# Prevalence and Significance of Restrictive Filling Pattern in an Echocardiography Laboratory

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**ABSTRACT:** **Background:** A cardiac restrictive filling pattern is associated with unfavorable prognoses. Cardiac interventions may change the natural history of patients.

**Objectives:** To investigate the prevalence of restrictive filling pattern in routine echocardiographic examinations and their association with morbidity and mortality.

**Methods:** The clinical and echocardiographic data of patients with newly diagnosed restrictive filling pattern were analyzed and summarized.

**Results:** Among 8000 patients who underwent an echocardiographic examination in our hospital in 2013, a restrictive filling pattern was identified in 256. Of these, 134 showed a restrictive filling pattern that was newly diagnosed. Mean age was 69 years. Hypertension, diabetes, and ischemic heart disease were found in 81%, 60%, and 53%, respectively. Left ventricular ejection fraction was 42% ± 16%. Severe valvular abnormalities were found in 18%. During follow-up (29 ± 15 months), 40% of patients died. The strongest predictor of mortality (73%) was moderate or more advanced aortic stenosis, $P = 0.005$. Renal failure was an important independent predictor of mortality (52%, $P < 0.05$). A very high E/E' ratio ≥ 20, was another independent mortality predictor (50%, $P < 0.03$). Patients who died were less likely to have undergone cardiac interventions than those who survived (26% vs. 45%, $P < 0.03$).

**Conclusions:** Prevalence of restrictive filling among echocardiographic studies is 3.2%. In a half of these, the restrictive filling pattern is a new diagnosis. Patients who are diagnosed with a new restrictive filling pattern have higher mortality rates. Patients with restrictive filling should be evaluated thoroughly for possible coronary artery or valvular heart disease.

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**KEY WORDS:** cardiac surgery, diastolic function, restrictive filling

Accurate evaluation of diastolic function has become a routine part of the echocardiographic study. A comprehensive evaluation of diastolic function began in the 1980s and 1990s [1-3]. With the development of Doppler tissue imaging, the evaluation of diastolic function became more precise and concrete. The problem of heart failure with preserved ejection fraction (HFpEF) is associated with diastolic dysfunction. Diastolic dysfunction is observed in elderly patients [4,5], and sometimes can be a part of normal aging, but more often diastolic dysfunction is a marker of serious cardiac pathology. The restrictive filling is predictive of progressive left ventricular dilatation and cardiac death in patients with a first myocardial infarction [6,7]. The persistence of left ventricular restrictive filling in patients with dilated cardiomyopathy is associated with high mortality [8]. In patients with congestive heart failure, restrictive filling is associated with worsening of the functional class and a decrease in exercise tolerance [9]. In patients with preserved left ventricular function, restrictive filling often indicates a significant infiltrative heart disease, such as cardiac amyloidosis [10] or hypertrophic cardiomyopathy. In patients with hypertrophic cardiomyopathy, the restrictive filling is associated with pathological remodeling of the left ventricle and overt dysfunction, complications, and adverse outcome [11]. Restrictive mitral inflow pattern has been predictive of the lack of viable myocardium after myocardial infarction [12]. Restrictive left ventricular filling is associated with severe valvular heart disease, particularly with severe aortic stenosis [13,14]. In this study, we identified patients with restrictive filling who underwent a routine echocardiography study at a busy echocardiography lab and determined the clinical course and outcome of these patients.

## PATIENTS AND METHODS

A digital database of our hospital was evaluated to identify echocardiographic examinations conducted in 2013 in which restrictive filling pattern was found. All of these echocardiographic examinations were revised to determine the presence of restrictive filling pattern: E wave amplitude, A wave amplitude, E/A ratio, E wave deceleration time, tissue Doppler E' septal velocity (E's), and tissue Doppler E' lateral velocity (E'l). A restrictive filling pattern was diagnosed when the deceleration time of E diastolic velocity was < 160 msec, E/E' > 14, and E/A ≥ 2. Echocardiographic examinations with significant mitral annular calcifications that altered mitral inflow were not reviewed. Additional available echocardiographic parameters were reevaluated and calculated. They included left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter

(LVESD), wall thickness, left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), and ejection fraction (EF). The parameters were based on the most recent guidelines for chamber quantification [15]. Regional wall motion abnormalities were determined and valvular function was assessed. Pulmonary artery pressure was estimated according to the current recommendations [16]. Clinical data of the patients were collected, including demographic parameters (e.g., age, gender) and common cardiovascular co-morbidities (e.g., hypertension, diabetes mellitus, ischemic heart disease, congestive heart failure). The outcome for these patients was assessed based on the database of Ministry of Internal Affairs, the patient's hospital files, and a detailed telephone follow-up. During the telephone follow-up, the patients were asked about their current condition and past hospitalizations/interventions. The diagnosis of restrictive filling was made initially by the physician who was responsible for the echocardiographic report and the sonographer who performed the echocardiographic exam. All reports were also evaluated by the authors.

The study was approved by the local ethics committee.

### STATISTICAL METHODS

Student's *t*-test was used for the linear data and $P < 0.05$ was accepted as significant. Multivariate MATLAB analysis of variance (ANOVA) was applied to calculate death rates according to clinical and echocardiographic parameters including age, diagnosis of diabetes, hypertension, ischemic heart disease, ejection fraction, pulmonary artery pressure, presence of moderate or more valvular heart disease, diastolic dysfunction parameters (high E/E' ratio, high E/A ratio, short deceleration time), and cardiac intervention during follow-up. These data were presented as a color-coded model, where orange color was associated with the highest risk of mortality and a blue color with the lowest risk. [Figure 1] A similar color-coded model has been used in our previous work [17].

## RESULTS

Out of 8000 echocardiographic examinations conducted in 2013, in 256 patients (3.2%) a restrictive filling pattern had been originally reported. All these echocardiographic examinations were retrieved and revised. In 134 patients, restrictive filling pattern was newly diagnosed in 2013 (1.7%), and only these patients with a new diagnosis of restrictive filling were included in the current study. All of the patients were in sinus rhythm during the echocardiographic examinations. Clinical and echocardiographic characteristics of the patients are presented in Table 1.

**Figure 1.** Predictors of mortality in patients with restrictive filling. The strongest independent predictor of mortality in patients with restrictive filling is moderate or severe aortic stenosis. With mitral regurgitation or older age the risk is even higher. The second independent clinical predictor of mortality is renal failure, in association with low EF, pulmonary hypertension, or ischemic heart disease, or conservative strategy mortality rate is higher. The third independent clinical predictor of death is a conservative approach. If ischemic heart disease is also present, the risk is significantly higher. Severe restrictive filling with E/E' ≥ 20 is an independent echocardiographic predictor of high mortality. Multivariate analysis results with $P < 0.05$.

| | Age ≥ 70 years | Renal failure | EF ≤ 40 | PAP > 45 | E/E' ≥ 20 | Edec < 130 | AS ≥ Mod | MR ≥ Mod | IHD | Conservative |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age ≥ 70 years** | | 63% $P < 0.007$ | | | | 75% | 82% $P = 0.003$ | | | |
| **Renal failure** | 63% $P < 0.007$ | 52% $P < 0.05$ | 69% $P = 0.01$ | 60% $P < 0.03$ | | | | | 63% $P < 0.007$ | 58% $P < 0.009$ |
| **EF ≤ 40** | | 69% $P = 0.01$ | | | 63% $P < 0.007$ | | | | | 61% $P = 0.002$ |
| **PAP > 45** | | 60% $P < 0.03$ | | | 58% $P < 0.03$ | | | | | 53% $P < 0.03$ |
| **E/E' ≥ 20** | | | 63% $P < 0.007$ | 58% $P < 0.03$ | 50% $P < 0.03$ | 57% $P = 0.005$ | | | | 64% $P = 0.002$ |
| **Edec < 130** | 75% | | | | 57% $P = 0.005$ | | 75% $P = 0.01$ | | 54% $P = 0.009$ | 53% $P > 0.004$ |
| **AS ≥ Mod** | 82% $P = 0.003$ | | | | | 75% $P = 0.01$ | 73% $P = 0.005$ | 77% $P = 0.004$ | | |
| **MR ≥ Mod** | | | | | | | 77% $P = 0.004$ | | | |
| **IHD** | | 63% $P < 0.007$ | | | | 54% $P = 0.009$ | | | | 63% $P = 0.0005$ |
| **Conservative** | | 58% $P < 0.009$ | 61% $P = 0.002$ | 53% $P < 0.03$ | 64% $P = 0.002$ | 53% $P > 0.004$ | | | 63% $P = 0.0005$ | 48% $P < 0.03$ |

Color code: orange = risk of death is ≥ 80%, green = risk of death is 70–79%, pink = risk of death is 60–69%, grey = risk of death is 50–59%, blue = risk of death is less than 50%, white = low number of cases < 10.

AS = aortic stenosis, Edec = E-wave deceleration, EF = ejection fraction, IHD = ischemic heart disease, Mod = moderate, MR = mitral regurgitation, PAP = pulmonary artery pressure (mmHg)

**Table 1.** Clinical and demographic characteristics of the patients

| | Died | Lived | Total | *P* value |
|---|---|---|---|---|
| Number of patients | 54 (40%) | 80 (60%) | 134 | |
| Age, years | 67 ± 14 | 73 ± 12 | 69 ± 13 | 0.01 |
| **Gender** | | | | |
| Male | 38 (70%) | 56 (70%) | 94 (70%) | 1 |
| Female | 16 (30%) | 24 (30%) | 40 (30%) | 1 |
| **Co-morbidities** | | | | |
| Hypertension | 43 (80%) | 66 (83%) | 109 (81%) | 0.5 |
| Diabetes mellitus | 34 (63%) | 46 (58%) | 80 (60%) | 0.7 |
| Ischemic heart disease | 34 (63%) | 37 (46%) | 71 (53%) | 0.1 |
| Congestive heart failure | 35(65%) | 47(59%) | 82 (61%) | 0.5 |
| Renal failure | 23 (43%) | 21(26%) | 44 (33%) | ‹ 0.05 |
| Chronic pulmonary diseases | 9 (17%) | 10 (13%) | 19 (14%) | 0.5 |
| Cerebral vascular disorders | 9 (17%) | 6 (8%) | 15 (11%) | 0.1 |
| Malignancy | 7 (13%) | 8 (10%) | 15 (11%) | 0.6 |
| Other severe diseases* | 4 (7%) | 3 (4%) | 7 (5%) | 0.3 |
| Ejection fraction, % | 43 ± 15 | 41 ± 17 | 42 ± 16 | 0.5 |
| E/A | 2.6 ± 0.9 | 2.4 ± 0.8 | 2.5 ± 0.8 | 0.3 |
| E deceleration, msec | 116 ± 20 | 113 ± 25 | 115 ± 23 | 0.5 |
| E/E’ | 20 ± 6 | 20 ± 6 | 20 ± 6 | 0.9 |
| Severe mitral regurgitation | 6 (11%) | 8 (10%) | 14 (10%) | 0.8 |
| Severe aortic stenosis | 6 (11%) | 3 (4%) | 9 (7%) | ‹ 0.0001 |
| ≥ Moderate aortic stenosis | 11 (20%) | 4 (5%) | 14 (10.4%) | ‹ 0.01 |
| Severe aortic regurgitation | 1(2%) | 0 | 1 (0.7%) | NA |
| Severe tricuspid regurgitation | 4 (7%) | 4 (5%) | 8 (6%) | 0.5 |
| Pulmonary artery pressure, mmHg | 56 ± 15 | 51 ± 13 | 53 ± 13 | 0.09 |

*Other severe diseases included alcoholism, amyloidosis, human immunodeficiency virus, liver cirrhosis

**Table 2.** Interventions in the patients with restrictive filling

| | Died | Lived | *P* value |
|---|---|---|---|
| Total Interventions | 14 (26%) | 36 (45%) | 0.02 |
| Percutaneous interventions | 7 (13%) | 18 (23%) | 0.1 |
| Stent to left main coronary artery | 2 (4%) | 2 (2.5%) | 0.7 |
| LAD stenosis | 3 (6%) | 12 (15%) | 0.09 |
| Stent to LAD | 2 (4%) | 6 (8%) | 0.3 |
| Diagonal brunch stenosis | 4 (7%) | 6 (8%) | 1.0 |
| Stent to diagonal brunch | 4 (7%) | 3 (4%) | 0.4 |
| Stenosis of circumflex/marginal | 4 (7%) | 20 (25%) | ‹ 0.01 |
| Stent to circumflex/marginal | 2 (4%) | 13 (16%) | 0.02 |
| RCA stenosis | 5 (9%) | 15 (19%) | 0.1 |
| Stent to RCA | 3 (6%) | 3 (4%) | 0.6 |
| Multi-vessel coronary artery disease | 6 (11%) | 18 (23%) | 0.08 |
| CABG | 2 (2%) | 3 (4%) | 0.9 |
| Mitral valve surgery* | 2 (4%) | 3 (4%) | 1 |
| Aortic valve replacement (total)** | 1 (2%) | 3 (4%) | 0.5 |
| TAVI | 1 (2%) | 1 (1%) | 0.8 |
| CRT-D, ICD, DDD*** | 3 (6%) | 14 (18%) | 0.04 |

*Mitral valve replacement and one case of repair

**Total of surgical AVR and TAVI. Among patients who died, one refused AVR/TAVI and two were not referred to surgery due to severe cognitive impairment

***CRT-D 6, ICD-6, DDD-2; one of the alive patients refused of CRT-D

AVR = aortic valve replacement, CABG = coronary artery bypass graft, CRT-D = cardiac resynchronization therapy defibrillator (CRT-D), ICD = implantable cardioverter defibrillator, LAD = left anterior descending coronary artery, RCA = right coronary artery, TAVI = transcatheter aortic valve implantation

Mean age was 69 ± 13; 94 patients were male (70%) and 40 were female (30%), $P <$ e-11. Mean left ventricular ejection fraction (LVEF) was 42% ± 16%. The pulmonary artery systolic pressure was 53 ± 13 mmHg. Severe mitral regurgitation was found in 14 patients, severe aortic stenosis in 9, aortic regurgitation in 1, and severe tricuspid regurgitation in 8. There were 109 patients (81%) diagnosed with hypertension, 82 (61%) with diabetes, and 71 (53%) with ischemic heart disease.

Mean follow-up was 29 ± 15 months. During the follow-up, 54 patients (40%) died and 80 (60%) were alive at the end [Table 1].

Outcome data were available for all patients. Detailed clinical follow-up was available for 72 of 80 alive patients (90%). Of these 72 patients, 36 (50%) underwent cardiac interventions: 5 underwent valvular surgery, 21 underwent revascularization, 18 underwent percutaneous coronary intervention [PCI], and 3 underwent coronary artery bypass graft [CABG]). [Table 2].

In 17 patients, electronic cardiac devices were inserted. Among alive patients, 14 (18%) underwent implantation of an electronic device (cardiac resynchronization therapy defibrillator [CRT-D] 6, implantable cardioverter defibrillator [ICD] 6, or DDD-2) which was significantly higher than in the group of patients who died, 14 (18%) vs. 3 (6%), $P = 0.04$. One of the alive patients refused CRT-D implantation. There were no other patients in either group who were eligible for implantation of electronic devices [Table 2].

Among alive patients, two underwent surgical aortic valve replacement (AVR) and one underwent transcatheter aortic valve implantation (TAVI). Among those who died, one underwent AVR and one underwent TAVI. In the latter group, one of the patients with severe aortic stenosis refused any intervention AVR or TAVI, and two others with severe aortic stenosis were not referred for intervention due to severe cognitive impairment.

Telephone follow-up was available in 54 of 80 alive patients (68%). In these patients, 30 (56%) were at New York Heart Association (NYHA) functional class III and 11 (20%) were at functional class IV. Nine (17%) met the criteria for functional class I and four (7%) were at functional class II.

Out of the entire cohort of 134 patients, no differences were found regarding demographic data (age, gender), occurrence of hypertension, diagnosis of diabetes mellitus, ischemic heart disease, chronic pulmonary diseases, cerebrovascular diseases, malignancy, and other severe disorders in the groups, with the exception of renal failure, which occurred more often in the patients who died, 43% vs. 26%, $P < 0.05$ [Table 1]. Echocardiographic parameters were similar in both groups, apart from the somewhat higher proportion of severe aortic stenosis in the group of patients who died. Alive patients underwent interventions (coronary revascularization, valvular surgery, and insertion of pacemaker/defibrillator) significantly more often (45% vs. 26%, $P < 0.03$). Sub-analysis of the patients who underwent interventions showed reduced mortality (28% vs. 50%) over those who were managed conservatively, $P < 0.006$.

Multivariate analysis was performed across all 134 patients [Figure 1]. The strongest independent predictor of mortality was the presence of moderate or more aortic stenosis, which was associated with a mortality risk of 73%, $P = 0.005$. In association with older age, moderate and more aortic stenosis was predictive of mortality risk (82%, $P = 0.003$). A combination of at least moderate aortic stenosis and at least moderate mitral regurgitation was associated with a mortality risk of 77%, $P = 0.004$. The second independent predictor of mortality was renal failure, which was associated with a mortality risk of 52%, $P < 0.05$. In association with older age, lower EF, pulmonary hypertension, or ischemic heart disease, the risk of mortality increased ≥ 60%.

Very high E/E‘ ratio ≥ 20 independently predicted a mortality rate of 50%, $P < 0.03$, in association with lower EF mortality risk was 63%, $P < 0.007$, and in combination with conservative strategy, mortality was projected to be 64%, $P = 0.002$.

A conservative strategy was independently associated with a mortality risk of 48%, $P < 0.03$. In association with ischemic heart disease or lower EF, the risk of mortality increased ≥ 60%. In association with at least moderate pulmonary hypertension or renal failure the risk of mortality was 53% ($P < 0.03$) and 58% ($P < 0.009$), respectively.

## DISCUSSION

As has been shown previously, restrictive filling is associated with bad prognosis in patients with heart failure [18]. In patients with non-ischemic cardiomyopathy, restrictive filling was a marker of poor prognosis [19]. In patients with myocardial infarction, restrictive filling was a strong predictor of death [7]. Patients with moderate to severe aortic stenosis develop left ventricular hypertrophy due to abnormal Ca handling, apoptosis, and fibrosis. Subtle systolic dysfunction can progress to overt systolic heart failure. Secondary mitral regurgitation may develop as a result of annular dilatation, and pulmonary artery pressure rises due to diastolic dysfunction and mitral regurgitation [20]. Timely aortic valve replacement can improve diastolic dysfunction pattern.

Severe aortic stenosis is not always associated with restrictive filling. Only in extreme cases of severe aortic stenosis was a restrictive filling pattern found [14]. In patients with low-flow/low-gradient severe aortic stenosis, restrictive filling was associated with a lack of contractile reserve during low-dose dobutamine stress echocardiography [21]. In severe mitral regurgitation, shorter E wave deceleration time and high E/A ratio may be observed; however, in these cases E’ myocardial Doppler tissue velocity will be high and the E/E’ ratio will not be elevated, as is seen in true diastolic dysfunction. The mechanism of diastolic dysfunction may be more complex in secondary mitral regurgitation due to significant myocardial impairment [22], but in patients with organic mitral regurgitation referred for surgery, the E/E’ represented good filling pressure and correlated with pulmonary artery systolic pressure [23].

In our study, we found that a restrictive filling pattern is an infrequent finding among routine echocardiographic examinations, and a new diagnosis of restrictive filling is even more rare (1.7%). In the majority of patients with restrictive filling, underlying ischemic heart disease may be found. In 18%, severe left-sided valvular heart disease (severe aortic stenosis or severe mitral regurgitation) was present.

Of non-cardiac co-morbidities, renal failure in patients with restrictive filling was found to be an important independent predictor of mortality. This finding is in agreement with a previous investigation in which renal failure was established as a predictor of mortality in patients with heart failure [24]. One important co-morbidity, which might affect clinical decisions and prognosis in patients with restrictive filling but could not be evaluated systematically in this retrospective study, was frailty.

Mean EF in our study was 42%. In Israeli patients who participated in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT), mean EF was 45%, mean EF among the patients from other countries was 38% [25]. EF in our study was not an independent predictor of mortality among patients with restrictive filling. However, advanced restrictive filling, with E/E’ ≥ 20, was an independent significant predictor of death.

As was mentioned previously, newly diagnosed restrictive filling was associated with a high mortality rate (40% of our patients died during a 2 year follow-up) and most of those who survived were in advanced functional classes of heart failure FC III (56%) and FC IV (20%).

In addition, restrictive filling in combination with moderate or severe aortic stenosis was an independent predictor of a high rate of mortality, and in association with at least moderate mitral regurgitation or with older age, mortality was even higher. Patients with ischemic heart disease who were treated conservatively also had a high mortality rate (63%). Conservative strategy was an independent predictor of mortality in the entire cohort of patients with restrictive filling (48%).

We found that when restrictive filling is associated with moderate or more aortic stenosis and/or ischemic heart disease, the prognosis of these patients is dismal. In cases with moderate aortic stenosis, the restrictive filling may not be the result of the valvular abnormality, but rather may represent sub-clinical myocardial changes in spite of apparently normal systolic function at this time. Furthermore, such a pattern may represent sub-clinical coronary artery disease as well. Not all patient interventions may be appropriate due to significant non-cardiac co-morbidities and frailty. However, in eligible patients with restrictive filling, close follow-up and earlier intervention, if appropriate, may result in a better prognosis.

### STUDY LIMITATIONS

This investigation was a retrospective observational study. The patient population was mixed, as had been the purpose of the study, to identify restrictive filling in an unselected population of patients undergoing an echocardiography study. When examining the patient population in detail [Table 1, Table 2], the subgroups are small, thus limiting true statistical evaluation between those who died and those who lived.

Despite these limitations, we believe that the results are potentially important. The current study underscores the poor prognosis of all patients in whom a restrictive filling pattern is diagnosed.

### CONCLUSIONS

A restrictive filling pattern is an infrequent echocardiographic finding among routine echocardiographic examinations in a busy echocardiographic laboratory. A new diagnosis of restrictive filling is even more rare. A restrictive filling pattern is often associated with ischemic heart disease, valvular heart disease, and renal failure. When it is associated with moderate and more aortic stenosis, very high E/E‘, or renal failure, the prognosis is likely to be dismal. Careful follow-up of these patients is recommended.

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**"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world"**

Louis Pasteur, (1822–1895), French scientist know for his work in vaccines, pasteurization, and debunking spontaneous generation