

# Consensus Statement on Acute Heart Failure with Preserved Systolic Function

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## Abbreviations >

<b>AA</b>	Aldosterone antagonist	<b>DHF</b>	Diastolic heart failure
<b>ARB</b>	Angiotensin II receptor blocker	<b>HFPSF</b>	Heart failure with preserved systolic function
<b>BB</b>	Beta blocker	<b>SHF</b>	Systolic heart failure
<b>BNP</b>	B-type natriuretic peptide	<b>ACEI</b>	Angiotensin-converting enzyme inhibitor
<b>AF</b>	Atrial fibrillation	<b>pro-BNP</b>	Pro B-type natriuretic peptide
<b>DF</b>	Diastolic function	<b>ANS-RAAS</b>	Autonomic nervous system-renin-angiotensin-aldosterone system
<b>EF</b>	Ejection fraction	<b>RAS</b>	Renin-angiotensin system
<b>SF</b>	Systolic function	<b>LV</b>	Left ventricle
<b>HT</b>	Hypertension		
<b>LVH</b>	Left ventricular hypertrophy		
<b>MI</b>	Myocardial infarction		
<b>HF</b>	Heart failure		

The *Council on Heart Failure of the Argentine Society of Cardiology* has recently developed and published the *Consensus Statement on Congestive Heart Failure*, in which chronic (1), acute and advanced heart failure with left ventricular dysfunction (SHF) have been analyzed. (2) The conclusions of the *Consensus Statement on Heart Failure with Preserved Systolic Function (HFPSF)* are presented in this issue. This type of heart failure is frequent, yet difficult to understand, and with scarce and controversial evidence.

The goal of this document is to guide physicians in the management of patients with HFPSF and does not try to replace the criterion of the attending physician in individual patient care. It is the intention of this Consensus Statement to develop general rules to suggest recommendations, and does not ignore that the implementation of new recommendations may be affected by the availability of procedures and the experience of the environment. These recommendations may be modified in a near future by the new evidence arising from novel clinical trials.

Patients with heart failure (HF) can be divided into two broad categories: systolic HF (SHF) and diastolic HF (DHF). There are significant differences between the two groups of patients. (3) Patients with SHF have progressive ventricular dilation, eccentric left ventricular hypertrophy (LVH) and decreased

systolic function (SF) in the left ventricle (LV). DHF, a trendy term introduced a little over 20 years, (4) is characterized by normal ventricular volumes, concentric LVH, preserved systolic function (SF) and abnormal diastolic function (DF) (5)

However, it may be occasionally difficult to distinguish SHF from DHF with physical examination, and echocardiography is the method to differentiate them. (6) The differential diagnosis between DHF and SHF is based on the ejection fraction (EF). The EF cutoff value used to differentiate SHF from DHF has ranged from 40% to 50% in a variety of studies; yet, the use of other cutoff points modifies the proportion of patients with SHF and DHF.

There are discrepancies about the correct terminology to refer to this group of patients. As the abnormalities in DF are always present in all types of HF, it has been postulated that the term DHF is inappropriate. In addition, the assessment of DF is not a rule in the evaluation of patients. (7) For this reason, it has been suggested to use the term HF with preserved systolic function (HFPSF) to differentiate it from HF with decreased systolic function or systolic HF (SHF).

However, different physiopathological mechanisms may play a role in patients with preserved SF, including impairment of DF, abnormalities in ventricular-

vascular coupling and arterial distensibility, and renal dysfunction with impaired fluid management. For this reasons, the underlying mechanisms in different patients with HF and preserved SF are not uniform. In addition, other conditions (obesity, anemia, pulmonary disease) may produce a clinical picture similar to that of HF: Thus, not all patients with a clinical presentation of HFPSF do necessarily have diastolic dysfunction. (8)

The differences in the prevalence and incidence in different clinical and epidemiological studies are also related to different diagnostic criteria. (9) Vasan and Levy criteria for DHF consider: clinical evidence of HF, EF >50% within 3 days of HF event, and evidence of LV diastolic dysfunction (cardiac catheterization is required). If all 3 criteria are met, the diagnosis of definite diastolic heart failure is made; in the absence of cardiac catheterization data, a diagnosis of probable diastolic heart failure is made. The diagnosis of possible diastolic heart failure is made if the EF was not measured near the time of the patient's presentation with heart failure (>72 hours of the heart failure event). (10)

The last European Consensus Statement refers to the diagnostic criteria of HFPSF and includes: a) signs or symptoms of HF; b) EF > 50% and a LV end-diastolic volume index < 97 ml/m<sup>2</sup> and, c) evidence of abnormal diastolic function measured by tissue Doppler imaging, biomarkers or direct hemodynamic measurement (11)

The necessity of evaluating the diastole has been discussed by those who understand that, in the presence of a history of HF, the combination of normal EF and concentric LVH are enough to define the diagnosis. (12)

Several registries of outpatients or patients hospitalized with HF have reported that the incidence of HFPSF in more than 50%. (13) In clinical series, the frequency of DHF among patients with HF ranges from 13% to 74% (14) due to differences in the population studied, such as age, prevalence of female gender and sources of information, the criteria used to diagnose HF, and the cutoff values for defining systolic dysfunction. (15) For the same reasons, the prevalence of HFPSF in the general population varies from 1% to 5% according to different epidemiological studies. (16, 17)

The incidence of both types of HF increases with age; yet, HFPSF is more frequent in elder populations compared to SHF. (18) In the same sense, the prevalence of HFPSF has increased in the last 15 to 20 years, while that of SHF has not varied. Several factors are associated with the greater prevalence of HFPSF: increased prevalence of the conditions related to diastolic impairment (Table 1), progressive aging of the population and the fact that the attending physicians are more aware about the existence of the disease and thus are more prone to making the diagnosis, indicating echocardiographic evaluation and measuring natriuretic peptides. (20)

Compared to patients with systolic dysfunction, subjects with HFPSF are older and the prevalence of female gender, (21) hypertension (HT), diabetes and

obesity is greater. Blood pressure levels and the presence of few comorbidities are greater in these patients. However, the history of previous myocardial infarction (MI) is significantly lower. (22, 23)

Long-term prognosis varies depending on the study. (24) The results of randomized studies including a broad spectrum of heart failure patients revealed that the prognosis of patients with an EF < 45% was better than that of patients with worse ventricular function. (25, 26) In population-based series and hospitalized heart failure patients (50% of them with preserved EF), the prognosis is similar to that of patients with SHF, or slightly better. (22) The annual mortality rate in outpatients is 5% to 8% in HFPSF versus 10% to 15% in SHF.

The clinical differences between both types of HF in hospitalized patients have already been mentioned; in-hospital outcomes are slightly more favorable for HFPSF. (28) Some series have reported that adjusted mortality rate at one year and rehospitalizations are similar in patients with EF > 50 and in those with EF < 40%, (29) while in other series long-term outcomes are even worse for HFPSF compared to SHF. (30)

However, data from epidemiological studies should be considered cautiously due to the different criteria used, the differences in the evaluation of DF and the possible inclusion of patients with conditions which have a similar clinical presentation with HF but do not have HF. (31)

It is also clear that patients with normal EF also have some degree of systolic dysfunction, as evidenced by tissue-Doppler imaging. For this reason, it has been postulated that HF is a single syndrome with a unimodal distribution of LVEF. (32) However, different patterns of LVH, structural proteins and enzymes, and differences in the population affected and in the response to treatment support the theory that clinical heart failure presents and evolves not as a single syndrome but as two syndromes.

Thus, this Consensus has decided to adopt the definition of HFPSF based on the aforementioned information, daily practice (as measurement of DF is not the rule) and the variations of the diastole due to changes in load conditions, heart rate and medication.

In order to determine an EF cutoff value, we have taken into account that most randomized trials evaluating SHF included patients with EF < 35-40%. For this reason, using an EF cutoff value > 50% for considering preserved systolic function would leave patients with EF between 40% and 50% in a grey zone. In order to avoid any doubts, and even assuming that any cutoff value is subject of discussion, the members of this Consensus have decided to consider an EF > 45% to differentiate SHF from HFPSF. (1)

There is a little evidence in favor of a specific treatment in patients with HFPSF. This lack of evidence, mostly due to the heterogeneity of the studies conducted, prevents us from elaborating a consensus

statement with the classic structure. Thus, we only make recommendations about diagnosis and treatment and do not provide classification of recommendations or level of evidence.

## DIAGNOSIS

**Three obligatory conditions need to be satisfied for the diagnosis of HFPSF: presence of signs or symptoms of HF; response to therapy with diuretics, and normal or mildly abnormal SF. This Consensus considers a limit EF value > 45%.**

The diagnosis of HFPSF is generally made by exclusion and requires echocardiographic evidence of normal EF. The presence of echocardiographic or hemodynamic parameters of diastolic dysfunction has an added value to classify the condition and contributes to understand the physiopathology; yet, these parameters are not exclusive of HFPSF.

HFPSF is more frequent in the elder, women and patients with obesity, HT, diabetes or atrial fibrillation (AF). (33, 34) Table 1 shows other etiologies and comorbidities associated with HFPSF.

### Medical history

Anamnesis and physical examination are essential to detect symptoms and signs suggestive of HF. The application of the Framingham criteria is useful for the diagnosis. The anamnesis should include history of alcohol intake, coronary artery disease, arrhythmias, HT, diabetes, thyroid diseases, anemia, etc.

### Electrocardiogram

The electrocardiogram is useful for identifying underlying conditions or triggers (arrhythmias, signs of LVH, left atrial enlargement, ischemic heart disease, etc.).

### Chest X-ray

Chest X-ray is useful for evaluating cardiac silhouette, signs of pleural and pulmonary involvement, congestion and pulmonary edema during decompensation. (1) Heart enlargement is infrequent, and other causes of dyspnea can be excluded.

### Laboratory tests

As for patients with SHF, the initial evaluation should include **routine lab tests**, such as complete blood count, erythrocyte sedimentation rate, blood sugar levels, BUN, creatinine, electrolytes, liver panel and urinalysis, which should be repeated during episodes of decompensation. (1) Thyroid hormones should be determined in cases of probable thyroid diseases, in patients with AF, tachycardia and HFPSF of unknown etiology.

**Table 1** Etiologies and conditions associated with HFPSF

– Advanced age
– Female gender
– Hypertension
– Ischemic heart disease
– Diabetes
– Obesity
– Anemia
– Chronic kidney failure
– Atrial fibrillation
– Tachyarrhythmias (shorter ventricular filling)
– Hypertrophic cardiomyopathy
– Aortic stenosis
– Mitral stenosis
– Restrictive cardiomyopathy
– Amyloidosis
– Hemochromatosis
– Fibroelastosis
– Fabry disease
– Radiation-induced myocardial fibrosis
– Use of NSAIDs or thiazolidinediones
– RV volume overload or dilation
– Non-myocardial causes: cardiac tamponade, constrictive pericarditis

NSAIDs: Non steroidal anti-inflammatory drug RV: Right ventricular.

Measurement of **natriuretic peptides** may be useful. Pro-BNP and BNP are released in cases of pressure or volume overload, in response to an increase of myocardial fibers stretch. The levels of these peptides are higher in patients with diastolic dysfunction, particularly in those with symptoms and more severe impairment of ventricular relaxation (restrictive pattern), as an expression of increased LV end-diastolic pressure. (35) Neuropeptides may also be elevated in patients with diabetes, > 60 years and in women, regardless of the presence of ventricular dysfunction in this population.

The usefulness of neuropeptides lies in their negative predictive value at the moment of ruling out the presence of heart failure in patients presenting to the ER with dyspnea. In addition, very high levels of neuropeptides have prognostic value in patients with decompensated HF.

### Doppler echocardiography

Doppler echocardiography is the most useful diagnostic method for HFPSF. It allows the evaluation of ventricular function, an essential requirement to define whether the patient has HF with systolic dysfunction or pure or predominant diastolic dysfunction (EF > 45%). In addition, echocardiography is the most versatile and validated

tool for non-invasive assessment of diastolic function. (36)

The evaluation of LV morphology and wall motion orientates towards the etiology of diastolic dysfunction (presence of LVH, signs suggestive of restrictive cardiomyopathy, wall motion abnormalities suggestive of ischemic cardiomyopathy). Left atrium diameter, area and index volume should be routinely measured as the presence of diastolic dysfunction produces left atrial enlargement due to abnormal relaxation of the LV. (37)

Mitral inflow filling velocities measured by tissue Doppler imaging allow the recognition of different filling patterns (normal, delayed relaxation, pseudonormal and restrictive filling pattern) which orientate about the different stages of diastolic dysfunction and the impact on filling pressures. Tissue Doppler imaging measured at the level of the mitral annulus (Ea wave, from tissue Doppler interrogation) and particularly its relationship with the E wave corresponding to mitral filling is useful to differentiate pseudonormal patterns from normal patterns. It is also possible to estimate pulmonary capillary wedge pressure using a validated formula. (38)

In patients with depressed SF, measurement of the slope using color M-mode Doppler is useful in order to determine elevation on filling pressures and gives supplementary information. This information has diagnostic and prognostic value. During follow-up, mortality is significantly higher in patients with pure diastolic dysfunction and Ea wave < 3.5 m/s and in those with pseudonormal or restrictive filling patterns, compared to patients with normal or delayed relaxation patterns. (39) After myocardial infarction, mortality increases significantly in patients with EF < and > 40% with mitral E/Ea ratio 15 or higher. This was also demonstrated in patients with chronic renal disease and preserved SF. (40)

Non-invasive assessment of pulmonary pressures by echocardiography provides diagnostic and prognostic information that has been validated in daily practice. (11)

Strain and strain rate imaging for the estimation of diastolic function are under study and the diagnostic and prognostic value of this technique has not been clearly established yet.

**Stress echocardiography** may be useful in patients with effort dyspnea and inconclusive findings during rest echocardiography, or to evaluate the response of filling patterns and pulmonary pressures during exercise.

### Nuclear medicine

Although cardiac radionuclide imaging techniques, in particular myocardial perfusion SPECT, may have a role in the evaluation of SF and DF, they are mainly used for the assessment of diagnosis and prognosis of myocardial ischemia and/or necrosis. (41)

### Magnetic resonance imaging

Cardiac magnetic resonance imaging is not used to evaluate DF. The usefulness of this method is to determine the presence of cardiac conditions that evolve with diastolic dysfunction (LVH, hypertrophic or restrictive cardiomyopathies).

### Coronary angiography

Coronary angiography is indicated in patients with HFPSF with angina, electrocardiographic changes suggestive of myocardial ischemia and/or evidence of extensive ischemic territories in myocardial perfusion tests. Patients with acute pulmonary edema in whom ischemia is suspected should also undergo coronary angiography. Multidetector-row computed tomography might play a role to rule out coronary artery disease in a non-invasive fashion when indicated.

### Hemodynamic monitoring

Occasionally, invasive hemodynamic monitoring using a Swan-Ganz catheter may be indicated in patients who remain with symptoms with inconclusive non-invasive studies.

### Recommendations for the diagnosis of patients with HFPSF

The following recommendations should be considered for the initial diagnosis, follow-up or decompensation of patients in whom HFPSF is suspected:

- Medical history
- Electrocardiogram
- Chest X-ray
- Laboratory tests
- Transthoracic Doppler echocardiography.

The following tests should be considered in special situations.

- Thyroid hormones, in patients with AF, tachycardia and HFPSF of unknown etiology.
- Exercise stress test, SPECT, or stress echocardiography to rule out myocardial ischemia.
- Coronary angiography in patients with HFPSF and angina, electrocardiographic changes suggestive of ischemia or in those identified as having moderate or high risk in the stress tests .

In addition, the following tests might be considered:

- Specific laboratory tests (pro-BNP, BNP) in patients in whom the diagnosis is inconclusive or with acute decompensation of HFPSF. They are not indicated in stable patients with an established diagnosis.
- Magnetic resonance imaging for the diagnosis of hypertrophic or restrictive cardiomyopathies that are not diagnosed by other methods.
- Screening for hemochromatosis, sleep apnea syndrome, amyloidosis, rheumatological diseases,



sarcoidosis and pheochromocytoma according to the clinical picture.

- Endomyocardial biopsy in cases of suspicion of systemic diseases with myocardial involvement (hemochromatosis, sarcoidosis, amyloidosis, Loeffler endocarditis or endomyocardial fibrosis).

## TREATMENT

The evidence for treatment of HFPSF is not well documented as for SHF. Most of the interventional studies performed with these patients have important methodological limitations: less rigid criteria for the diagnosis of HF, heterogeneous EF cutoff values and subgroups of patients with different characteristics. In addition, as these patients are older and present many comorbidities, a unified response to treatment is improbable.

Bearing these limitations in mind due to the lack of evidence supporting the different treatments, the Editorial Committee has decided to establish recommendations and does not provide level of evidence.

### General measurements

The last ACC/AHA Task Force on Practice Guidelines has established some general premises in treatment that are recommended in the management of patients with HFPSF (42)

- Control of hypertension
- In patients with AF, sinus rhythm should be restored and maintained when patients are likely to respond.
- Rate control in patients with permanent AF.
- Revascularization in patients with coronary artery disease and inducible ischemia producing HF.
- The following recommendations are similar to those previously described in the Consensus Statement for SHF: adherence to dietetic measures and pharmacological treatment, weight control, low sodium intake, diabetes control, vaccination, smoking cessation, low alcohol intake, physical activity and HF programs. (1)

### Pharmacologic treatment

#### *Renin-angiotensin system inhibitors*

Therapy with renin-angiotensin system (RAS) inhibitors has been widely proved in patients with SHF. However, this does not apply for HFPS.

The heterogeneity of the studies is one of the main limitations. Only three studies could be evaluated in a recent meta analysis. (43) A systemic review included a total of 382 articles; yet, only PEP-CHF, CHARM-Preserved and I-PRESERVE trials were eligible for analysis. (44-47) The analysis found no clear benefit

with regard to all-cause mortality (OR 1.03, 95% CI, 0.92-1.15;  $p = 0.62$ ), or HF hospitalization (OR 0.90, 95% CI 0.80-1.02;  $p = 0.9$ ).

When the large trials examining the role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) were evaluated, we found the PEP-CHF study firstly. This study had important methodological limitations: a high crossover rate and number of patients without treatment at 2 years, and a significantly lower number of events in terms of morbidity and mortality.

None of the two studies on ARBs had a significant impact on mortality. The CHARM-Preserved trial showed a modest reduction in HF hospitalization (HR 0.85; 95% CI, 0.70-1.03;  $p = 0.072$ , after adjusting for covariables:  $p = 0.047$ ). In this way, this therapeutic option may be possible.

Despite of lack of conclusive evidence, these patients might benefit from RAS inhibition. In addition, many of these patients have HT and diabetes, conditions with indication of treatment with ACEIs or ARBs.

#### *Beta blockers*

Treatment with beta blockers is controversial due to the lack of studies specially designed to evaluate mortality and hospitalization due to HF. The information currently available comes from studies that included small number of patients, or from sub-studies of trials with HF patients with depressed and normal HF. (48-52)

The SENIORS trial substudy used 35% as a cutoff for preserved versus impaired EF. The 14% reduction in HF hospitalization and mortality is not comparable to other studies due to the low EF cutoff value.

Currently, BBs are clearly indicated for the treatment of underlying or associated conditions, as HT, myocardial ischemia or for heart rate control in patients with AF.

#### *Diuretics*

Diuretics are indicated to improve symptoms in patients with congestion. (53) There is no evidence showing reduction in mortality during chronic treatment of patients with HFPSF. However, the use of diuretics cannot be avoided.

Diuretics should be dosed with care, considering that they are generally administered to elder and diabetic patients with chronic kidney failure. Thus, therapy should be adjusted to avoid hypovolemia and subsequent greater morbidity.

#### *Aldosterone antagonists*

The use of aldosterone antagonists seems attractive due to fibrosis inhibition and other mechanisms of action; yet, there is no evidence of the use of aldosterone antagonists (AAs) in patients with HFPSF. We still have to wait for the results of ongoing trials to define the usefulness of these agents. (54) They may be occasionally used in patients with restrictive

cardiomyopathy with signs of congestion and even in anasarca.

### *Digitalis*

Digitalis is indicated for heart rate control in patients with AF with high ventricular response. (42)

A substudy of the DIG trial showed reduction in hospitalizations due to HF without impact on mortality; no other studies had similar results. (55, 56)

### *Calcium channel blockers*

The indication of calcium channel blockers in HFPSF is controversial. They are used for heart rate control in AF with high ventricular response, as anti-ischemic therapy or to prevent decompensation or development of HF in HT. (57, 58) Yet, there is no clear evidence that calcium channel blockers reduce morbidity and mortality in specially designed studies.

### *Statins*

The use of statins in patients with HFPSF was evaluated in two observational studies that showed a significant reduction in mortality. (59) The beneficial cardiovascular pleiotropic effects of statins support their use. Anyway, and similarly to trials in SHF, further studies designed to evaluate mortality are necessary to support the use of statins.

### **FINAL COMMENT**

The presence of associated comorbidities should be considered before indicating the above mentioned drugs. Hypertension, diabetes, kidney dysfunction, ischemic heart disease and AF are very frequent in this population and might guide the type of treatment. For example, BBs may be used for coronary artery disease or HT, ACEIs or ARBs for HT, etc.

HFPSF includes a heterogeneous group of patients, with several factors contributing for the development of the syndrome. Increased arterial stiffness and renal dysfunction, typical of HFPSF, are less sensitive to the inhibition of the ANS-RAAS axis; thus, ACEIs and ARBs are less likely to be as efficient as they are for the treatment of SHF: (18)

Currently, several ongoing trials are being conducted to elucidate this question. These studies evaluate aldosterone inhibition with espironolactone (TOP-CAT, ALDO-HF, PIE II) or eplerenone (PREDICT). Two beta blockers, nebivolol (ELANDD) and metoprolol succinate (B-PRESERVE), are also under investigation.

The physiopathology of this syndrome remains unclear; thus, we can fail in our attempt to go on looking for old formulas to treat HFPSF from the knowledge obtained from studies of SHF. (60) The high prevalence and increasing incidence of HFPSF generate frequent hospitalizations that affect the quality of life and survival of patients, resulting in

significant costs to the health system. For this reason, we should encourage every effort to understand this syndrome and find effective treatment to improve the outcomes and prevent decompensations.

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