitive and 92% specific for the diagnosis of CP. Adding HV ratio ≥0.79 to the above combination decreased the sensitivity to 70%, but increased the specificity to 97% (Table 2).

Discussion

The main findings of our study are as follows: (1) Medial e' velocity ≥9 cm/sec is independently associated with the diagnosis of CP, (2) combination variable of ventricular septal shift + medial e' velocity ≥9 cm/sec was 80% sensitive and 92% specific for the diagnosis of CP, and (3) adding HV diastolic reversal ratio ≥0.79 decreased the sensitivity to 70%, but increased the specificity to 97% when compared with a group of RCM patients.

Increased incidence of ventricular septal shift (due to interventricular dependence) in patients with CP compared with patients with RCM is consistent with that found in the Mayo Clinic study.[11] However, its presence is sensitive but not very specific, as it can be seen in conduction abnormalities postcardiac surgery.[5] The respiratory variability in the mitral (Figure 2) and tricuspid inflow in CP[5,6] is less specific for the diagnosis of CP and is consistent with that reported by the Mayo study. This is because this variable is load dependent and can also be seen in patients with chronic
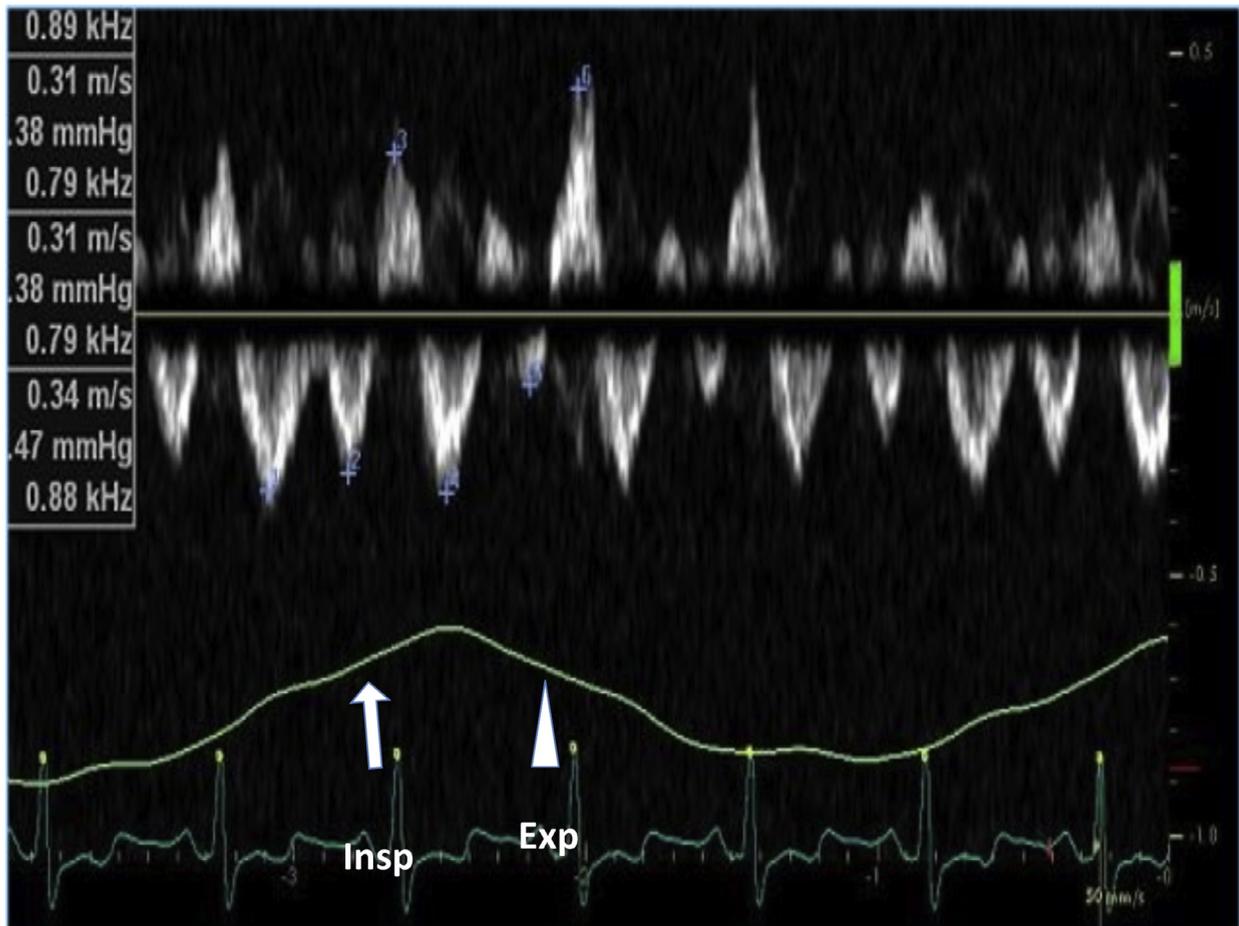
Figure 4. Pulsed-wave (PW) Doppler recording (*subcostal window*) at the level of the hepatic vein in a patient with constrictive pericarditis. Note larger diastolic forward flow velocity (*arrow*) and smaller diastolic flow reversal velocity in inspiration (*arrow*). With expiration (*arrowhead*) there is smaller diastolic forward flow and larger diastolic flow reversal.

obstructive pulmonary disease and those on mechanical ventilation.[13]

Medial e' that measures the intrinsic mechanical elastic property of the LV is preserved in CP.[4] Medial e' velocity ≥9 cm/sec has higher specificity (100%) in our cohort compared to the Mayo Clinic study as our control group is composed of patients only with RCM that have biopsy proven cardiac amyloidosis. These oate have intrinsic myocardial disease (low tissue Doppler mitral annular velocity) versus the Mayo study control group which was composed of patients with RCM and severe TR. Given its high specificity, using this variable in combination with the other appears to have the highest diagnostic accuracy. Medial and lateral e' are increased in patients with CP, with medial e' being larger (Figure 3) in amplitude than lateral e'(Figure 3) (termed "annulus reversus"),[9] due to tethering of the lateral pericardium by increased pericardial thickness.[8] However, annulus reversus was not very sensitive nor specific in our cohort compared to the Mayo group. This may be due to significant variation in the degree and pattern of pericardial thickening that has been reported by other studies.[13]

The prominent reversal of expiratory late diastolic flow in the HVs seen in CP[4,5] (Figure 4) is seen due to reduced reduce right-sided filling (Figure 2) due to rightward septal shift, reducing the HV forward velocity and exaggerating the late diastolic reversal velocity. This is not seen in RCM as it does not show respirophasic changes in ventricular filling.[6] The HV diastolic reversal ratio ≥0.79 (defined as expiratory diastolic reversal velocity divided by the diastolic forward velocity) was found to be highly specific for the diagnosis of CP in the Mayo study. We had a much lower specificity in our group. This may be due to a smaller number of patients having adequate quality tracings (n = 79). However, combining it with medical e' ≥9 cm and septal shift further increased the specificity. This result is consistent with the Mayo study.

This is a large single center study with high level of expertise in CP, that aimed to reproduce the diagnostic accuracy of previously described echocardiographic and Doppler characteristics for CP. Quality HV tracings were available in only 79 pts. in CP group. These smaller samples may have affected the specificity of this variable. We excluded patients with severe TR from the control group (included in the Mayo Clinic study) since we wanted a strict comparison between CP and RCM and did not want the confounders of severe TR in the population. This may limit the ability to generalize these results. In healthy individuals,
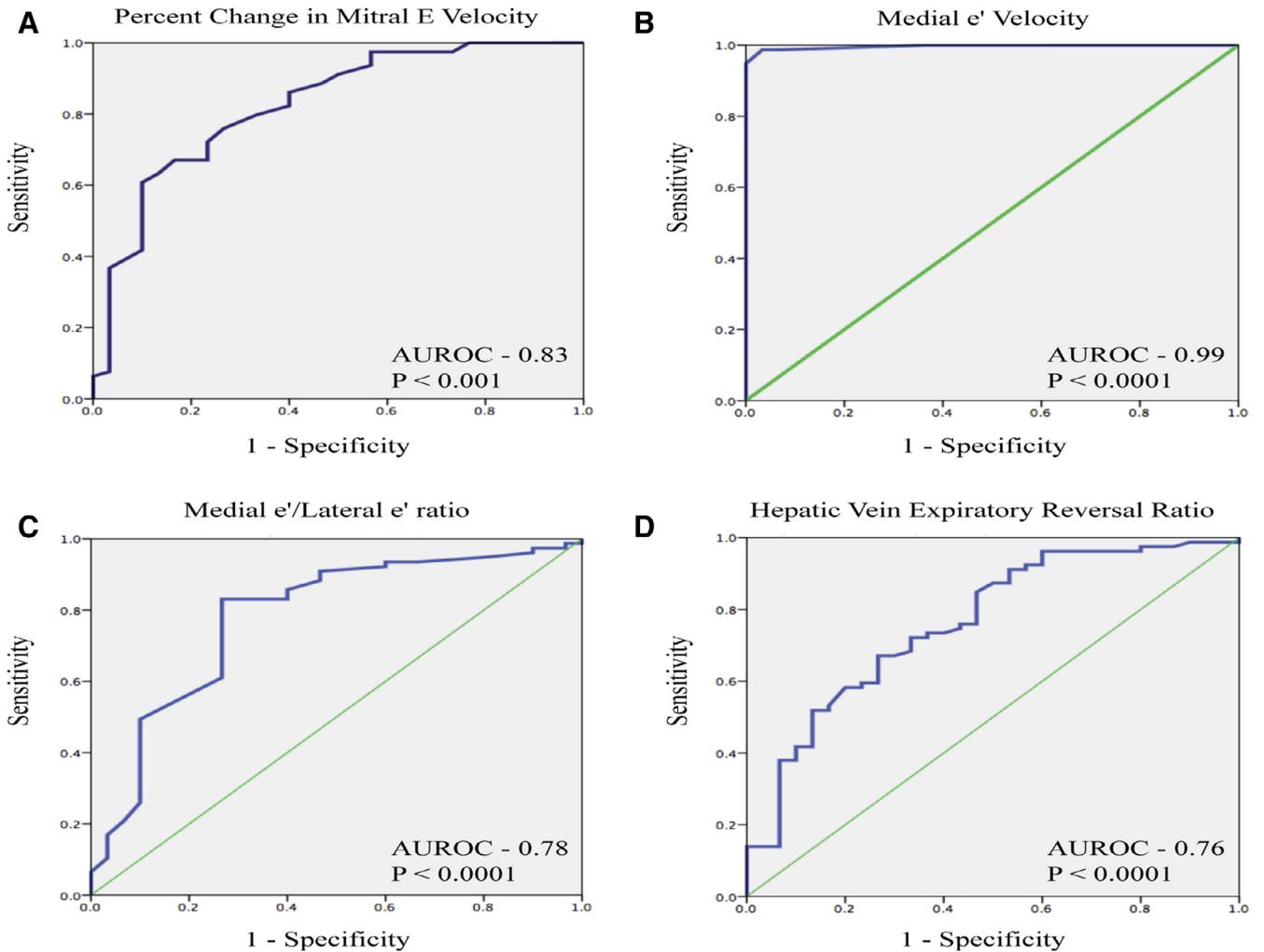
Figure 5. Area under receiver operating characteristic curves (AUROC) for continuous variables. (A) Percent change in Mitral E early diastolic velocity with inspiration; (B) Medial mitral annular early (e') diastolic tissue Doppler velocity; (C) Medial e'/Lateral e' velocity ratio (ratio of medical mitral annular early (e') diastolic tissue Doppler velocity to lateral mitral annular (e') early diastolic tissue Doppler velocity; (D) Hepatic vein expiratory diastolic reversal ratio (defined as ratio of pulsed wave diastolic reversal velocity/forward diastolic velocity in expiration).

Table 2

Test performance characteristics for the diagnosis of CP in our study versus Mayo Clinic Study

Echocardiographic variables	Sensitivity Mayo/Study	Specificity Mayo/Study	Positive predictive value Mayo/Study	Negative predictive value Mayo/Study
#1 Ventricular septal shift	93%/94%	69%/77%	92%/94%	74%/79%
#2 Percent change in mitral E velocity ≥14.6%	84%/75%	73%/73%	92%/91%	55%/46%
#3Medial e' velocity ≥9 cm/sec	83%/79%	81%/100%	94%/100%	57%/59%
#4Medial e'/Lateral e' ≥0.91	75%/67%	85%/73%	95%/90%	50%/39%
#5 HV ratio in expiration ≥0.79	76%/70%	88%/43%	96%/76%	49%/35%
Ventricular septal shift + medial e' velocity ≥9 cm/sec **#1 and #3**	80%/80%	100%/92%	97%/ 100%	56%59%

Ventricular septal shift + medial e'velocity ≥9 cm/sec
  +HV ratio ≥0.79
  #1 both with #3 and #5
	64/70	100/97	100/99	57/42

HV ratio, ratio of pulsed wave hepatic vein diastolic reversal velocity to forward velocity in expiration; Percent change in Mitral E velocity, defined as (Mitral early diastolic E wave velocity in expiration-Mitral early diastolic E velocity in inspiration/mitral early diastolic E wave velocity in inspiration × 100); Medial mitral e', Medial mitral annular early diastolic tissue Doppler (e') velocity; Medial e'/lateral e', ratio of medial to lateral Mitral annular early diastolic tissue Doppler (e') velocity.

Medial e' ≥9 cm/sec is a normal finding and alone may not be significant value, but in patients with high suspicion of cardiac constriction, this parameter is highly specific for this diagnosis.

In conclusion, cardiac constriction is underdiagnosed and can be confused with cardiac restriction. Constrictive Pericarditis is potentially curable with pericardiectomy. Echocardiographic tools with high accuracy can help to differentiate this condition.

Disclosure

The authors declare no conflict of interests.

1. Yoo KJ, Youn YN, Chang BC, Jang Y, Chung N, Ha JW. The incidence and clinical outcome of constrictive physiology after coronary artery bypass graft surgery. *J Am Coll Cardiol* 2013;61:2110–2112.
2. Matsuyama K, Matsumoto M, Sugita T, Nishizawa J, Yoshioka T, Tokuda Y, Ueda Y. Clinical characteristics of patients with constrictive pericarditis after coronary bypass surgery. *Jpn Circ J* 2001;65: 480–482.
3. Wood P. Chronic constrictive pericarditis. *Am J Cardiol* 1961;7: 48–61.
4. Bertog SC1, Thambidorai SK, Parakh K, Schoenhagen P, Ozduran V, Houghtaling PL, Lytle BW, Blackstone EH, Lauer MS, Klein AL. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. *J Am Coll Cardiol* 2004;43:1445–1452.
5. Oh JK, Hatle LK, Seward JB, Danielson GK, Schaff HV, Reeder GS, Tajik AJ. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol* 1994;23:154–162.
6. Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989;79:357–370.
7. Klein AL, Abbara S, Agler DA, Appleton CP, Asher CR, Hoit B, Hung J, Garcia MJ, Kronzon I, Oh JK, Rodriguez ER, Schaff HV, Schoenhagen P, Tan CD, White RD. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. *J Am Soc Echocardiogr* 2013;26:965–1012.
8. Ha JW, Ommen SR, Tajik AJ, Barnes ME, Ammash NM, Gertz MA, Seward JB, Oh JK. Differentiation of constrictive pericarditis from restrictive cardiomyopathy using mitral annular velocity by tissue Doppler echocardiography. *Am J Cardiol* 2004;94:316–319.
9. Choi JH, Choi JO, Ryu DR, Lee SC, Park SW, Choe YH, Oh JK. Mitral and tricuspid annular velocities in constrictive pericarditis and restrictive cardiomyopathy: correlation with pericardial thickness on computed tomography. *JACC Cardiovasc Imaging* 2011;4: 567–575.
10. Reuss CS, Wilansky SM, Lester SJ, Lusk JL, Grill DE, Oh JK, Tajik AJ. Using mitral 'annulus reversus' to diagnose constrictive pericarditis. *Eur J Echocardiogr* 2009;10:372–375.
11. Welch TD, Ling LH, Espinosa RE, Anavekar NS, Wiste HJ, Lahr BD, Schaff HV, Oh JK. Echocardiographic diagnosis of constrictive pericarditis: Mayo Clinic criteria. *Circ Cardiovasc Imaging* 2014;7:526–534.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015 Mar;16:233–270.
13. Talreja DR, Edwards WD, Danielson GK, Schaff HV, Tajik AJ, Tazelaar HD, Breen JF, Oh JK. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation* 2003;7.