## ORIGINAL ARTICLE

# Echocardiographic Hemodynamic Heterogeneity of Advanced Heart Failure Patients as Compared to Patients with „Pre-Heart Failure"

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**ABSTRACT**

**Background:** Advanced heart failure (HF) represents a clinical entity encompassing severely symptomatic HF with severely dysfunctional left ventricles (LV). The single most important parameter for defining severe LV dysfunction and indicating the prescription of evidence-based therapies is LV ejection fraction (EF). We sought to investigate the hemodynamics by echocardiography in a cohort of advanced HF patients during a hospitalization for HF decompensation and assess the relevant differences when compared to a control cohort of asymptomatic patients with minor structural/functional cardiac abnormalities.

**Methods and results:** In this prospective study we selected 18 advanced HF patients and 12 asymptomatic pre-HF patients with only minor structural/functional abnormalities. The 2 groups were clearly delineated by size parameters (end -systolic and -diastolic diameters and volumes respectively, with very low p values $p<0.0001$). Hemodynamic parameters were significantly different as well in the advanced HF group vs the 'pre-HF' group, including: ventricular-arterial coupling 1.745 vs. 0.895, $p=0.0007$; cardiac power output 0.762 vs. 0.932, $p=0.044$, systolic times ratio 0.406 vs. 0.200, $p=0.0001$. There were no significant differences for neither effective arterial elastance (Ea) and nor for cardiac index. Inside the advanced HF group, no correlation between LVEF and other parameters were found and none of these parameters could predict outcome. We observed a highly skewed variation of Ea in advanced HF patients.

**Conclusion:** Among the most severe HF patients, the hemodynamic interaction between the dysfunctional LV and the compensatory response of the peripheral system is heterogenous and cannot predict outcome by single parameters. In these patients, assessment of cardiac performance should no longer rely on LEVF alone.

**Keywords:** echocardiography, hemodynamic heterogeneity, heart failure, patients.

**REZUMAT**

**Introducere:** Insuficiența cardiacă (IC) avansată reprezintă o entitate clinică ce cuprinde pacienți severi simptomatici cu afectare severă a ventriculului stâng. Parametrul esențial utilizat în practica clinică și în studiile clinice pentru a defini severitatea afectării cardiace este fracția de ejecție a ventriculului stâng (FEVS). Am dorit să investigăm prin ecocardiografie, hemodinamica unui grup de pacienți cu IC avansată comparativ cu un grup de pacienți asimptomatici cu anomalii structurale/funcționale minore.

**Metodă și rezultate:** Acesta a fost un studiu prospectiv în care am selectat 18 pacienți cu IC avansată și 12 pacienți asimptomatici, la care s-a reușit efectuarea în condiții corecte a unei investigări ecocardiografice complete. Cele două grupuri au fost clar delimitate de către parametri precum diametrele și volumele indexate telesistolic și respectiv, telediastolic ($p<0,0001$). De asemeni, parametrii hemodinamici au diferit semnificativ în grupul cu IC avansată versus grupul asimptomatic (cuplajul ventriculo-arterial 1,745 vs. 0,895, $p=0,0007$; puterea cardiacă 0,762 vs. 0,932, $p=0,044$, raportul timpilor sistolici 0,406 vs. 0,200, $p=0,0001$). Nu au existat diferențe semnificative pentru elastanța arterială efectivă și nici pentru indexul cardiac. În interiorul grupului de pacienți cu IC avansată, nu au existat corelații între FEVS și ceilalți parametri hemodinamici și niciunul din acești parametri nu a identificat pacienții cu prognostic precar. Am observat o variație semnificativ asimetrică a valorilor elastanței arteriale în grupul de IC avansată.

**Concluzie:** Printre cei mai severi pacienți cu IC avansată, interacțiunea hemodinamică între VS disfuncțional și răspunsul compensator al sistemului arterial este complexă și eterogenă. La acești pacienți, evaluarea strict prin FEVS nu poate fi suficientă.

**Cuvinte cheie:** ecocardiografie, heterogenitate hemodinamică, insuficiență cardiacă, pacienți.

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## INTRODUCTION

Advanced heart failure (HF) represents a clinical entity encompassing severely symptomatic HF with severely dysfunctional left ventricles (LV)[1]. The single most important parameter for defining severe LV dysfunction and indicating the prescription of evidence-based therapies is LV ejection fraction (EF)[1,2]. While LV EF is a good parameter of cardiac performance as it has the advantage of integrating the interplay between contractility and load (both preload and afterload), it has a poor discriminatory capacity/ability to assess the severity of myocardial disease and hemodynamic dysfunction[3]. Its limitations in assessing HF hemodynamics have been previously described[4-6]. The latest therapeutic advances in the most severe HF patients (advanced HF and cardiogenic shock patients) rely on the good understanding of hemodynamics, stepping away from the central mechanism[7,8].

Reliable tools for diagnosis and assessment of cardiac function are crucial for the treatment of HF and the evaluation of efficacy of treatment in clinical trials. Global cardio-vascular performance, including several indexes of myocardial contractility and loading conditions, provides important contributions to the understanding of the pathophysiology, diagnosis, and treatment of various HF phenotypes.

Global cardio-vascular performance is probably best described by analysis of pressure-volume loops (PVL) (Figure 1). Additional information on cardiac function can be found not only in the shape and position of the PV loop in the PV plot but also in the quantification of contractility, compliance of the myocardial tissue and ventricular-arterial coupling. Therefore, PV loops allow for a more comprehensive analysis of a patient's cardiac function compared with sole volumetric efficiency measurement of EF. Several metrics collected by invasive hemodynamics, although described more than 30 years ago, remain centerpiece for the understanding of HF physiopathology and are now available by echocardiographic imaging and MRI[9-12]. Noninvasive pressure-volume loop analysis enables quantification of stroke work and contractility—clinically important aspects of ventricular function inaccessible by other methods. Echocardiographic LV pressure-strain loop area approximates well invasive pressure-volume loop and allows for regional and global work analysis[10,13]. But as invasive methods are more a matter of research and non-invasive methods for PVL computing

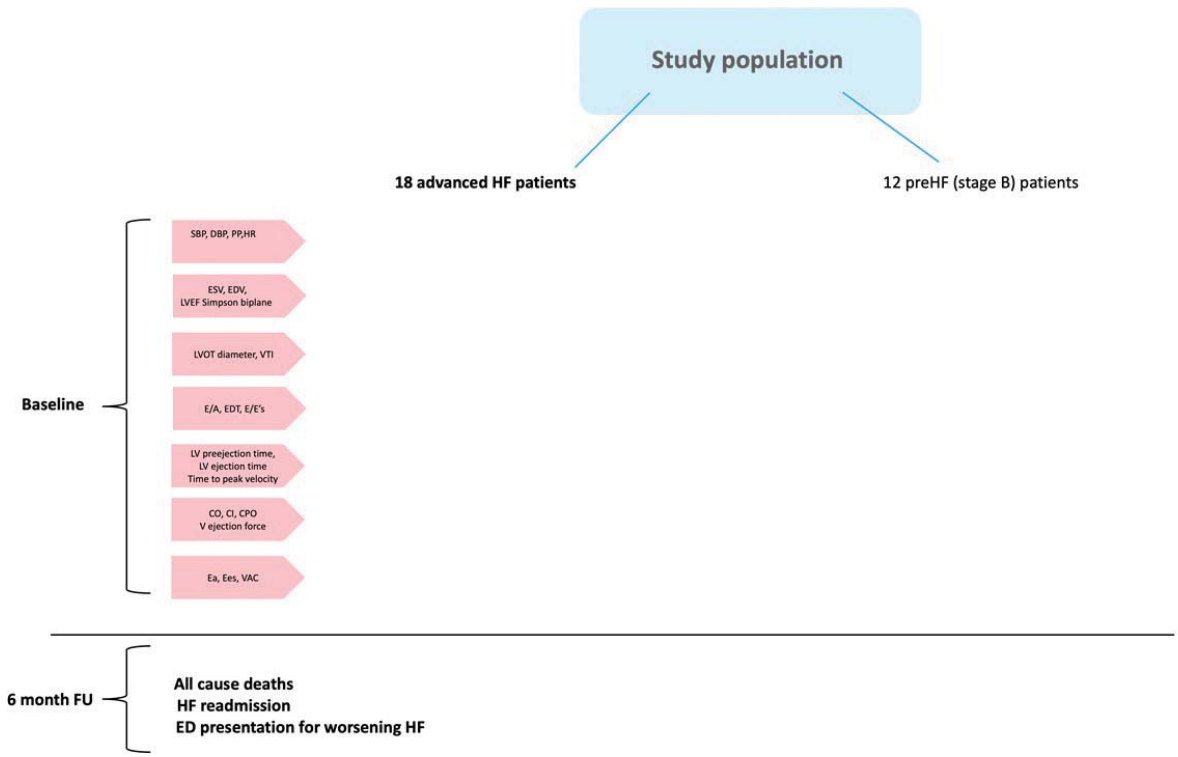


**Figure 1.** Study design.
SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, HR heart rate, LVEF left ventricular ejection fraction, ESV end-systolic volume, EDV end-diastolic volume, ESVi indexed ESV, EDVi indexed EDV, EDT E wave deceleration time, CI cardiac index, CPO cardiac power output, VTI velocity time integral, VAC ventricular-arterial coupling, Ea effective arterial elastance, Ees ventricular elastance, SV stroke volume, FU follow-up

require complex software and/or good cardiac acoustic imaging, simpler parameters available for daily practice are required.

Effective arterial elastance (Ea), ventricular-arterial coupling (VAC) as the ratio between Ea and ventricular elastance (Ees), LV size, LV ejection force (LVF), cardiac power output (CPO), the ratio between isovolumic contraction time (PEP) and ejection time (LVET) have each been shown to relate to the severity of HF and predict prognosis in both acute and chronic HF settings[14-20].

Nonetheless the most effective method of profiling these patients has remained clinical and most relevant risk scores rely on clinical and biology variables[21-23]. Beyond the measures of LV EF and congestion, routine echocardiographic evaluation is often focused on the central myocardial function only. Furthermore, when assessed, integrating the multitude of available individual hemodynamic parameters into clinical practice is not standardized and confounding. The latest document of the Joint European, American and Japanese societies for HF still consider the hemodynamic characterization of HF among the gaps in the current definitions and unreliable[24]. Echocardiographic studies, have not reported so far the concomitant variation of the previously mentioned hemodynamic parameters.

We sought to investigate the hemodynamics by echocardiography in a cohort of advanced HF patients during a hospitalization for HF decompensation and assess the relevant differences when compared to a control cohort of asymptomatic patients with minor structural/functional cardiac abnormalities.

## METHODS

### Population included

This a prospective single-centre study (Figure 2). We selected 18 consecutive patients hospitalized in the HF department for HF decompensation during a 3 year period (2018-2021) who met the Heart Failure Association criteria for advanced HF, representing stage D according to the 2021 universal definition and classification and who had a complete standardized echocardiographic evaluation during the hospitalization[1,24]. We excluded patients with significant aortic valvular disease, congenital heart disease, hypertrophic cardiomyopathy, valvular prosthesis, significant co-morbidities, unsatisfactory imaging of LV, patients with cardiogenic shock during the index hospitalization or in atrial fibrillation.

Patients hemodynamics data were compared, for consistency, to a control group comprised of 12 asymptomatic patients with 'preHF' — stage B[24].

### Non-invasive echocardiographic hemodynamic assessment

Advanced HF patients underwent a complete standard study by two-dimensional transthoracic echocardiography with concomitant ECG monitoring in a quiet

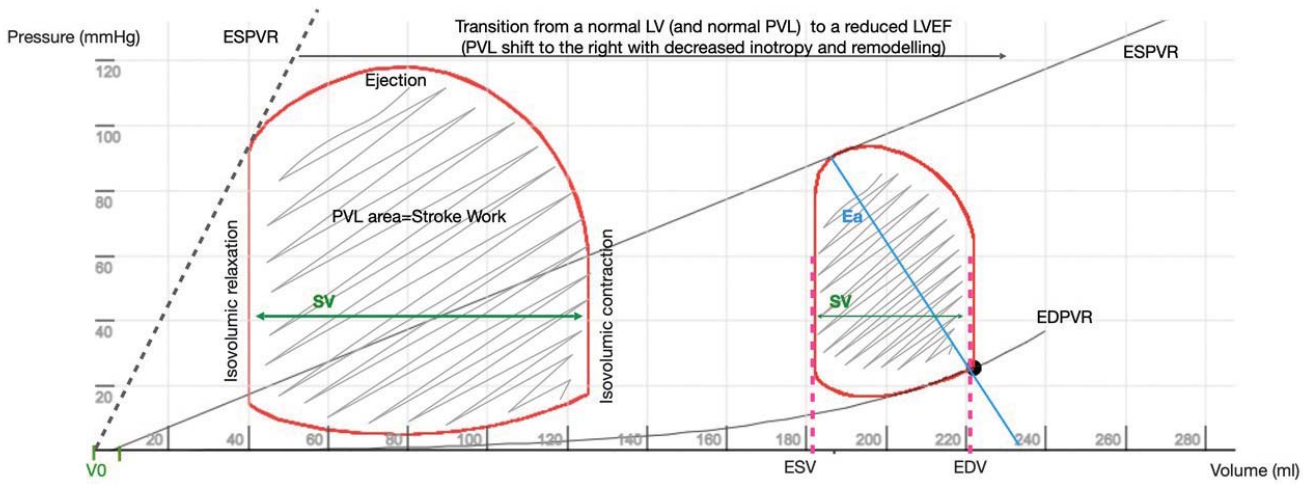


**Figure 2.** Pressure-volume analyses demonstrating the normal PV loop (PVL) and the determinants of ventricular function, including the ESPVR (characterized by the slope [Ees] and the volume axis intercept [V0] and the EDPVR. Shifts in the ESPVR are often equated with changes in inotropic state (rightward shift with decreased LVEF), while remodelling with increased valumes shifts the EDPVR. Stroke volume is EDV - ESV; SW is the PVL area, which multiplied by heart rate results in cardiac power.
Ea, effective arterial elastance; EDPVR, end-diastolic pressure–volume relationship; EDPVR, end diastolic pressure volume relation, Ees, end-systolic elastance; ESPVR, end-systolic pressure–volume relationship; V0, volume at a Pes of 0 mmHg. SV, Stroke volume; EDV, end-diastolic volume ; ESV, end-systolic volume; SW, stroke work.

environment, during the hospitalization for acute HF. The control group was evaluated during an ambulatory visit.

All standard acquisition and measurements were performed according to the current recommendations of the *European Society of Cardiovascular Imaging guidelines*[25].

All patients had their right arm blood pressure measured at the exact same time with the acquisition of the pulsed wave Doppler envelope in the LV outflow tract (LVOT) acquisition. In addition to

The values of Ees were computed using Pietro Bertini's 2017 phone application which references Chen's 2001 previously published formulas for non-invasive single beat Ees[26]:

Ees = (DBP – (End(est) × SBP × 0.9))/End(est) × SV (DBP: diastolic blood pressure cuff estimation; SBP: systolic arterial pressure by cuff estimation; End(est): estimated normalized ventricular elastance at the onset of ejection; SV: Doppler- derived stroke volume)

End(est) = 0.0275 – 0.165 × LVEF + 0.3656 × (DBP/SBP × 0.9) + 0.515 × End(avg)

End(avg) = 0.35695 – 7.2266 × tNd + 74.249 × $tNd^2$ – 307.39 × $tNd^3$+ 684.54 × $tNd^4$ – 856.92 × $tNd^5$+ 571.95 × $tNd^6$ – 159.1 × $tNd^7$ (where tNd is the ratio of PEP to total systolic time).

Ea values ware calculated using the proposed formula by Sunagawa et al.[27] and Kelly[28]:

Ea = LVESP/SV, where LVESP represents LV end systolic pressure and was estimated as 0.9 × SBP.

The formula for CPO, CPO=MAPXCO/451 (MAP is mean arterial pressure and CO is cardiac output), was invasively validated in the SHOCK trial and in advanced HF patients, but it was subsequently referred to and used as such in non-invasive studies as well[16,29-31].

LV ejection force (LVF) represents the mass of blood accelerated across aortic valve over a time period and was estimated as: LVF = (1.055 × CSA × ascVTI) × (PSV/TTP) (where CSA is cross-sectional area, ascVTI is the ascending limb of the VTI, PSV peak systolic velocity in the outflow tract, TTP is time to peak velocity integral)[15,32].

Analysis of Pulsed Doppler envelope in the LV outflow tract is essential for deriving accurate systolic times and VTI that are further incorporated in the aforementioned formulas - as depicted in Figure 3.

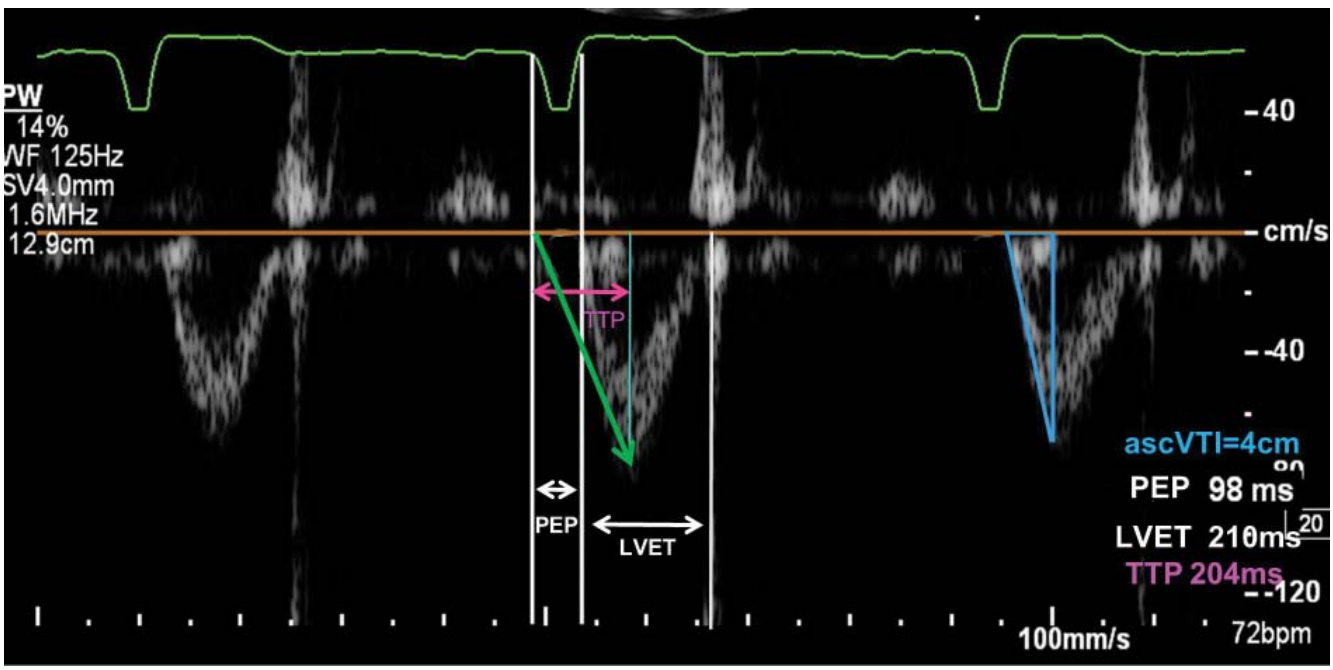


**Figure 3.** Pulsed wave Doppler (PW) envelope in left ventricular ejection fraction. showing systolic times and acceleration to peak systolic LVOT velocity. Measurements are averaged over 3 cycles.
PEP preejection time, measured from beginning of QRS to start of ejection; LVET ejection time, measured from beginning to end of the PW envelope; TTP time to peak systolic velocity, Green arrow depicts the initial systolic acceleration.

LV filling pressures were evaluated by measuring E/A, E/e', indexed left atrial volume, tricuspid regurgitation jet velocity according to the 2016 recommendations as these were confirmed to give a fair good estimate of LV end-diastolic presssure[33,34].

## FOLLOW-UP

Advanced HF patients were followed up for 6 months after the index hospitalization. We studied the time to a first major event represented by (death, HF hospitalization or ER admission requiring iv medication).

## STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Inc statistical software, version 2020. Continuous variables were expressed as mean +/- standard deviation (SD) and categorical variables as percentages. Variables were tested for normal distribution calculating skewness and using the Shapiro-Wilk test. Patient characteristics were compared using the Fisher's exact test for categorical variables, the independent t test for normally distributed continuous variables. All significance tests were conducted at the 1% significance level.

## RESULTS

### Baseline characteristics of the study population

The study cohort was comprised of 18 male patients with advanced HF which was defined by severe cardiac dysfunction (LV EF <35%, elevated levels of NT-proBNP (mean level 2898pg/ml SD 4096pg/ml)), severe symptoms (NYHA class IV at admission for the index evaluation) and repeated hospitalizations (at least 1 prior hospitalization in the previous 6 months). Most patients were adequately treated, 83% (n=15) having more than 50% of the target beta-blocker dose and 77% (n=14) more than 50% of the target ACEI or ARNI target doses.

The control group was comprised of asymptomatic hypertensive patients with structural or functional cardiac abnormalities (either mildly enlarged LV or left atrium, hypertrophic LV, mildly or moderately reduced LVEF, altered regional kinetics, mild diastolic dysfunction); a significant proportion (58%) also had a history of myocardial infarction. Given the significant cardiac history and/or the cardiac abnormalities identified during the echocardiographic study we classified these patients as stage B - 'preHF'.

More detailed demographic and clinical characteristics are presented in Table 1.

**Table 1. Demographic and clinical data in advanced (stage D) HF patients compared to asymptomatic 'pre-HF' (stage B) patients**

| Variable | adavanced HF patients (n=18) | 'pre-HF' patients (n=12) | p value |
|---|---|---|---|
| Age (y) | 59+/-9,3 | 56+/-13,8 | 0.48 |
| Males (%) | 100 (n=18) | 77 (n=8) | 0.018 |
| BSA (mean) | 1,97+/-0,14 | 1,91+/-0,19 | 0.32 |
| Hemoglobin g/dl (mean) | 13,1+/-1,7 | 13,6+/-0,9 | 0.5 |
| Hypertension (%) | 77 (n=14) | 83 (n=10) | 1 |
| Diabetes mellitus (%) | 44 (n=8) | 25 (n=3) | 0.44 |
| Chronic kidney disease (%) | 66 (n=12) | 17 (n=2) | 0.010 |
| Ischemic etiology (%) | 39 (n=7) | 58 (n=7) | 0.457 |
| Prolonged QRS (%) | 28 (n=5) | 0 | 0.0657 |
| Left bundle branch block (%) | 16 (n=3) | 0 | 0.252 |
| ACEI (%) | 44 (n=8) | 50 (n=6) | 1 |
| ARNI (%) | 33 (n=6) | 17 (n=2) | 0.419 |
| BB (%) | 83 (n=15) | 66 (n=8) | 0.3915 |
| Pulse pressure (mean) | 42+/-16 | 58+/-11 | 0.0054 |

BSA body surface area, ACEI angiotensin converting enzyme inhibitor, ARNI angiotensin receptor neprilysin inhibitor, BB beta-blocker

### Echocardiographic parameters of the study population

Primary analysis of basic echocardiographic parameters consistently shows, as expected, that the LVs of the advanced HF group are significantly larger, with a more profound remodeling, as depicted in Table 2. Although left atrial size is also larger, diastolic function parameters did not differ significantly (Table 2). While all patients in the stage B group had a normal, non-dilated, compliant inferior vena cava, this was only found 7 patients in the advanced HF group (p=0.0006).

## HEMODYNAMIC PARAMETERS DERIVED FROM ECHOCARDIOGRAPHIC DATA

Most of the investigated hemodynamic variables, including LV systolic times, LV elastance, VAC, LV ejection force and CPO, differed significantly between the 2 groups (Table 3). Stroke volume and Ea were the only exceptions, with similar values among the two groups (Table 3).

When testing for normal distribution of the variables inside the advanced HF group, we found a fairly symmetrical distribution for LVEF, CPO, VAC, Ees, indexed ESV and LV ejection force.

Significantly, we found a highly skewed distribution for Ea (skewness 2,326, p<0.001). Ea values significantly correlated with Ees (r=0.766, p<0.001).

LVEF did not correlate to any other relevant hemodynamic parameter (Table 4).

All variables appeared normally distributed in the control group.

Intra- and interobserver variability has been performed for all patients from group D and 5 patients from group B, with less than 5% coefficient of variation.

**Table 2. Comparison of basic echocardiographic parameters of the studied groups**

| Variable | advanced HF patients (n=18) | 'pre-HF' patients (n=12) | p value |
|---|---|---|---|
| EDV End-diastolic diameter | 67+/-6.8 | 49+/-7.7 | 0.0001 |
| ESV End-systolic diameter | 62+/-5.9 | 35+/-8.3 | 0.0001 |
| LVMi Indexed left ventricular mass | 130+/-40 | 83+/-21 | 0.0017 |
| LAVi Indexed left atrial volume | 51+/-17 | 24+/-6 | 0.0130 |
| EDVi Indexed end-diastolic volume | 117+/-43 | 43+/-11 | 0.0001 |
| ESV End-systolic volume | 183+/-74 | 36+/-18 | 0.0001 |
| ESVi Indexed end-systolic volume | 93+/-38 | 18+/-8 | 0.0001 |
| Mitral E/A | 1.89+/-1 | 1.26+/-0.1 | 0.2411 |
| EDT E wave deceleration time | 146+/-69 | 184+/-36 | 0.32 |
| E/septalE' | 22+/-13 | 10+/-3.5 | 0.0697 |

**Table 3. Comparison of hemodynamic parameters between stage D HF patients and asymptomatic stage B patients**

| Variable (mean value +/-SD) | advanced HF patients (n=18) | 'pre-HF' patients (n=12) | p value |
|---|---|---|---|
| PP Pulse pressure | 42+/-16 | 58+/-11 | 0.0054 |
| LVEF left ventricular ejection fraction | 25+/-7.7 | 57+/-7 | 0.0001 |
| TVI-LVOT Time velocity integral in the LVOT | 12.2+/-3.9 | 18.1+/-4 | 0.0004 |
| max lvot velocity | 72.5+/-13.6 | 95.8+/-19.2 | 0.0006 |
| SV stroke volume | 58.5+/-14 | 68.3+/-11.4 | 0.0534 |
| CI cardiac index | 1.96+/-0.34 | 2.35+/-0.52 | 0.0189 |
| PEP preejection time | 102+/-23 | 65+/-27 | 0.0004 |
| LVET LV ejection time | 261+/-43 | 322+/-27 | 0.0002 |
| PEP/LVET | 0.406+/-0.122 | 0.200+/-0.078 | 0.0001 |
| Ea effective arterial elastance (median) | 1.865+/-0.607 | 1.749+/-0.476 | 0.5806 |
| Ees ventricular elastance | 1.127+/-0.303 | 2.299+/-1.092 | 0.0002 |
| VAC ventriculo-arterial coupling | 1.745+/-0.353 | 0.895+/-0.340 | 0.0007 |
| CPO cardiac power output | 0.762+/-0.207 | 0.932+/-0.230 | 0.0440 |
| LVF left ventricular ejection force | 7.9+/-3.3 | 12.3+/-4.1 | 0.0041 |

**Table 4. Correlation analysis between LV ejection fraction (LVEF) and hemodynamic variables in advanced HF patients**

| | | Ea | Ees | VAC | LV Force |
|---|---|---|---|---|---|
| LVEF | r | -.434 | -.225 | -.324 | .405 |
| | p | .072 | .370 | .190 | .119 |

Ea=effective arterial elastance, Ees=ventricular elastance, VAC=ventricular-arterial coupling

### Follow-up outcomes of the study population

All patients were followed-up for at least 6 months after the initial echocardiographic evaluation. In the advanced HF group, 10 patients experienced one adverse event. 6 of the remaining patients were followed up for up to 2 years, without any significant event. None of the investigated variables was able to predict the combined end-point inside the advanced HF group.

## DISCUSSION

The interaction between a dysfunctional LV and the arterial system is complex and governed by many parameters, but echocardiography can investigate macro-hemodynamics. Simple measurements of LV function (i.e.LVEF, PEP/LVET) and LV size (iESV and iEDV) can appropriately identify severe HF patients and the progressive deterioration and differentiate them from those with pre-HF at risk of developing HF. This approach continued without major changes even as newer medications that impact reverse-remodeling and acute and chronic hemodynamics have been consistently introduced over the time. Nonetheless, more thorough evaluation is important to understand the differences among these groups of patients. In the group of the most severe patients, LVEF doesn't have the incremental value or accuracy to further identify the extent of cardiac dysfunction, since it is highly dependent of loading conditions.

Successful chronic HF therapies such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor neprilysin inhibitor (ARNI) act as vasodilators and acutely influence hemodynamics by decreasing Ea and with direct result of increasing cardiac index and thus, CPO[35,36]. Nonetheless, with the exception of VAC and Ea, and arguably of left ventricular filling pressures (PCWP), none of the previously mentioned parameters have been proven to be of consistent value as therapeutic targets[36].

As mean values for E/A and E/E' ratios did not differ between the two groups, our data give further proof that basic diastolic function evaluation cannot be used to guide decongestive therapy. Inferior vena cava evaluation is probably more informative and better reflects elevated filling pressures.

The most significant finding is the identification of a highly asymmetrical distribution of Ea among advanced HF patients, who are otherwise a homogenous selected group (relatively to 'classic' echocardiographic and clinical parameters), suggesting different patterns of hemodynamic adaptation to a severely diseased LV. Despite of a relatively small sample size, patients with advanced HF included in this study display minimal dispersion of the standard echocardiographic measurements, but a large dispersion of elastances values, suggesting a wide range of ventricular-arterial coupling and possible distinct responses to inotropic therapies, both findings being clinically relevant.

Figure 4 depicts the important variation of Ea as compared to an otherwise linear distribution of LVEF. Ea phenotypes are very diverse for the same LVEF intervaland Ea variation should not be considered erratic. Its strong correlation with Ees, suggests that 'adaptation' of peripheral hemodynamics can have different patterns. Full assessment of changes in contractility requires as well, accounting for changes in Ees at markedly reduced levels of contractility and in hearts that have undergone extreme degrees of remodeling - as LVEF is no longer sufficiently informative.

This observation reinforces the idea that the most efficient mean to influence HF macro-hemodynamics is through Ea modulation.

Our data show conclusively, that inside the most severe HF group, 'classic' hemodynamic parameters fail to further sub-classify patients and to identify those at highest risk for adverse events. The cut-off values of classical parameters for selecting severe cardiac dysfunction appear too broad, as newer medications acting on peripheral resistance and preload, may enable some patients to better adapt their hemodynamics than others.

As rest echocardiographic examination appears unsensitive, we suggest that the ability to modify Ea during low dose dobutamine stress testing could

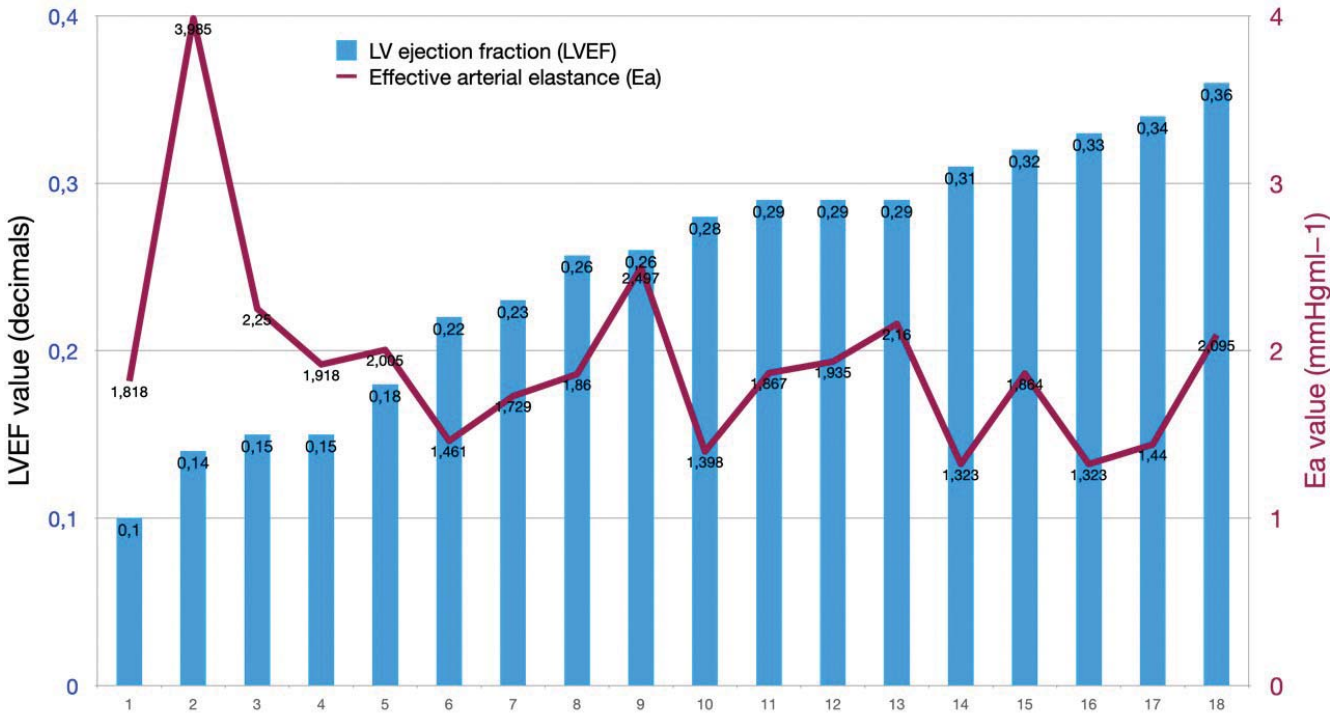


**Figure 4.** The variation of LV ejection fraction (LV EF) compared to that of effective arterial elastance (Ea) in patients with advanced HF (r=0.434, p=0.72).

be more informative for prognosis and better guide therapies. To note, such granular hemodynamic evaluation by echocardiography requires good acoustic window. Further research, including less complex/sophisticated parameters, such as PEP/LVET ratio or LV ejection force, may contribute to the understanding of the contractility abnormalities seen in advanced HF patients.

## LIMITATIONS

The small sample size of the present study is one of the main limitations of this type of research, and is found in all such studies reported in literature. Although the study included a small sample size, the patients were highly selected to define a homogenous group of advanced HF patients. We found similar cut-off values to the previously published data for CPO and PEP/LVET that were able to identify severe patients. Dynamic tests were not performed in the present study. Any type of sensitivity analysis was beyond of the scope of this research, and limited due to the low sample size. We cannot exclude that many other variables, not collected in the present study, might be influenced the results. Our main scope was to validate a research protocol to demonstrate a significant dispersion of the elastance values regardless of baseline LVEF.

## CONCLUSION

Echocardiographic measures of LV function as LVEF, LV force, LV size, CPO, VAC maintain their ability to differentiate advanced HF patients from pre-HF patients, but are load dependent and miss discriminatory capacity to further characterize advanced HF in clinical relevant and hemodynamic phenotypes. Among the advanced HF patients, the hemodynamic interaction between the dysfunctional LV and the compensatory response of the peripheral system is heterogenous and cannot predict outcome by single parameters. In these patients, assessment of cardiac performance should no longer rely on LEVF alone.

### Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

### References

1. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(11):1505-35.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats

AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
3. Mihaileanu S, Antohi EL. Revisiting the relationship between left ventricular ejection fraction and ventricular-arterial coupling. ESC Heart Fail. 2020.
4. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J. 2016;37(21):1642-50.
5. Marwick TH. Ejection Fraction Pros and Cons: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(19):2360-79.
6. Antohi EL, Chioncel O. Understanding cardiac systolic performance beyond left ventricular ejection fraction. Exploration of Medicine. 2020;1(1):75-84.
7. Altenberger J, Gustafsson F, Harjola VP, Karason K, Kindgen-Milles D, Kivikko M, et al. Levosimendan in Acute and Advanced Heart Failure: An Appraisal of the Clinical Database and Evaluation of Its Therapeutic Applications. J Cardiovasc Pharmacol. 2018;71(3):129-36.
8. Chioncel O, Collins SP, Ambrosy AP, Pang PS, Radu RI, Antohi EL, et al. Therapeutic Advances in the Management of Cardiogenic Shock. Am J Ther. 2019;26(2):e234-e47.
9. Green P, Kodali S, Leon MB, Maurer MS. Echocardiographic assessment of pressure volume relations in heart failure and valvular heart disease: using imaging to understand physiology. Minerva Cardioangiol. 2011;59(4):375-89.
10. Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Remme EW, et al. A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. Eur Heart J. 2012;33(6):724-33.
11. Seemann F, Arvidsson P, Nordlund D, Kopic S, Carlsson M, Arheden H, et al. Noninvasive Quantification of Pressure-Volume Loops From Brachial Pressure and Cardiovascular Magnetic Resonance. Circ Cardiovasc Imaging. 2019;12(1):e008493.
12. Papadopoulos K, Ozden Tok O, Mitrousi K, Ikonomidis I. Myocardial Work: Methodology and Clinical Applications. Diagnostics (Basel). 2021;11(3).
13. Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Gjesdal O, et al. Assessment of wasted myocardial work: a novel method to quantify energy loss due to uncoordinated left ventricular contractions. Am J Physiol Heart Circ Physiol. 2013;305(7):H996-1003.
14. Lewis RP, Rittogers SE, Froester WF, Boudoulas H. A critical review of the systolic time intervals. Circulation. 1977;56(2):146-58.
15. Isaaz K, Ethevenot G, Admant P, Brembilla B, Pernot C. A new Doppler method of assessing left ventricular ejection force in chronic congestive heart failure. Am J Cardiol. 1989;64(1):81-7.
16. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol. 2004;44(2):340-8.
17. Antonini-Canterin F, Enache R, Popescu BA, Popescu AC, Ginghina C, Leiballi E, et al. Prognostic value of ventricular-arterial coupling and B-type natriuretic peptide in patients after myocardial infarction: a five-year follow-up study. J Am Soc Echocardiogr. 2009;22(11):1239-45.
18. Ky B, French B, May Khan A, Plappert T, Wang A, Chirinos JA, et al. Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure. J Am Coll Cardiol. 2013;62(13):1165-72.
19. Kerkhof PL. Characterizing heart failure in the ventricular volume domain. Clin Med Insights Cardiol. 2015;9(Suppl 1):11-31.
20. Ikonomidis I, Aboyans V, Blacher J, Brodmann M, Brutsaert DL, Chirinos JA, et al. The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association. Eur J Heart Fail. 2019;21(4):402-24.
21. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41(10):1797-804.
22. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424-33.
23. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: Validation of a Simple Tool for the Prediction of Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2018;7(20):e009594.
24. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352-80.
25. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301-10.
26. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol. 2001;38(7):2028-34.
27. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol. 1983;245(5 Pt 1):H773-80.
28. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;86(2):513-21.
29. Cortigiani L, Sorbo S, Miccoli M, Scali MC, Simioniuc A, Morrone D, et al. Prognostic value of cardiac power output to left ventricular mass in patients with left ventricular dysfunction and dobutamine stress echo negative by wall motion criteria. Eur Heart J Cardiovasc Imaging. 2017;18(2):153-8.
30. Yildiz O, Aslan G, Demirozu ZT, Yenigun CD, Yazicioglu N. Evaluation of Resting Cardiac Power Output as a Prognostic Factor in Patients with Advanced Heart Failure. Am J Cardiol. 2017;120(6):973-9.
31. Lim HS. Cardiac Power Output Revisited. Circ Heart Fail. 2020;13(10):e007393.
32. Saxena T, Patidar S, Saxena M. Assessment of left ventricular ejection force and sympathetic skin response in normotensive and hypertensive subjects: A double-blind observational comparative case-control study. Indian Heart J. 2016;68(5):685-92.
33. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60.
34. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. Eur Heart J Cardiovasc Imaging. 2017;18(9):961-8.
35. DiCarlo L, Chatterjee K, Parmley WW, Swedberg K, Atherton B, Curran D, et al. Enalapril: a new angiotensin-converting enzyme inhibitor in chronic heart failure: acute and chronic hemodynamic evaluations. J Am Coll Cardiol. 1983;2(5):865-71.
36. Fonarow GC. The treatment targets in acute decompensated heart failure. Rev Cardiovasc Med. 2001;2 Suppl 2:S7-S12.