Annals of Clinical and Medical Case Reports

DOI: https://doi.org/10.47829/ACMCR.2023.11701

Review Article

ISSN 2639-8109 | Volume 11

In Search for the Right Track from Definition to Diagnosis and Treatment for Heart Failure

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Received: 03 Aug 2023

Accepted: 25 Sep 2023

Published: 02 Oct 2023

J Short Name: ACMCR

Citation:

Karamichalakis N, In Search for the Right Track from Definition to Diagnosis and Treatment for Heart Failure. Ann Clin Med Case Rep. 2023; V11(7): 1-6

Keywords:

Heart Failure; Ejection Fraction; Index; Volumetric; Filling Pressures

1. Abstract

Left ventricular ejection fraction (LVEF), a phenotypic artificial marker of cardiac systolic function, has been traditionally used for the classification of heart failure (HF) patients. However, LVEF suffers from several limitations and drawbacks that make its use debatable. Recently, a new index, myocardial work index, has been proposed. This novel index contains two variables: global longitudinal strain and branchial artery pressure that is also affected by a number of limitations. According to pathophysiological mechanisms, heart failure (HF) is defined when elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise are present. In the present work we propose a relatively easy algorithm showing the different clinical scenarios and therapeutic perspectives, based on LV volumetric and filling pressure indices. The proposed algorithm has to be evaluated in a large cohort of individuals both normal and HF patients and most importantly as a follow-up index. In conclusion although LVEF remains a powerful index enormously used there is a need to move forward searching for a new path that incorporate volumetric and left ventricular filling pressure according to the definition of HF syndrome.

2. Introduction

From the very first, until the recently published heart failure (HF) guidelines the definition of HF is given in two paragraphs [1, 2]. The first one defines HF as 'not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms that may be accompanied by signs. Symptoms, that are similar regardless of the level of left ventricle ejection fraction (LVEF), due to either congestion (dyspnea, orthopnea etc.) or to decreased output (fatigue, weakness etc.) or both. Symptoms that are more severe with exertion and are not dependent on LVEF. The second one underlines that 'It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise'. At the same time, it is written that 'traditionally HF syndrome, is divided in 3 different phenotypes based on LVEF'. A sentence including a phenotype classification that does not fulfill the basic concept of the aforementioned two paragraphs and contain different mutable trajectories [3]. Therefore, from a scientific point of view, this categorization seems meaningless and explains why HF clinical trials are in part inefficient [4-7]. On the other hand, the second paragraph confirms the timeless definition of HF that defines this syndrome as the incapacity of the heart, under normal filling pressure, to adequately satisfy the metabolic needs of the periphery; that includes intracardiac pressure and cardiac output.

The LVEF fans/supporters, claim that this index is more accurate than stroke volume since the former incorporate Frank-Starling relationship. This is not entirely correct, since both incorporate volumetric measurements; stroke volume is the difference of End-diastolic to End-systolic volume; that is indeed the Frank –Starling relationship. Accordingly, both LVEF and stroke volume are depended on the same variables (pre-post load, contractility, heart rate) suggesting that to some extents are more or less comparable since EF is almost exclusively determined by End-systolic volume [8, 9]. Of note, it has been suggested that 'Under nearly ideal imaging conditions, LVEF errors range from 10% to 37% when applying the common geometric models to 3 or fewer measurements, and 3% to 7% when using the composite midpoint method to stacks of 4 to 6 short-axis slices, but larger errors are expected clinically [10]. It is true that for decades the cardiology community is accustomed in measuring LVEF and consequently many studies using this index have been conducted and many books have been written. LVEF has become the common language and the variable to lie on under different conditions and is extended not only in cardiological environment but also in different medical specialties. However, there are several conditions where the clinical usefulness of LVEF is debatable. For instance, what do we have to think when left ventricle is enlarged and thus end-diastolic and end-systolic volume are increased, LVEF is reduced but stroke volume is preserved? Accordingly, what we have to think when left ventricle is small, with preserved or even normal LVEF, but stroke volume is reduced? Indeed, there are Pros and Cons related to this index [11] and when we take under consideration the phenotypic presentation of HF as this is presented by LVEF, we must be very cautious and to take into account additional variables to confirm our diagnosis and consequently to propose the best medical and device treatment for HF patients.

Based on the recommendations of the European Society of Cardiology HF guidelines, it seems that in patients with acute HF there is a need to use hemodynamic measurements on top of clinical data [1, 12] a fact that can be also recommended for patients with advanced HF [1, 13]. Indeed, it has been reported that in hospitalized HF patients, LVEF cannot predict the adverse events; mortality after 5-years follow-up [14]. To overcome the various conventional LVEF- measurement drawbacks, 3D heart acquisition has been proposed (which requires a standard quality of images), a technique that is characterized by low temporal resolution, leading thus to miss-estimation of end-diastolic and end-systolic volumes and hence EF [11, 15]. Indeed, even using 3D echocardiography, it remains a fact that in several regions, tracing is sparse and noisy [10]. Thus, new indices related to myocardial deformation have been proposed. However, the measurements of these indices are time consuming; they need an excellent imaging acquirement/processing and under certain circumstances are characterized by misleading tracing of cardiac layers – borders. Moreover, there is a diversity of the current software algorithms, these indices are also load depended and are proposed to be used on top of LVEF and not instead. Consequently, there might be a source of errors, depending either or both on imaging, on software and on operator factors [16]. Of note, not all cardiologists in their everyday clinical practice have the financial sources to use devices with this capability; such as 3D echocardiography and speckle tracking acquisition. Interestingly, there is yet no answer to the question: which device to select for use, since echo machines algorithms are not well comparable. Despite the drawbacks of the aforementioned techniques, a new index, the myocardial work index, has been proposed, incorporated in only one system-software, making thus the vast availability limited, [17]. This novel index contains two variables: global longitudinal strain and branchial artery pressure. However, global longitudinal strain is affected by the previously reported limitations along with load conditions. Additionally, the measurement of brachial artery pressure varies during the cardiac cycle, is affected by branchial artery disease and in different clinical scenarios does not coincide with intracardiac pressure [17-19]. Accordingly, since this index is affected by these limitations, the trace of volume - pressure curve and hence the calculation of myocardial work index seems to be under certain circumstances rather inaccurate.

To overcome human weaknesses, a contemporary approach has been proposed; enter artificial intelligence (AI). An approach that has the capability to explore cardiovascular genotypes and phenotypes giving thus a more accurate conclusion. An effort that tries to substitute human limitations-errors with computer capability on learning capacity, and knowledge storage [20] but again this approach still carries the attempt to measure and calculate LVEF. Additionally, given the fact that AI platform is not yet ready and a high level of training, validation of clinical characteristics, machine vendors, and image quality must be determined, limititation on the generalizability of the resulting platforms can occur [21]. Importantly, is largely relied on human interpretation that involves the inherent human variability in interpretation and measurement making thus the final results depend on human errors. Although symptoms and signs are the cornerstones of HF syndrome, they demonstrate a low accuracy. To overcome this drawback, the measurement of natriuretic peptides (NPs) has been proposed. Elevated concentrations of NPs are suggesting of HF, but it has to be noticed that here are various clinical scenarios cardiac and extracardiac, that may increase NPs such as atrial fibrillation, advanced age, chronic kidney or liver disease, severe infections etc. [2, 22] or even decrease the levels of NPs such as obesity, acute mitral regurgitation, cardiac tamponade etc. [2, 23]. Therefore, since in HF patients, a high percentage of comorbidities (renal dysfunction, anemia etc.) coexist, the global use of NPs, although tempting, to some extent is problematic. Moreover, the measurements of NPs do not fulfill the basic concept of HF syndrome definition.

3. Medical Treatment

Returning to the first paragraph of HF definition, it is clear that this syndrome is a clinical entity characterized by symptoms; dyspnea either at rest or exertional, fatigue, fluid retention, and eventually signs. Clearly, muscle fatigue or even decreased renal perfusion and urine output are attributed to reduced cardiac output. Additionally, the flooding with transudate of the lungs causing cough, dyspnea etc. and thus to venous blood backlogs leading to the right ventricle involvement and consequently to liver, renal, gastrointestinal and peripheral congestion. In this respect, the following cardiac enlargement along with neurohumoral and sympathetic activation are compensatory mechanisms. Thus, the categorization of patients according to LVEF, although easily obtained and widely used, does not entirely fulfill the scientific definition of HF syndrome. Moreover, although there is a continuum of HF syndrome there is a vast discrepancy in definition and enrollment of HF patients. Indeed, many studies enroll patients with different levels of EF, incorporate different etiologies and structural heart diseases, as well different level of NPs, leading to conclusions from a non-homogenous poll and insufficiently studied [24, 25]. Regardless of the above-mentioned thoughts, the guideline-directed optimal medical treatment is based on the dichotomized categorization according to LVEF [3]. Although, there are enough and conclusive data concerning medical treatment in patients with HFrEF (LVEF<40%) [26], data for patients with HFpEF (LVEF>50%) are conflicting. Enrollment in this category of patients is ambiguous and methodologically unorthodox, since some of the enrolled patients are part of the HFmrEF group [27]. Additionally, in patients with HFmrEF (LVEF=40-49%) the outcomes of medical therapy are unpredictable, because in this category of patients there might be an undiscovered group of patients who improve EF and is unknown if this occurs because of medical treatment or due to the withdrawn of the index event and the capacity of the homeostatic status to recover. Of note, there are researchers that enroll, without any scientific rational, this group of patients either in HFpEF or HFrEF studies.

4. If not EF then what?

According to the timeless definition of HF, we have to consider and put into consideration both volumetric measurements and intracardiac pressure. It is obvious that stroke volume and cardiac output are determinants for organ perfusion are metabolic needs of the periphery. The easily cost-effective, but time consuming, still reliable under various physiological conditions and widely proposed tool to calculate the above-mentioned index is echocardiography [28-31] Stroke volume by echo is calculated as the product of cross-sectional area multiplied to velocity time integral of left ventricular outflow tract. However, the cross-sectional area is derived from squared diameter outflow tract trace that might be subjected to mathematical miss-calculation. Therefore, to overpass these errors it could be reasonable and worthy to measure just the VTI at the outflow tract and consider it as stroke volume [32-34]. Interestingly, if we measure stroke volume in the same person repetitively, since the sectional area does not change through time, we can speculate that VTI at the left ventricular outflow tract represent stroke volume. Indeed, the LVOT VTI measurement has been reported and validated successfully in several clinical scenarios [35-40]. Regarding feasibility, it has been reported that this index was obtained in a high percentage of patients (95%) with high repeatability [31]. Additionally, under difficult conditions at the emergency department, a rather high volume of accurate measurement of LVOT VTI has been performed [35, 40-42] in order to predict the survival rate [32, 43, 44]. However, LVOT VTI albeit a well-established reproducible index in patients with chronic HF [32, 45] is subjected to several limitations. Specifically, its reliability is problematic when we face clinical conditions such as severe aortic disease, LVOT obstruction, extreme myocardial hypertrophy as well as rhythm disturbances [36, 46-48]. Concerning the measurement of LV filling pressures, the European Society of Cardiology [2] and the American Society of Echocardiography and the European Association of Cardiovascular Imaging [49] recommend the E mitral wave velocity to E' prime of myocardial velocity ratio (normal 8, abnormal>14, and 8-14 of borderline significance) calculation. Based on the above expressed variables, it is reasonable to investigate whether the product of these two parameters (volumetric and filling pressure indices), might offer a new easily performed index evaluating HF status and progression. In this respect, taking as normal values, for VTI normal range 17-23 cm and for E/E' < 9 we can detect the following scenarios (Table 1). Accordingly, the following algorithm is produced (Figure 1). In the present manuscript we consider as normal values for E/E' lateral, a value of <9, while values 9 - ≤14 were considered of borderline significance, and values >14 were considered as representing high left ventricular filling pressure [2]. This is because we suggested the easiest way to measure filling pressure and thus, we consider part of equation only the lateral and not the average (lateral + septal) E' wave [49, 50]. Furthermore, we have to admit that lateral E' wave is dependent on gender and age showing a progressive increase in males and older in age patients [51]. In this respect, the proposed algorithm has to be evaluated in a large cohort of individuals both normal and HF patients and most importantly as a follow-up index.

Table 1: Range of Volumetric and filling pressure product.

Normal VTI x Normal E/E'	Range: 34-184cm
Normal VTI x Normal E/E'	Range: 153-645 cm
Normal VTI x Normal E/E'	Range: 20-128 cm
Normal VTI x Normal E/E'	Range: 90-124

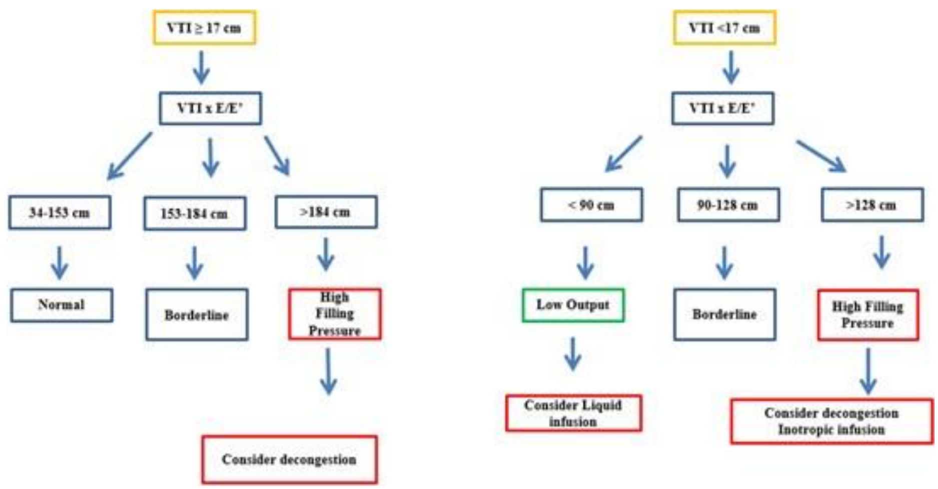

Figure 1: An algorithm showing the different clinical scenarios and therapeutic perspectives, based on left ventricular volumetric and filling pressure product, depending on whether we face a normal or abnormal left ventricular Ejection Fraction (EF). VTI: Velocity Time Integral.

5. Conclusion

In conclusion, LVEF remains a powerful index enormously used. However, there is a need to move forward searching for a new path to incorporate volumetric and LV filling pressure, according to the definition of HF syndrome. The quest is ongoing and under investigation are key elements such as restore of energy deficiency, metabolic imbalance, mitochondrial involvement, genetic distortion etc. Taking into account, novel and conventional indices and incorporating contemporary features such as AI, a method to approach, evaluate and accordingly treat HF patients could be already on its way.

6. Author Contributions

Conceptualization, I.P. and E.T.; methodology, N.K; software, N.K., E.T.; data curation, I.P.; writing—original draft preparation, I.P., writing—review and editing, N.K., E.T.; visualization, I.P., N.K, E.T.; supervision, I.P. All authors have read and agreed to the published version of the manuscript.

7. Funding

This research received no external funding

8. Institutional Review Board Statement

Not applicable

9. Informed Consent Statement

Not applicable.

10. Data Availability Statement

Not applicable.

11. Conflicts of Interest

The authors declare no conflict of intrest.

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