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### Diastolic Dysfunction and Diastolic Heart Failure: Part Two – Clinical Applications



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In part one of this article, we presented the pathophysiology associated with diastolic dysfunction and diastolic heart failure and touched on the paucity of related research. In this follow-up article, we look at some of the clinical studies and what they have revealed, and discuss treatment options for diastolic heart failure.

#### Clinical Studies in Patients with Diastolic Dysfunction

Patients with conditions such as left ventricular hypertrophy have elevated left ventricular end diastolic pressure and decreased compliance, which affects the length-tension relationship by decreasing muscle fibre stretch at any given peak systolic stress. This might explain why decreased exercise tolerance is one of the first clinical symptoms associated with echocardiographically-diagnosed diastolic dysfunction.

Exercise tolerance may be compromised in patients with left ventricular diastolic dysfunction that are asymptomatic at rest, secondary to the inability to enhance diastolic filling by the degree necessary to increase cardiac output during exercise without causing an abnormal elevation in left atrial pressure. Diastolic dysfunction has been found to be aggravated by exercise, especially with an increase in blood pressure. Recent studies have observed the development of left ventricular diastolic dysfunction in the presence of hypertension prior to the development of ventricular hypertrophy. Left ventricular diastolic dysfunction can therefore represent myocardial end-organ damage prior to progression to clinically relevant heart failure, although further trials are needed to support this hypothesis.

#### Prevalence of Left Ventricular Diastolic Dysfunction Unclear

The magnitude of asymptomatic left ventricular diastolic dysfunction in the general population is still unclear. In an attempt to determine the prevalence of preclinical diastolic dysfunction, Redfield et al. Performed a cross-sectional survey of 2,042 randomly selected residents over the age of 45 years in Olmsted County, Minnesota, U.S. The authors found the prevalence of asymptomatic, echocardiographically-diagnosed

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diastolic dysfunction to be 28 percent with an increased prevalence seen in the elderly, diabetics, and in patients with cardiovascular disease such as hypertension, coronary artery disease or cardiomyopathies.

A prospective trial in 206 patients with the clinical diagnosis of heart failure (New York Heart Association Grade II or higher) reported that – based on echocardiographic parameters – 91 percent of 102 patients with an EF greater than 50 percent had some degree of diastolic dysfunction, and 92 percent of 71 patients with an EF of less than 40 percent suffered from left ventricular diastolic dysfunction. Patients with reduced ejection fraction were more likely to have moderate to severe diastolic dysfunction in comparison to patients with preserved ejection fraction (27 vs. 62 percent, respectively). In patients with heart failure with preserved EF, left ventricular diastolic dysfunction was accompanied by left ventricular hypertrophy, while in patients with heart failure and reduced EF, left ventricular diastolic dysfunction was associated with left ventricular dilation and marked systolic dysfunction. The overall prognosis and mortality appears to be significantly influenced by the degree of left ventricular diastolic dysfunction in heart failure patients, regardless of ejection fraction.

#### **Clinical Studies in Patients with Diastolic Heart Failure**

An American College of Cardiology and American Heart Association (ACC/AHA) task force stated that a definitive diagnosis can be made in heart failure patients with preserved EF if there is a decreased rate of ventricular relaxation with elevated LV filling pressure, clarifying the need for coexistence of normal contractility (LV systolic function) and LV volume. In further assessing such assumptions, Zile et al. Compared 75 patients with heart failure and normal ejection fraction with 75 patients without cardiovascular disease, as controls. After analysing both echocardiographic parameters and data derived from cardiac catheterisation, it appeared that left ventricular systolic function, contractility and performance was intact in patients with presumed diastolic heart failure (with normal ejection fraction, 32). In a review of data on left ventricular structure and function in heart failure patients with normal ejection fraction and hypertension, Zile and Lewinter have argued that left ventricular end-diastolic volume is within normal range in patients with diastolic heart failure.

#### **Progression of Diastolic Heart Failure**

In 2001, Aurigemma et al. published the possible rate of progression from asymptomatic diastolic dysfunction to clinical heart failure. The study analysed 2,671 individuals without coronary heart disease, congestive heart failure, or atrial fibrillation. At baseline, 15 percent of the patients had diastolic dysfunction by echocardiography, with 170 participants eventually developing heart failure after a five-year follow up period (6.4 percent), concluding that echocardiographic findings can be suggestive of the development of heart failure.

Despite arguments regarding exercise limitations and left ventricular diastolic dysfunction representing a possible early marker of myocardial damage, the rate of progression from diastolic dysfunction to diastolic heart failure remains uncertain. Currently there are no large clinical trials assessing the possible progression from asymptomatic right ventricular diastolic dysfunction to clinical right ventricular failure.

#### **Therapy and Guidelines for the Management of Diastolic Heart Failure**

The difficulties in the diagnosis of diastolic heart failure have been partly responsible for the limited number of larger randomised controlled trials to guide treatment. In 1998, the European Study Group published one of the first widely analysed guidelines for diagnosis of diastolic heart failure, stating the need for evidence of heart failure with normal systolic function ( $LVEF \geq 0.50$ ) as well as evidence of abnormal filling, diastolic distensibility, LV relaxation or diastolic stiffness. The European Society of Cardiology (ESC) recently published their latest guidelines for diagnosis of diastolic heart failure in 2007; providing specific guidelines on “How to diagnose heart failure with normal ejection fraction” and “How to exclude heart failure with normal ejection fraction”. The guidelines have three major criteria for diagnosing heart failure with normal ejection fraction:

- 1) Signs/symptoms of heart failure;
- 2) Normal or mildly reduced systolic function ( $EF > 50\%$  with a left ventricular end-diastolic volume index less than  $97\text{ml/m}^2$ ), and
- 3) Evidence of left ventricular diastolic dysfunction.

The diagnostic strategy provided in this set of guidelines allows for non-invasive methods of assessing for left ventricular diastolic through tissue Doppler parameters (early mitral valve flow velocity to early tissue Doppler lengthening velocity ( $E/E'$ )  $>15$ ) and routine blood tests for biomarkers (brain natriuretic peptide  $>200\text{ pg/mL}$ ) to play a role in situations when invasive haemodynamic measurements (LV end-diastolic pressure  $>16\text{mmHg}$  or mean pulmonary capillary wedge pressure  $>12\text{mmHg}$ ) are not available.

#### **Current Treatment of Diastolic Heart Failure**

Current treatment of diastolic heart failure has been aimed at controlling blood pressure and tachycardia, using diuretics to control pulmonary congestion and peripheral oedema, and alleviation of myocardial ischaemia. The ACC/AHA also recommend using beta-adrenergic blocking agents, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, calcium antagonists in those patients with controlled blood pressure, and digitalis in order to control heart failure symptoms. In the latest update of the ACC/AHA practice guidelines for the diagnosis and management of chronic heart failure in the adult that comprises a document of 63 pages, the treatment of diastolic heart failure is summarised in less than one page.

Chinnaiyan et al. described the combined use of beta-blockers, angiotensinconverting enzyme inhibitors, angiotensin II receptor blockers,

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calcium channel blockers, and spironolactone as potential disease modifying therapy. The authors believe that the effects of these drugs improve diastolic dysfunction and diastolic heart failure by regression of left ventricular hypertrophy and decreased collagen content. They recommend these drugs to be utilised in both in decompensated diastolic heart failure and for chronic outpatient management of diastolic heart failure. In the recently published Hong Kong diastolic heart failure study 150 patients with heart failure and preserved ejection fraction were randomised to diuretics, ACE inhibitors or angiotensin II receptor blocker therapy. Only diuretic therapy reduced symptoms and improved quality of life during a one-year follow up.

Currently there are no large randomised clinical trials that have assessed the possible benefit of pharmacotherapy at different stages of noninvasively diagnosed diastolic dysfunction. Small trials have been carried out in an attempt to evaluate possible benefits of pharmacotherapy for patients with left ventricular diastolic dysfunction and decreased exercise tolerance. Warner et al. studied twenty patients with mild diastolic dysfunction diagnosed by Doppler echocardiography with a marked hypertensive response to exercise. The authors reported that using the angiotensin II receptor blocker losartan, resting blood pressure was unchanged but the hypertensive response to exercise was reduced.

Similar studies confirmed the benefits of angiotensin II receptor blockers on exercise tolerance by comparing its effects with calcium channel blockers (verapamil) or diuretics (hydrochlorothiazide). In two separate trials, Little et al. demonstrated that angiotensin II receptor blockers, calcium channel blockers, and diuretics all have the ability to blunt an increase in SBP during exercise in patients with asymptomatic left ventricular diastolic dysfunction, but only angiotensin II receptor blocker therapy increased exercise duration and improved quality of life, as assessed by questionnaires.

## Conclusions

Further research is needed to improve current knowledge of diastolic dysfunction and diastolic heart failure. Due to a lack of larger randomised trials, the management of diastolic heart failure is currently aimed at symptomatic management and control of physiologic factors known to affect ventricular relaxation. A timeline for initiation of treatment for diastolic dysfunction has yet to be defined. It is anticipated but not proven whether early initiation of pharmacotherapy will prevent or delay the onset of symptomatic heart failure once diastolic dysfunction has been diagnosed, even in the absence of symptoms.

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