

Echocardiographic Diagnosis of Constrictive Pericarditis Mayo Clinic Criteria

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Background—Constrictive pericarditis is a potentially reversible cause of heart failure that may be difficult to differentiate from restrictive myocardial disease and severe tricuspid regurgitation. Echocardiography provides an important opportunity to evaluate for constrictive pericarditis, and definite diagnostic criteria are needed.

Methods and Results—Patients with surgically confirmed constrictive pericarditis (n=130) at Mayo Clinic (2008–2010) were compared with patients (n=36) diagnosed with restrictive myocardial disease or severe tricuspid regurgitation after constrictive pericarditis was considered but ruled out. Comprehensive echocardiograms were reviewed in blinded fashion. Five principal echocardiographic variables were selected based on prior studies and potential for clinical use: (1) respiration-related ventricular septal shift, (2) variation in mitral inflow E velocity, (3) medial mitral annular e' velocity, (4) ratio of medial mitral annular e' to lateral e', and (5) hepatic vein expiratory diastolic reversal ratio. All 5 principal variables differed significantly between the groups. In patients with atrial fibrillation or flutter (n=29), all but mitral inflow velocity remained significantly different. Three variables were independently associated with constrictive pericarditis: (1) ventricular septal shift, (2) medial mitral e', and (3) hepatic vein expiratory diastolic reversal ratio. The presence of ventricular septal shift in combination with either medial e' ≥ 9 cm/s or hepatic vein expiratory diastolic reversal ratio ≥ 0.79 corresponded to a desirable combination of sensitivity (87%) and specificity (91%). The specificity increased to 97% when all 3 factors were present, but the sensitivity decreased to 64%.

Conclusions—Echocardiography allows differentiation of constrictive pericarditis from restrictive myocardial disease and severe tricuspid regurgitation. Respiration-related ventricular septal shift, preserved or increased medial mitral annular e' velocity, and prominent hepatic vein expiratory diastolic flow reversals are independently associated with the diagnosis of constrictive pericarditis. (*Circ Cardiovasc Imaging*. 2014;7:526–534.)

Key Words: echocardiography ■ pericarditis, constrictive

Constrictive pericarditis is a potentially reversible cause of heart failure. Diagnosis may be challenging because the presentation can be similar to that of restrictive myocardial disease, severe tricuspid regurgitation, and some noncardiac conditions. Occasionally, these conditions may even coexist. Echocardiography is recommended for all patients with heart failure¹ and, therefore, provides an important opportunity to evaluate for constrictive pericarditis.

Clinical Perspective on p 534

Prior studies have shown the usefulness of respiration-related ventricular septal shift,² respiratory variation in transmitral and hepatic vein Doppler profiles,^{2,3} and mitral annular early diastolic tissue Doppler velocity^{4,5} in diagnosing constrictive pericarditis and distinguishing it from restrictive myocardial disease. A recent consensus document recommends these echocardiographic parameters.⁶ However, the sensitivity and

specificity of these and other echocardiographic parameters, alone and in combination, have not been well established. This study provides a large-scale and blinded appraisal of a set of modern echocardiographic criteria that may be used readily in clinical practice for detecting constrictive pericarditis.

Methods

Patient Population

The study population consisted of patients with surgically confirmed constrictive pericarditis at the Mayo Clinic (Rochester, MN) from January 2008 to December 2010. The Mayo Clinic cardiothoracic surgical database was searched for all cases that included pericardiectomy. These were then reviewed to ensure that the pericardiectomy was performed for a surgically confirmed diagnosis of constrictive pericarditis and that there was a preoperative comprehensive 2-dimensional (2D) and Doppler echocardiogram with simultaneous recording of respiration. Of 206 cases, 130 were eligible for inclusion. Constrictive pericarditis was thought to be idiopathic or related to rheumatologic

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disease or prior pericarditis in 77 patients, related to prior cardiac surgery in 39 patients, and related to prior chest radiation in 14 patients.

The comparison group consisted of patients with restrictive myocardial disease or severe tricuspid regurgitation during the same time period in whom constrictive pericarditis was considered in the differential diagnosis but rigorously excluded. The Mayo Clinic cardiac catheterization, echocardiography, and cardiothoracic surgical databases were searched for patients with either restrictive cardiomyopathy or severe tricuspid regurgitation who had also undergone comprehensive 2D and Doppler echocardiography with simultaneous recording of respiration because of clinical concern for concomitant constrictive pericarditis. The resulting comparison group (n=36) consisted of 22 patients with restrictive myocardial disease, 12 patients with severe tricuspid regurgitation, and 2 patients with evidence of both severe tricuspid regurgitation and restrictive myocardial disease. Constrictive pericarditis had been considered in the differential diagnosis for all of these patients in the comparison group and was ruled out through complex hemodynamic catheterization (including endomyocardial biopsy) and, in some cases, direct surgical inspection. Of the 36 patients in the comparison group, 25 underwent complex hemodynamic catheterization. Constrictive physiology was ruled out through demonstration of concordant respiration-related changes in simultaneously obtained right and left ventricular pressure waveforms.⁷ Ten patients also underwent right ventricular endomyocardial biopsy that showed pathological changes consistent with a primary restrictive cardiomyopathy in all cases. Thirteen patients underwent direct surgical inspection that ruled out constriction.

All patients presented with dyspnea (at least New York Heart Association functional class II) and on examination had increased jugular venous pressure and lower extremity edema. The protocol was approved by the Institutional Review Board of the Mayo Clinic.

Echocardiographic Examination

All patients underwent comprehensive evaluation using commercially available ultrasound equipment with an imaging transducer having pulsed-wave and tissue Doppler capabilities. A nasal respirometer was used for simultaneous recording of respiration. All measurements and assessments were confirmed by consensus among ≥ 2 echocardiographers who were blinded to the diagnosis.

Two-dimensional imaging was performed from parasternal, apical, and subcostal windows. The parasternal and apical views were used to detect the presence of ventricular septal shift, defined as any degree of cyclic movement of the ventricular septum toward the left ventricle with inspiration and toward the right ventricle with expiration. When available, M-mode recordings of ventricular septal motion were incorporated into the assessment. A beat-to-beat septal diastolic shudder was also noted when present. Apical views were also used to detect distortion of the normal ventricular contours by a constrictive pericardium. The subcostal view was used to identify tethering of the right ventricular free wall at its interface with the liver and also to measure maximum and minimum (with inspiration) diameters of the inferior vena cava at the entrance of the hepatic vein. All 3 windows were used to assess for pericardial thickening and pericardial effusion by qualitative visual assessment.

Doppler information was obtained from apical, subcostal, right supraclavicular, and parasternal imaging windows. From the apical window, pulsed-wave Doppler recordings at the level of the mitral leaflet tips were used to measure early (E) and atrial (A) diastolic velocities, deceleration time of the E wave, and respiratory variation in the E velocity. The respiration-related percent change in E was calculated as $(E_{\text{Expiration}} - E_{\text{Inspiration}}) / E_{\text{Inspiration}} \times 100$. Tissue Doppler assessment of mitral annular motion was used to record and compare medial and lateral early (e') relaxation diastolic velocities. From the subcostal window, pulsed-wave Doppler recordings of hepatic vein velocities allowed measurement of forward and reversal velocities in systole and diastole during both inspiration and expiration. The hepatic vein expiratory diastolic reversal ratio was defined as follows: (diastolic reversal velocity/forward velocity) in expiration. The inferior vena cava diameter was measured in the long axis in expiration and in inspiration (using the sniff test). From the right supraclavicular window, pulsed-wave Doppler recordings of superior vena cava forward velocities allowed comparison of systolic flow in inspiration and expiration.

The respiration-related percent change in velocity was calculated as $(V_{\text{Expiration}} - V_{\text{Inspiration}}) / V_{\text{Inspiration}} \times 100$. All of these imaging windows and the parasternal window were used to determine the maximum tricuspid regurgitation velocity using continuous wave Doppler.

Statistical Analysis

In general, differences in echocardiographic variables between patients with a diagnosis of constrictive pericarditis and those with either restrictive myocardial disease or severe tricuspid regurgitation were assessed using a Student *t* test for continuous data and a χ^2 test for categorical data. Exceptions to this included continuous variables that were highly skewed from visual inspection, which were assessed using a Wilcoxon rank sum test, and categorical variables with extremely sparse data for which a Fisher exact test was performed.

Among the echocardiographic variables, 5 a priori selected variables were further evaluated for test performance. These were selected by consensus among the authors based on extensiveness of prior study and potential for widespread clinical adoption. In particular, receiver operating characteristic (ROC) curves from univariable logistic regression models were generated for each of the 4 continuous scaled variables for purposes of quantifying discriminative ability (via *c*-statistic, equivalent to the area under the ROC curve) and selecting a cut point along the curve yielding optimal test performance by minimizing the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$.² Sensitivity, specificity, positive predictive value, and negative predictive value were then estimated based on the dichotomous versions for each of the 5 echocardiographic variables.

Finally, all 5 candidate variables were entered into a multivariable logistic model, which was pruned with stepwise variable selection using an α level of 0.05. We treated each variable, except septal shift, as continuous in the model. For the 3 variables that were ultimately selected from this modeling process, we summarized all possible combinations of these criteria (using dichotomous cut points described above) in terms of their combined test performance for distinguishing patients with constrictive pericarditis from those with restrictive myocardial disease or severe tricuspid regurgitation.

For secondary analyses, similar methods as those described above (Student *t* test, analysis of variance, or χ^2 test as appropriate) were used to test the association of each of the 5 echocardiographic variables with a diagnosis of constrictive pericarditis in the subset of patients with atrial fibrillation or flutter and with types of pathogenesis in the subset of patients with constrictive pericarditis.

All analyses were performed using the SAS statistical software package (version 9.2, SAS Institute Inc, Cary, NC) and R (version 2.14.0, R Development Core Team [2011]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>).

Results

Demographics

There were 130 patients in the constrictive pericarditis group and 36 patients in the nonconstrictive pericarditis group. Although mean age was similar for the 2 groups (62.0 ± 12.2 versus 61.3 ± 13.3 years; $P=0.74$), there were significantly more men in the constrictive pericarditis group (82% versus 47%; $P<0.001$).

With univariable analysis, numerous echocardiographic variables were associated with the diagnosis of constrictive pericarditis. Results are summarized in Table 1.

2D Echocardiographic Data

The diagnosis of constrictive pericarditis was associated with a higher left ventricular ejection fraction ($60.2 \pm 6.9\%$ versus $55.9 \pm 11.6\%$; $P=0.006$) and greater presence of pericardial thickening (85% versus 19%; $P<0.001$), ventricular septal

diastolic shudder and respiration-related shift (93% versus 31%; $P<0.001$; Figure 1), distortion of the ventricular contour (34% versus 0%; $P<0.001$), and tethering of the right ventricular free wall (61% versus 30%; $P=0.003$). Pericardial effusion was observed more commonly in the nonconstrictive pericarditis group (28% versus 10%; $P=0.006$). The inferior

vena cava was plethoric (diameter >21 mm or $<50\%$ collapse with inspiration) in nearly all patients in both groups.

Doppler Echocardiographic Data

The diagnosis of constrictive pericarditis was associated with greater respiration-related change in mitral E velocity

Table 1. Summary of Demographic and Echocardiographic Data

Variable	Other Diagnosis (n=36)		Constrictive Pericarditis (n=130)		P Value†
	n	Mean±SD*	n	Mean±SD*	
Age	36	61.3±13.3	130	62.0±12.2	0.74
Male sex, n (%)	36	17 (47%)	130	107 (82%)	<0.001
EF, %	36	55.9±11.6	130	60.2±6.9	0.006
Pericardial thickening, n (%)	36	7 (19%)	129	110 (85%)	<0.001
Effusion, n (%)	36	10 (28%)	130	13 (10%)	0.006
Ventricular septal shift, n (%)	36	11 (31%)	130	121 (93%)	<0.001
Ventricular septal shudder, n (%)	36	16 (44%)	130	125 (96%)	<0.001
Mitral E velocity in inspiration, cm/s	33	110.6±43.3	123	80.9±35.8	<0.001
Mitral E velocity in expiration, cm/s	33	123.3±46.0	123	101.7±38.2	0.007
Percent change in mitral E velocity	33	13.7±17.0	123	30.7±20.4	<0.001
Mitral A velocity in inspiration, cm/s, median (Q1, Q3)	31	18.0 (0, 77.0)	123	41.0 (25.0, 51.0)	0.39
Mitral A velocity in expiration, cm/s, median (Q1, Q3)	31	22.0 (0, 83.0)	123	44.0 (29.0, 61.0)	0.28
E/A ratio in inspiration	17	1.9±1.0	98	1.6±0.8	0.23
E/A ratio in expiration	17	2.0±1.0	98	1.9±0.8	0.73
Deceleration time expiration/inspiration	29	1.1±0.1	119	1.2±0.2	0.06
Medial e' velocity, cm/s	36	7.0±2.6	128	12.9±4.1	<0.001
Medial E/e' ratio, median (Q1, Q3)	33	16.1 (11.6, 21.2)	123	5.8 (3.6, 9.3)	<0.001
Lateral e' velocity, cm/s	33	9.0±2.5	114	11.9±3.9	<0.001
Lateral E/e' ratio, median (Q1, Q3)	30	12.0 (8.9, 16.1)	111	6.4 (4.3, 9.7)	<0.001
Medial e'/lateral e' ratio	33	0.8±0.2	114	1.2±0.4	<0.001
Right ventricle tethered to liver, n (%)	30	9 (30%)	112	68 (61%)	0.003
Left or right ventricular distortion, n (%)	36	0 (0%)	130	44 (34%)	<0.001
IVC max diameter, cm	36	2.5±0.6	130	2.6±0.5	0.65
IVC min diameter, cm	36	2.0±0.7	129	2.2±0.5	0.12
Percent change in IVC	36	22.5±14.8	129	16.3±11.3	0.008
IVC max diameter >21 mm or % change $<50\%$, n (%)	36	33 (92%)	130	128 (98%)	0.06
HV systolic velocity in inspiration, cm/s, median (Q1, Q3)	34	0 (0, 20.0)	127	28.0 (17.0, 37.0)	<0.001
HV systolic velocity in expiration, cm/s, median (Q1, Q3)	34	0 (0, 14.0)	127	23.0 (14.0, 31.0)	<0.001
HV systolic reversal velocity in inspiration, cm/s	34	35.1±16.6	127	17.0±9.4	<0.001
HV systolic reversal velocity in expiration, cm/s	34	34.6±15.7	127	24.3±12.0	<0.001
HV diastolic velocity in inspiration, cm/s	34	69.5±25.1	127	50.7±21.5	<0.001
HV diastolic velocity in expiration, cm/s	34	48.1±20.1	127	30.9±16.7	<0.001
HV diastolic reversal velocity in inspiration, cm/s	34	21.2±15.1	127	24.3±10.9	0.18
HV diastolic reversal velocity in expiration, cm/s	34	24.1±16.7	127	35.0±12.7	<0.001
HV diastolic reversal/velocity in expiration	33	0.5±0.4	124	1.4±0.7	<0.001
HV diastolic reversal expiration/inspiration	26	1.1±0.6	125	1.5±0.6	0.001
Percent change in SVC velocity	17	-2.7±32.5	108	-5.8±18.5	0.57
TR velocity max, m/s	35	2.8±0.7	124	2.6±0.5	0.027

A indicates atrial; E, early; EF, ejection fraction (left ventricle); HV, hepatic vein; IVC, inferior vena cava; Q, quartile; SVC, superior vena cava; and TR, tricuspid regurgitation.

*Mean±SD unless otherwise noted.

†P values are from Student *t* tests or Wilcoxon rank sum tests as appropriate for continuous variables. P values for categorical variables are from χ^2 tests. The left or right ventricular distortion P value is from a Fisher exact test.

($30.7 \pm 20.4\%$ versus $13.7 \pm 17.0\%$; $P < 0.001$; Figure 2) and a marginally greater ratio of deceleration time in expiration versus inspiration ($P = 0.06$). Mitral inflow E/A ratios did not differ significantly between the groups in either inspiration (1.6 ± 0.8 versus 1.9 ± 1.0 ; $P = 0.23$) or expiration (1.9 ± 0.8 versus 2.0 ± 1.0 ; $P = 0.73$).

Higher mitral annular e' velocities were strongly associated with constrictive pericarditis (Figure 3). This was most pronounced at the medial mitral annulus, where mean (\pm SD) e' velocities were $12.9 (\pm 4.1)$ cm/s in the constrictive pericarditis group and $7.0 (\pm 2.6)$ cm/s in the nonconstrictive pericarditis group ($P < 0.001$). The presence of annulus reversus, or medial e' > lateral e', was also associated with constrictive pericarditis, with a mean medial e'/lateral e' ratio of $1.2 (\pm 0.4)$ in the constrictive pericarditis group and $0.8 (\pm 0.2)$ in the nonconstrictive pericarditis group ($P < 0.001$). Higher average e' values in the constrictive pericarditis group naturally led to lower E/e' ratios ($5.8 [3.6, 9.3]$ versus $16.1 [11.6, 21.2]$; $P < 0.001$ at the medial mitral annulus).

Hepatic vein velocities differed widely between the 2 groups. The constrictive pericarditis group had higher forward systolic velocities, lower systolic reversal velocities, and lower forward diastolic velocities in both inspiration and expiration ($P < 0.001$ for each). The constrictive pericarditis group also had higher diastolic reversal velocities in expiration only ($P < 0.001$). A higher expiratory diastolic reversal ratio (1.4 ± 0.7 versus 0.5 ± 0.4 ; $P < 0.001$) was strongly associated with constrictive pericarditis (Figure 4). On average, the superior vena cava systolic velocity changed minimally with respiration in both groups ($-5.8 \pm 18.5\%$ in constrictive pericarditis versus $-2.7 \pm 32.5\%$; $P = 0.57$).

Compared with the constrictive pericarditis group, a higher average maximum tricuspid regurgitation velocity (2.8 ± 0.7 versus 2.6 ± 0.5 ; $P = 0.027$) was observed in the nonconstrictive pericarditis group, although the average maximum tricuspid regurgitation velocity was noticeably elevated in the constrictive pericarditis group as well.

Multivariable Analysis

Five a priori selected variables were evaluated in multivariable analysis on the basis of developing criteria to identify the

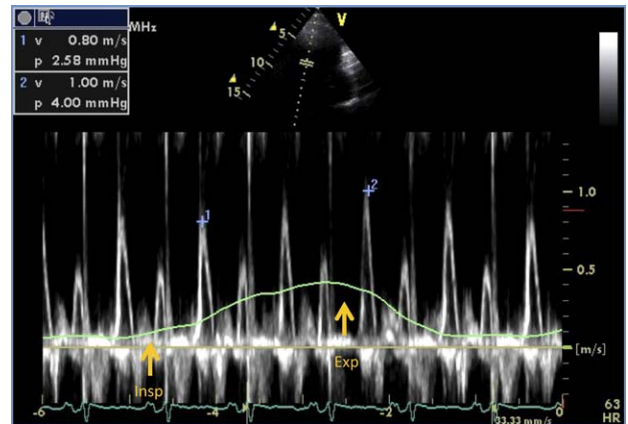


Figure 2. Pulsed-wave Doppler recording (apical window) at the level of the open mitral leaflet tips in a patient with constrictive pericarditis. Note inspiratory decrease and expiratory increase in early (E) inflow velocity. Exp indicates expiration; and insp, inspiration.

likelihood of constrictive pericarditis: (1) ventricular septal shift, (2) % change in mitral E velocity, (3) medial e' velocity, (4) medial e'/lateral e', and (5) hepatic vein expiratory diastolic reversal ratio. From a stepwise-selected multivariable model of the 5 candidate variables, the presence of ventricular septal shift (odds ratio=7.71; 95% confidence interval, 2.28–26.09; $P = 0.001$), increased levels of medial e' velocity (odds ratio=5.11 expressed per 5 cm/s; 95% confidence interval, 1.91–13.66; $P = 0.001$), and hepatic vein diastolic flow reversal ratio (odds ratio=3.02 expressed per 0.5; 95% confidence interval, 1.31–6.99; $P = 0.010$) corresponded to a significantly increased likelihood of constrictive pericarditis. Neither respiratory variation in mitral E velocity nor annulus reversus (medial e' > lateral e') was independently associated with constrictive pericarditis.

Test Performance Characteristics

Based on ROC analyses for 4 of the 5 candidate variables that were continuous, each showed excellent discriminative ability as measured by area under the ROC, which ranged from 0.79 to 0.89 (Figure 5). For each of these 4 variables dichotomized at the optimal cut point on the ROC curve and presence of septal shift, Table 2 summarizes the test performance characteristics. Sensitivities ranged from 75% to 93%, with the presence of a ventricular septal shift being the most sensitive finding. Positive predictive values were uniformly high and ranged from 92% to 96%, with a hepatic vein expiratory diastolic reversal ratio ≥ 0.79 having the highest positive predictive value. Table 2 also summarizes the test performance characteristics of combinations of the 3 factors found to be independently associated with constrictive pericarditis.

Atrial Fibrillation or Flutter

In a small subgroup of patients with atrial fibrillation or flutter ($n = 29$), each of the 5 key variables except for variation in mitral inflow velocity demonstrated an association with constrictive pericarditis in univariable analysis (Table 3).

Results by Pathogenesis

The group of patients with constrictive pericarditis was divided into 3 subgroups according to pathogenesis: (1) idiopathic, postpericarditis, and rheumatologic ($n = 77$); (2) postcardiac

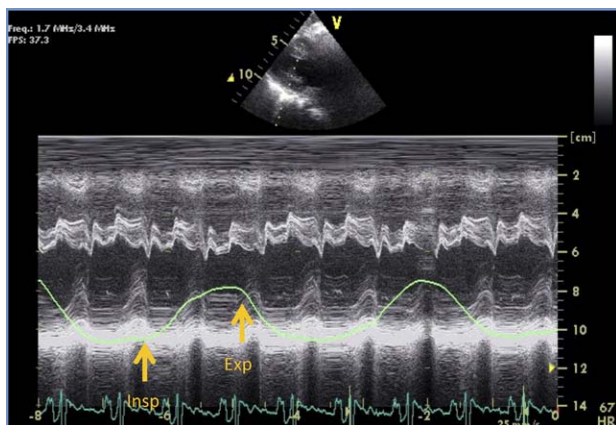


Figure 1. Midventricular septal M-mode recording (parasternal long axis) in a patient with constrictive pericarditis. Note leftward ventricular septal shift in inspiration. Also evident is a beat-to-beat septal diastolic shudder. Exp indicates expiration; and insp, inspiration.

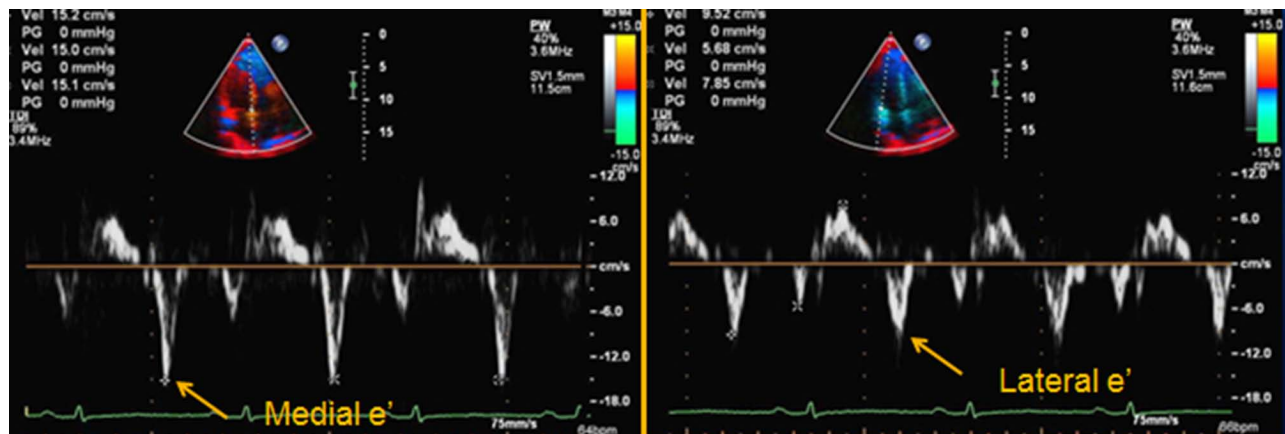


Figure 3. Medial (left) and lateral (right) mitral annular tissue Doppler recording (apical window) in a patient with constrictive pericarditis. Note normal to increased early relaxation velocity (e'), with medial velocity greater than lateral (annulus reversus).

surgery ($n=39$); and (3) chest radiation ($n=14$). Results for the 5 candidate echocardiographic variables are shown in Table 4. Compared with patients with an idiopathic, postpericarditis, or rheumatologic pathogenesis, patients after cardiac surgery had lower medial e' velocity ($P<0.001$) and hepatic vein expiratory diastolic reversal ratios ($P=0.002$), whereas patients after chest radiation had less mitral inflow variation ($P=0.010$) and lower medial e' velocity ($P<0.001$).

Discussion

To our knowledge, this is the largest and only blinded evaluation of modern echocardiographic criteria for the diagnosis of constrictive pericarditis among patients presenting with heart failure.

The fundamental pathophysiologic mechanisms in constrictive pericarditis include dissociation of intrathoracic and intracardiac pressures along with interventricular coupling or dependence within a fixed space. These mechanisms can be identified with 2D and Doppler echocardiography based on the position and motion of the ventricular septum, variation in the mitral inflow velocity, and variation in the hepatic

vein profile. The use of tissue Doppler to measure the velocity of the mitral annulus and compare medial and lateral velocities completes the assessment. These 5 principal echocardiographic criteria are the focus of this study and are consistent with a recently published consensus statement.⁶

Abnormal Ventricular Septal Motion

Abnormalities in ventricular septal position and motion often provide the first clue to the diagnosis of constrictive pericarditis because analysis of ventricular wall motion is a fundamental part of nearly every echocardiographic examination.

Dissociation of intrathoracic and intracardiac pressures leads to a decreased gradient for diastolic filling of the left-sided cardiac chambers during inspiration. The pulmonary venous system, which is intrathoracic, experiences

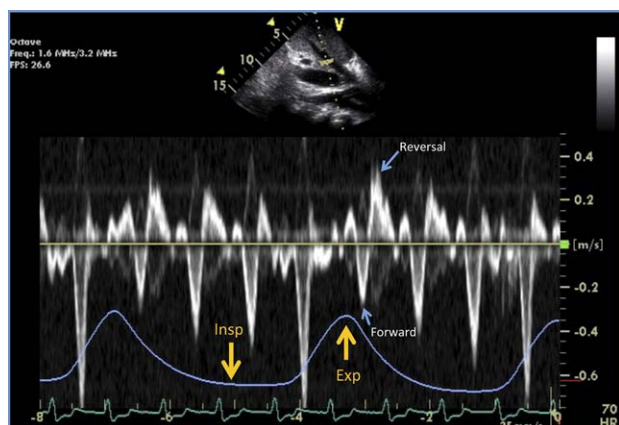


Figure 4. Pulsed-wave Doppler recording (subcostal window) within the hepatic vein in a patient with constrictive pericarditis. Note prominent diastolic flow reversals in expiration, with the diastolic reversal ratio defined as reversal velocity divided by forward velocity (≈ 0.35 m/s reversal velocity divided by ≈ 0.30 cm/s forward flow velocity yields a diastolic reversal ratio of 1.2). Exp indicates expiration; and insp, inspiration.

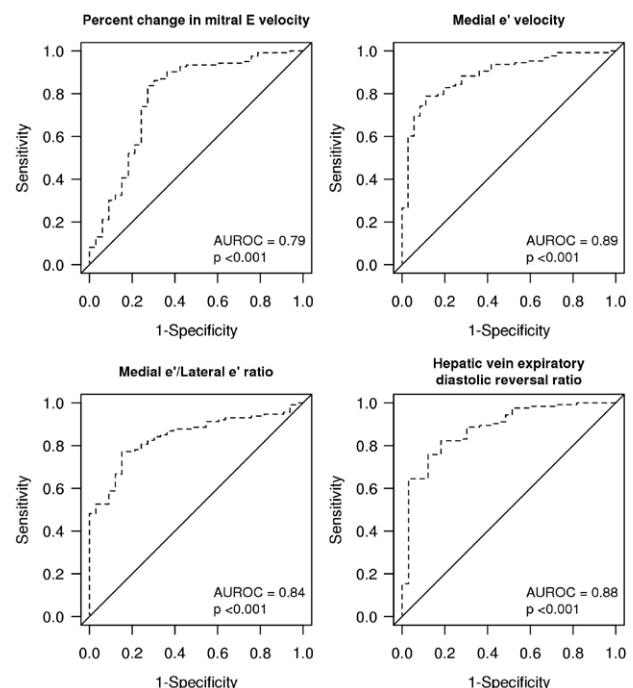


Figure 5. Receiver operating characteristic (ROC) curves for continuous echocardiographic variables. AUROC indicates area under ROC.

Table 2. Test Performance Characteristics for the Diagnosis of Surgically Confirmed Constrictive Pericarditis

Variable	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Individual variables				
No. 1 ventricular septal shift	93	69	92	74
No. 2 change in mitral E velocity $\geq 14.6\%$	84	73	92	55
No. 3 medial e' velocity ≥ 9 cm/s	83	81	94	57
No. 4 medial e'/lateral e' ≥ 0.91	75	85	95	50
No. 5 HV ratio in expiration ≥ 0.79	76	88	96	49
Combinations among Nos. 1, 3, and 5*				
No. 1 (with or without Nos. 3 and 5)	93	69	92	74
Nos. 1 and 3 (with or without No. 5)	80	92	97	56
No. 1 with No. 3 or 5	87	91	97	65
No. 1 with both Nos. 3 and 5	64	97	99	42

HV indicates hepatic vein; and ROC, receiver operating characteristic.

*Combinations limited to factors significant from final selected multivariable model. Cut points for continuous variables were selected from ROC analysis: ventricular septal shift, medial e' velocity (≥ 9 cm/s), and HV diastolic reversal/velocity in expiration (≥ 0.79).

a larger pressure drop with inspiration compared with the left-sided cardiac chambers, which in constrictive pericarditis are usually encased or insulated in a noncompliant, thickened, fibrotic, and often calcified pericardium.

Shifting of the position of ventricular septum with inspiration is a manifestation of both the dissociation of intrathoracic and intracardiac pressures described above and the phenomenon of interventricular dependence within a fixed space. Decreased filling of the left-sided cardiac chambers in inspiration causes an obligatory shift of the interventricular septum toward the left ventricle and increased filling of the right-sided cardiac chambers. In expiration, left-sided filling increases and right-sided filling decreases; therefore, the septum shifts back toward the right ventricle. The finding of ventricular septal shift ranges from subtle to obvious and is best appreciated using long (eg, 10-beat) acquisitions of 2D wall motion from multiple imaging windows. M-mode is also helpful because of its superior temporal resolution.

The presence of ventricular septal shift in constrictive pericarditis has been recognized,² but test performance characteristics have not been evaluated previously. The presence of ventricular septal shift was the most sensitive (93%) of the 5 variables we evaluated and probably the most important for the diagnosis of constrictive pericarditis. This important finding may provide

an initial diagnostic clue for constrictive pericarditis during an echocardiographic examination in patients with heart failure, even when the diagnosis has not been clinically suspected.

Also present in nearly all patients with constrictive pericarditis was abnormal beat-to-beat (regardless of phase in respiratory cycle) diastolic ventricular septal motion. The motion is oscillatory, has the appearance of a shudder, and is best appreciated on M-mode recordings of ventricular septal motion. This has been reported previously⁸⁻¹⁰ and may relate to ventricular interdependence occurring on a millisecond scale because of subtle differences in timing of tricuspid and mitral valve opening and right and left atrial contraction. We elected not to assess test performance characteristics for the septal shudder or to include it in multivariable analysis because abnormal beat-to-beat septal motion from other mechanisms (eg, conduction abnormalities and postoperative septal motion) was present in a substantial number (44%) of patients without constrictive pericarditis and would be difficult to differentiate clinically.

Mitral Inflow Doppler Profile

Dissociation of intrathoracic and intracardiac pressures is revealed on Doppler evaluation by an inspiratory decrease in mitral E velocity and a shortening of the deceleration time, which is a measure of the rapidity with which left atrial

Table 3. Summary of Echocardiographic Data for Patients in Atrial Fibrillation or Flutter

Variable	Other Diagnosis (n=9)		Constrictive Pericarditis (n=20)		P Value†
	n	Mean \pm SD*	n	Mean \pm SD*	
Ventricular septal shift, n (%)	9	2 (22%)	20	15 (75%)	0.014
Percent change in mitral E velocity	8	12.4 \pm 23.1	17	24.3 \pm 20.1	0.20
Medial e' velocity, cm/s	9	8.3 \pm 3.5	20	11.9 \pm 3.9	0.027
Medial e'/lateral e' ratio	9	0.7 \pm 0.2	13	1.1 \pm 0.3	0.013
HV expiratory diastolic reversal/forward velocity	9	0.3 \pm 0.3	20	0.9 \pm 0.5	0.006

HV indicates hepatic vein.

*Mean \pm SD unless otherwise noted.

†P value from Student *t* tests or Fisher exact tests as appropriate.

Table 4. Summary of Echocardiographic Data According to Pathogenesis for Constrictive Pericarditis

Variable	Idiopathic, Rheumatologic, Postpericarditis (n=77)		Postcardiac Surgery (n=39)		History of Chest Radiation (n=14)		Unadjusted P Value†
	n	Mean±SD*	n	Mean±SD*	n	Mean±SD*	
Ventricular septal shift, n (%)	77	73 (95%)	39	37 (95%)	14	11 (79%)	0.08
Percent change in mitral E velocity	76	34.7±23.0	33	26.9±13.4	14	18.2±10.7	0.009
Medial e' velocity, cm/s	76	14.5±3.7	38	11.1±3.5	14	9.5±3.7	<0.001
Medial e'/lateral e' ratio	67	1.2±0.3	34	1.1±0.3	13	1.0±0.4	0.09
HV diastolic reversal/velocity in expiration	72	1.5±0.7	38	1.1±0.6	14	1.2±0.7	0.005

HV indicates hepatic vein.

*Mean±SD unless otherwise noted.

†Analysis of variance P value for continuous variables and χ^2 P value for categorical variables.

and ventricular diastolic pressures equilibrate. The opposite changes then occur with expiration, which leads to an increased gradient for filling of the left-sided cardiac chambers. Neither restrictive myocardial disease nor severe tricuspid regurgitation should cause dissociation of intrathoracic and intracardiac pressures and, therefore, would not be expected to lead to significant changes in mitral inflow velocity or deceleration time during the respiratory cycle.

This characteristic respiratory variation in mitral E velocity in constrictive pericarditis has been identified previously in smaller groups of patients by Hatle et al² and Oh et al.³ In these 2 studies, the average change in the E velocity between inspiration and expiration was 30% and 55%, respectively, compared with minimal (<5%) change in restrictive myocardial disease. Our results corroborate that constrictive pericarditis is associated with a significantly greater respiratory change in mitral E (mean of 30.7%), but it also demonstrated a modest degree of respiratory variation in the restrictive myocardial disease and severe tricuspid regurgitation group (mean of 13.7%). The optimal ROC cut point for distinguishing constrictive pericarditis from nonconstrictive pericarditis was $\geq 14.6\%$ change in mitral E velocity. We saw a trend toward a higher ratio of deceleration time in expiration to inspiration for the constrictive pericarditis group, although this was not statistically significant.

Based on our findings, the Doppler filling profile based on the E and A wave configuration was not significantly different between the 2 groups and was generally restrictive (mean E/A ≥ 1.6). This is also consistent with the report by Oh et al.³ Therefore, although not specific for the diagnosis of constrictive pericarditis, a mitral E/A > 1 is a typical finding, especially in the expiratory phase.

Hepatic Vein Doppler Profile

The hepatic veins also provide important evidence for the dissociation of intrathoracic and intracardiac pressures and inter-ventricular dependence expected in constrictive pericarditis. During expiration, the increased filling of the left-sided cardiac chambers shifts the ventricular septum back to the right, and right-sided cardiac chamber filling is reduced. This reduces the hepatic vein forward velocity and exaggerates the late diastolic reversal velocity. In restrictive myocardial disease and severe tricuspid regurgitation, right-sided filling is not as compromised in expiration. The expiratory diastolic forward velocity is, therefore, higher, and the late diastolic reversal velocity

is less pronounced. In isolated severe tricuspid regurgitation, hepatic vein flow reversal occurs during systole.

The prominent reversal of expiratory late diastolic flow in the hepatic veins has been described previously in smaller groups of patients.^{2,3} Our study builds on these findings in a larger group of patients with a novel quantitative measure that we term the hepatic vein expiratory diastolic reversal ratio. The use of this ratio, which is defined as the expiratory diastolic reversal velocity divided by the diastolic forward velocity, takes into account the expected diminution of the diastolic forward flow and accentuation of late-diastolic flow reversal. Higher values would be expected in the setting of constrictive physiology. The finding of a reversal ratio ≥ 0.79 was the most specific (88%) of the 5 variables we evaluated.

Mitral Annular Tissue Velocity

Doppler echocardiography also provides a noninvasive evaluation of myocardial relaxation through measurement of the early diastolic mitral annular tissue velocity (e'), which has been found to be relatively independent of loading conditions and inversely correlated with τ .¹¹ Decreased ventricular relaxation velocity, hence e' velocity, would be expected in heart failure because of myocardial disease but not in constrictive pericarditis.

Prior studies by Garcia et al⁴ and Ha et al⁵ have demonstrated the ability to discriminate between constrictive pericarditis and restrictive myocardial disease using e' velocity. Our study substantiates this finding in a larger number of patients, with an optimal ROC cut point of medial e' ≥ 9 cm/s for the diagnosis of constrictive pericarditis. The preserved or accentuated e' velocity in constrictive pericarditis also leads to a lower-than-expected E/e' velocity ratio in the setting of increased filling pressure. This has been termed annulus paradoxus.¹² In other words, an inverse relationship between the left-sided cardiac filling pressure and the E/e' has been described in constrictive pericarditis.

Another unique finding in constrictive pericarditis is that of the medial mitral e' velocity being equal to or greater than the lateral e' velocity on average, in contrast to what is seen in other forms of heart failure and in the absence of cardiac disease. This phenomenon has been termed annulus reversus and may occur because of tethering of the lateral annulus by the constrictive process.¹³ Our results confirm an association between annulus reversus and constrictive pericarditis with an optimal ROC cut point of ≥ 0.91 . However, this finding was not independently associated with constrictive pericarditis on multivariable analysis.

Other Echocardiographic Findings

Two additional 2D echocardiographic features differed significantly between the groups and could be helpful in making the diagnosis. In the majority (61%) of constrictive pericarditis cases, the right ventricular free wall had the appearance of being tethered at its interface with the liver rather than exhibiting the normal independent sliding motion during the cardiac cycle. However, this finding was also seen in a substantial number (30%) of patients without constrictive pericarditis.

Distortion of the left and right ventricular contour by the constrictive and usually calcified pericardium was a highly specific finding found only in patients with constrictive pericarditis, albeit a minority (34%).

Respiratory change in systolic forward flow velocity in the superior vena cava was minimal in both the constrictive pericarditis and nonconstrictive pericarditis groups, consistent with restricted cardiac filling. This stands in contrast to greater (>35%) changes in superior vena cava forward flow velocity in patients with obstructive lung physiology in whom there is ventricular interdependence and ventricular septal shift because of pronounced respiratory swings in intrathoracic pressure.¹⁴ Because severe obstructive lung disease or other conditions associated with increased respiratory effort may lead to abnormal ventricular septal wall motion and respiratory variation in mitral inflow velocity similar to that seen in constrictive pericarditis, this differentiating feature is clinically useful.

Suggested Diagnostic Approach

Of the 5 echocardiographic criteria studied, the 3 most important for the diagnosis of constrictive pericarditis seem to be the presence of respiration-related ventricular septal shift, preserved or increased medial mitral annular e' velocity, and prominent hepatic vein expiratory diastolic flow reversals. Each of these criteria was also significantly associated with constrictive pericarditis in the subset of patients with atrial fibrillation or flutter.

All patients in this study had clinical heart failure. Nearly every patient (all but 5) had some degree of inferior vena cava plethora (maximum diameter ≥ 21 mm and degree of inspiratory collapse <50%), and this might be considered a prerequisite. Then, a finding of ventricular septal shift provides a highly sensitive starting point. Thereafter, the presence of medial e' velocity ≥ 9 cm/s or hepatic vein expiratory diastolic reversal ratio ≥ 0.79 increases specificity.

The presence of ventricular septal shift and either medial e' velocity ≥ 9 cm/s or hepatic vein expiratory diastolic reversal ratio ≥ 0.79 corresponded to a desirable combination of sensitivity (87%) and specificity (91%). Requiring all 3 criteria to be present increases specificity further (97%) but at the expense of reduced sensitivity (64%).

A decision whether to perform additional testing, including invasive hemodynamics, needs to be individualized. This study was not intended to compare echocardiography to other diagnostic modalities, and in many cases, there will be a finding such as pericardial calcification on a chest radiograph that significantly affects the pretest probability of constrictive pericarditis. However, our data do illustrate that the diagnosis of constrictive pericarditis may be made in many cases by echocardiography without the need for invasive hemodynamic confirmation. Of the 130 real-world patients with surgically

confirmed constrictive pericarditis in this study, only 62 (48%) underwent hemodynamic catheterization before operation.

Study Limitations

Although our study is the largest to date, it is still limited by relatively small numbers of patients, particularly in the nonconstrictive pericarditis group. This affected the scope of our multivariable analysis and was the reason that only 5 echocardiographic variables were considered. These 5 were selected by consensus among the authors on the basis of prior publications and potential for widespread clinical adoption. All 5 of these criteria are featured in a recently published consensus statement on imaging in pericardial disease.⁶ For 4 of these 5 variables that were numeric, we transformed each into a binary classification for the purpose of test performance and ease of interpretation. However, it should be pointed out that these thresholds were based on ROC analysis and thus designed to optimize the test performance in our data. Accordingly, this potential source of optimism bias could mean our findings overestimate the true diagnostic accuracy, and external validation of these criteria is recommended.

Confirmation of constriction versus the other diagnoses was as rigorous as possible. All of the patients in the constrictive pericarditis group could be considered to have undergone gold standard assessment through direct surgical inspection. However, it would be difficult to exclude some concomitant restrictive physiology, particularly in patients with radiation-induced heart disease. Many (36%) in the nonconstrictive pericarditis group also ultimately underwent direct inspection. The remainder had a rigorous evaluation that included complex hemodynamic catheterization±endomyocardial biopsy. The possibility of having missed concomitant constrictive physiology is, therefore, unlikely.

Our ability to assess the rate of echocardiographic false-negatives is limited. Conceivably, there may be patients with constrictive pericarditis for whom echocardiography fails to detect the diagnosis and provides false reassurance to the referring clinician. However, because this study was performed in a single institution with a high-volume practice in management of pericardial diseases, we think this phenomenon to be unlikely.

We considered patients with constrictive pericarditis as 1 diagnostic group regardless of pathogenesis. The variation in echocardiographic parameters shown in Table 4, however, would suggest that these heterogeneous disease processes may affect the echocardiographic findings. Whether separate criteria are required for different pathogeneses of constrictive pericarditis is an area for future study because our sample size is not large enough to draw definitive conclusions.

We considered patients with restrictive myocardial disease and severe tricuspid regurgitation together in the nonconstrictive pericarditis group because these diagnoses may be included in the differential diagnosis for patients with suspected constrictive pericarditis,^{15,16} and indeed there was clinical concern for constrictive pericarditis in each of these patients. Although severe tricuspid regurgitation is not well known as a mimicker of constrictive pericarditis, the condition has been one of the more common pathologies referred to the Pericardial Diseases Clinic at our institution. Torrential tricuspid regurgitation can be missed even by technically adequate color flow imaging because of laminar flow that escapes visual detection. Occasionally, constrictive pericarditis may even coexist with severe tricuspid regurgitation. The number

of patients in the nonconstrictive pericarditis group did not allow for separate comparisons of restrictive myocardial disease and severe tricuspid regurgitation with constrictive pericarditis. One might speculate that if constrictive pericarditis were compared only with restrictive myocardial disease, some of the differences in echocardiographic variables (eg, mitral annular velocity) might be even more pronounced. However, arguing against this is the fact that our findings largely validate those of prior smaller studies that compared constrictive pericarditis only to restrictive myocardial disease. Moreover, we think that our proposed diagnostic algorithm is more clinically useful because it allows detection of constrictive pericarditis even in the most complex clinical situations where restrictive myocardial disease and significant tricuspid regurgitation are being considered or even coexist.

Conclusions

Echocardiography allows differentiation of constrictive pericarditis from restrictive myocardial disease and severe tricuspid regurgitation. Respiration-related ventricular septal shift, preserved or increased medial mitral annular e' velocity, and prominent hepatic vein expiratory diastolic flow reversals are independently associated with the diagnosis of constrictive pericarditis. The echocardiographic examination in patients presenting with heart failure should include evaluation for these findings.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Constrictive pericarditis is a potentially reversible cause of heart failure that may be difficult to differentiate from restrictive myocardial disease and severe tricuspid regurgitation. Echocardiography provides an important opportunity to evaluate for constrictive pericarditis, and definite diagnostic criteria are needed. We compared the echocardiographic findings in patients (n=130) with surgically confirmed constrictive pericarditis to patients (n=36) with either restrictive myocardial disease or severe tricuspid regurgitation (and in whom constriction had been considered but ruled out). The analysis is focused on 5 key echocardiographic variables: (1) respiration-related ventricular septal shift, (2) variation in mitral inflow E velocity, (3) medial mitral annular e' velocity, (4) ratio of medial mitral annular e' to lateral e', and (5) hepatic vein expiratory diastolic reversal ratio. All of these were found to be significantly different between the 2 groups of patients. With the exception of variation in mitral inflow velocity, these significant differences persisted even in patients with atrial fibrillation or flutter (n=29). Three of the 5 variables were independently associated with constrictive pericarditis: (1) ventricular septal shift, (2) medial mitral e', and (3) hepatic vein expiratory diastolic reversal ratio. The presence of ventricular septal shift in combination with either medial e'≥9 cm/s or hepatic vein expiratory diastolic reversal ratio ≥0.79 corresponded to the most desirable combination of sensitivity (87%) and specificity (91%). Echocardiography may, therefore, allow differentiation of constrictive pericarditis from restrictive myocardial disease and severe tricuspid regurgitation. The echocardiographic examination in patients presenting with heart failure should include evaluation for these 5 key echocardiographic findings.