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EDITORIAL

Diastolic Heart Failure: Current Data

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List of Abbreviations:
LV = left ventricle
MMP = metalo-proteinase

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ABSTRACT

The pathophysiology, structural and functional changes in diastolic heart failure are characterized by the lack of ventricular dilatation, normal left ventricular ejection fraction and increased fibrosis and left ventricular stiffness. The hemodynamic profile is similar to that of systolic heart failure. The therapeutic modalities available remain limited. Current data on diastolic heart failure are herein briefly reviewed.

DEFINITION

Several definitions of diastolic heart failure have been proposed.[1-5] One definition is, "a condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of congestion due to an inappropriate upward shift of the diastolic pressure –volume relation (that is during the terminal phase of the cardiac cycle)". Another proposed definition is that diastolic heart failure is a condition in which the "ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume". These definitions describe pathophysiology and functional abnormalities but cannot be applied in clinical practice.

The widely used clinical definition of diastolic heart failure is, "a clinical condition characterized by the presence of signs and symptoms of heart failure and preserved left ventricular ejection fraction". Based on this definition, diastolic heart failure is also termed "heart failure with preserved ejection fraction".

REMODELING

In diastolic heart failure, left ventricular (LV) cavity size is normal or decreased.[3-8] End-diastolic volume remains normal or even decreased. End-systolic volume is usually smaller and therefore ejection fraction is normal. Left ventricular dilatation does not occur without ischemic myocyte necrosis. Left ventricular wall thickness and mass is increased. The cavity/mass ratio is decreased.

Left ventricular hypertrophy is uniformly present. The myocyte diameter is increased but its length remains normal, thus the myocyte length/width ratio is decreased. The sarcomeres are replicated in parallel. There are also considerable

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changes in the matrix. The collagen volume is substantially increased. There is increased width and continuity of fibrillar collagen. Collagen cross-links are increased. In general, the matrix metallo-proteinases levels are decreased and their endogenous tissue inhibitors are increased in diastolic heart failure. The titin isoforms N2BA/N2B ratio is increased in diastolic heart failure.

FUNCTIONAL CHANGES

Increased LV passive stiffness and impaired LV relaxation is the principal functional abnormality in diastolic heart failure.[1-5] The diastolic pressure-volume relation shifts upward and to the left which is associated with a disproportionately greater increase in diastolic pressure for any increase in volume.

In advanced diastolic heart failure, LV end-diastolic pressure may exceed 20-25 mmHg which may cause pulmonary congestion and dyspnea. There is also a passive increase in pulmonary venous pressure which is associated with post-capillary pulmonary hypertension. Chronic increase in pulmonary venous pressure frequently causes mixed pulmonary hypertension. Because of pulmonary hypertension, right heart failure ensues with its signs and symptoms such as peripheral edema, hepatomegaly and even secondary tricuspid regurgitation. If there is also marked restriction of ventricular filling, stroke volume and cardiac output is decreased without any change in contractile function and ejection fraction. Thus, in advanced diastolic heart failure, the hemodynamic profile may be similar to those of severe systolic heart failure. The structural and functional changes in diastolic heart failure are summarized in Table 1.

DOES THE LEFT VENTRICLE DILATE IN DIASTOLIC HEART FAILURE?

There are controversies about changes in LV function and morphology in diastolic heart failure.[3-6] Some authorities have hypothesized that the left ventricle can dilate significantly along with reduced ejection fraction. However, recent studies have demonstrated that during an average of 64 months of follow-up, in patients with diastolic heart failure without coronary artery disease, LV volumes and ejection fraction remain unchanged. The LV end-diastolic pressures and stiffness increase, suggesting that LV diastolic function worsens in these patients.

TABLE 1. The structural and functional changes in diastolic heart failure.

Parameters	Diastolic heart failure
LV end-diastolic volume	Normal or decreased
LV end-systolic volume	Normal or decreased
Ejection fraction	Normal
LV mass	Increased
LV wall thickness	Increased
LV end-systolic stress	Normal
LV end-diastolic stress	Increased
Mechanical dyssynchrony	May be present
LV shape and geometry	Usually unchanged
Myocyte hypertrophy	Present
Myocardial fibrosis	Present
Calcium regulation	Abnormal
MMPs/TIMPs	Decreased
Collagen cross links	Increased
Titin isoforms N2BA/N2B	Decreased

LV = left ventricular; MMPs = matrix metalo-proteinases; TIMPs = tissue inhibitors of metalo-proteinases

THERAPEUTIC OPTIONS

Unlike systolic heart failure, there has been very little progress in the management of diastolic heart failure.[1,3,9] For the relief of congestive symptoms, diuretics and nitrates are necessary. However, excessive diuretic or nitrate therapy may be associated with inappropriate reduction of preload and cardiac output and hypotension.

To maintain appropriate time for ventricular filling, the heart rate needs to be controlled either pharmacologically or by pacemaker therapy. It is desirable to maintain sinus rhythm in diastolic heart failure to maintain adequate stroke volume and cardiac output.

To decrease mortality or morbidity, very few pharmacologic events have been evaluated. The "CHARM Preserved"[9] trial has reported that the angiotensin receptor blocking agent candesartan may decrease hospital admission rates. It should be emphasized that non-pharmacologic therapy, such as chronic resynchronization with or without defibrillator therapy, has not been shown to provide any benefit.[10]

It is apparent that further research and investigations are required to determine potential beneficial therapies for treatment of diastolic heart failure. There is, however, extensive research being undertaken to discover potential new and effective therapeutic agents for treatment of diastolic heart failure (Table 2).

TABLE 2. Potential new therapies for diastolic heart failure.

To decrease myocardial fibrosis
Aldosterone antagonists
Angiotensin inhibition
Chymase antagonists
TGF –beta
To improve relaxation
Phospholamban inhibitors
D- ribose
Modulation of collagen cross-links
Modulation of Titin isoforms
Modulation of MMPs/TIMPs

MMPs = metalo-proteinases; TIMPs = tissue inhibitors of metalo-proteinases; TGF = transforming growth factor

CONCLUSIONS

The pathophysiology, remodeling and functional changes in diastolic heart failure are characterized by the lack of ventricular dilatation, normal ejection fraction and increased fibrosis and left ventricular stiffness. The hemodynamic profile is similar to that of systolic heart failure. The therapeutic modalities available are limited. Further and continued research is necessary to discover new and effective treatment of this syndrome, which is associated with poor prognosis particularly in advanced diastolic heart failure.

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