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Treatment of Heart Failure in Patients with Diabetes Mellitus

Steven J. Lavine and *Steven D. Gellman*

Harper Hospital, Wayne State University, Detroit, Michigan, USA

Contents

Abstract

Patients with diabetes mellitus have an increased morbidity and mortality from cardiovascular disease. Both coronary artery disease and congestive heart failure (CHF) are largely responsible for the increased cardiovascular adverse events in patients with diabetes.

This review discusses the pathophysiology of CHF, the mechanisms of left

ventricular (LV) dysfunction and the neurohormonal mechanisms involved in both LV dysfunction and CHF. Diabetes with and without hypertension is an important cause of LV dysfunction and CHF. Diabetes may be responsible for the metabolic and ultrastructural causes of LV dysfunction, while hypertension may be responsible for the marked fibrotic changes that are found. Experimental induction of diabetes in animals has shed light on the biochemical and ultrastructural changes seen. The role of insulin to reverse both metabolic and structural changes is reviewed both from experimental data and with the limited amount of clinical data available.

The therapy of CHF in patients with diabetes is similar to that of patients without diabetes, with therapy directed toward the use of β-blockers and angiotensin converting enzyme (ACE) inhibitors. As the morbidity and mortality are higher in patients with diabetes, several studies have pointed out the importance of this subgroup where the opportunity to make a significant clinical impact exists. A significant opportunity exists to reduce morbidity and mortality with β-blockers and ACE inhibitors when ischaemia and CHF are both present. However, studies in patients diabetes have been limited to post hoc subgroup analyses and rarely as predefined subgroups. Clinical trials involving patients with diabetes with and without hypertension and LV dysfunction are clearly needed in the future to adequately address the needs of this high risk subgroup.

Patients with diabetes mellitus have an increased morbidity and mortality from cardiovascular disease, especially women who have a risk that is twice as great as men.[1-4] Specifically, after myocardial infarction (MI) there is greater left ventricular (LV) dysfunction despite similar infarct size but infarcts also tend to be larger. The incidence of overt congestive heart failure (CHF) in patients with similar sized infarcts is greater for patients with diabetes than for those without.[5-8] Consequently, in patients with diabetes (a subset with a higher risk) therapy with angiotensin converting enzyme (ACE) inhibitors offers the opportunity to increase the myocardial salvage rate and reduce morbidity after infarction.

In the presence of hypertension and diabetes, the incidence of LV dysfunction is substantially increased, as is chronic renal insufficiency, which further increases the morbidity and mortality.[9] As hypertension and diabetes are important risk factors for coronary and vascular disease, patients with diabetes often have concomitant coronary disease, previous MIs and pre-existing LV dysfunction. In addition, there exists an independent LV dysfunction termed diabetic cardiomyopathy that may lead to overt CHF.[10-12] Consequently, in the presence of comorbid conditions such as coronary disease or valvular disease, diabetes may also adversely affect the performance of the left ventricle and contribute to the development of CHF.[1-4] The high incidence of hypertension in patients with diabetes may place them at greater risk for coronary events and CHF[13] as the incidence and amount of LV hypertrophy is greater in patients with diabetes than in patients with hypertension alone. Furthermore, there may be a predilection for increased severity of CHF in women with hypertension and diabetes,[14] especially in patients who are glucose-intolerant.[15] Experimentally, in models of combined hypertension and diabetes, there is evidence of marked fibrosis, interstitial glycoprotein deposition and capillary microaneurysms which have similarities to human disease.[11,12,16] The combination of diabetes and hypertension may have devastating effects on the myocardium with hypertension being responsible for myocardial damage and diabetes responsible for myocardial cell dysfunction.[17-19]

1. Pathophysiology of Congestive Heart Failure (CHF)

1.1 Definition and Terms

CHF has been variably defined in a multitude of reviews. A simple definition proposed in the 1960s was the heart's inability to pump sufficient cardiac output to meet the body's metabolic demands. The compensatory mechanisms called into action to the meet the body's metabolic needs lead to the symptoms, signs and ultimate poor prognosis of patients with CHF. CHF has also been classified into right- or left-sided CHF, and systolic or diastolic heart failure. The term 'circulatory congestion' has been applied to the clinical circumstance where cardiac output may be adequate and there is fluid overload with pulmonary congestion and/or oedema. The aetiologies of CHF are listed in table I.

Table I. Aetiologies of heart failure

Myocardial failure
Ischaemic heart disease
Infiltrative diseases (amyloidosis, haemochromatosis)
Inflammatory (myocarditis)
Toxic (chemotherapy)
Cardiomyopathy
Valvular
Aortic stenosis or regurgitation
Mitral regurgitation
Mitral stenosis (pulmonary congestion and right heart failure)
Congenital
Pressure overload resulting in right or left ventricular dysfunction
valvular stenosis
conduit stenosis
Volume overload resulting in left or right ventricular dysfunction
valvular regurgitation
left to right shunts with left or right atrial and left ventricular volume overload
patent ductus arteriosus
ventricular septal defect
atrial septal defect
single ventricle, tricuspid atresia
Rhythm disorders
Rapid ventricular response to atrial fibrillation or flutter
Atrioventricular block with slow ventricular escape
Pacemaker (VVI)
Slow and persistent ventricular tachycardia
Pericardial
Constrictive pericarditis

Although CHF can be conveniently divided into left- and right-sided failure, these manifestations of CHF are parallel events more often than serial events. Traditional teaching has concentrated on symptoms of left-sided heart failure preceding manifestation of right-sided failure as two discrete events in the natural history of CHF. Symptoms of left-sided failure may coexist early on with manifestations of right-sided failure. Traditionally, a haemodymamic explanation is offered in that left-sided failure leads to pulmonary congestion with elevated pulmonary artery pressure and subsequent right-sided heart failure. However, neurohormonal adaptations are called into play leading to salt and fluid retention, circulatory congestion and leg oedema: a manifestation of right-sided heart failure. The situation is complicated by coexistent right ventricular dysfunction in dilated cardiomyopathy. The end result is that there is a blend of both right- and left-sided manifestations of CHF in any given patient, and these manifestations depend on the aetiology, the degree of neurohormonal stimulation and right ventricular performance.

More recently, the terms systolic and diastolic heart failure have been used. Systolic failure refers to significant left or right ventricular dysfunction associated with symptoms and signs of left- or right-sided failure or both. Diastolic dysfunction has applied to the situation where patients have no evidence of significant LV systolic dysfunction but have signs of pulmonary congestion with or without right-sided manifestations. Impedance to LV filling caused by prolonged relaxation and increased myocardial stiffness occurs in the setting of coronary artery disease, hypertension, diabetes and restrictive cardiomyopathy, and is the purported cause of pure diastolic dysfunction. A marker for abnormal relaxation may be the transmitral Doppler flow pattern (figure 1) of E to A reversal. Diastolic dysfunction coexists with systolic dysfunction, and is manifested by an abnormal pattern of diastolic filling with increased rate

and extent of rapid filling, decreased atrial filling and an increased rate of rapid filling decline. This pattern may appear normal (pseudonormalised) or have the appearance of reduced atrial filling (termed restrictive filling) with both representing milder and more significant degrees of elevated LV filling pressures.[20]

Circulatory congestion has been seen in the setting of hyperthyroidism, severe anaemia and fluid overload (dialysis, postoperative fluid replacement). There is the implication that LV systolic function is not significantly impaired, although cardiac output may not be sufficiently high to meet the body's metabolic demands. Fluid overload as a cause of circulatory congestion occurs often in the setting where the ability to excrete the excess volume is impaired. Over-vigorous fluid replacement postoperatively or missed dialysis are prime examples.

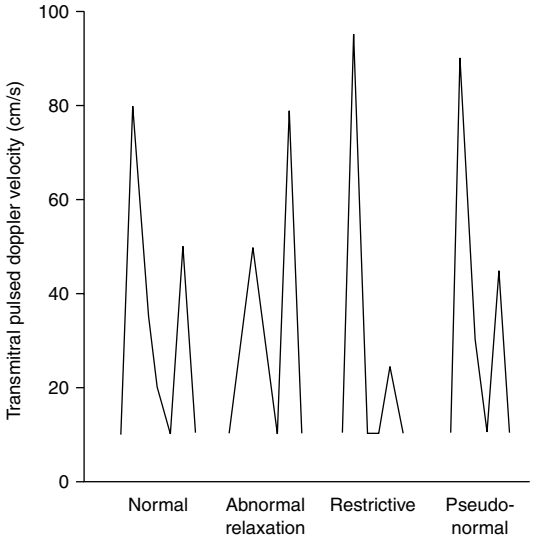

Fig. 1. Normal and abnormal diastolic filling curves obtained from transmitral pulsed Doppler are demonstrated. Abnormal filling curves may be an expression of abnormal relaxation (E to A reversal), an expression of abnormal chamber compliance (restrictive filling pattern), or combinations of both (pseudonormal filling pattern). Both the restrictive filling pattern and pseudonormal filling pattern are associated with increased left ventricular filling pressures.

1.2 Mechanisms of Left Ventricular (LV) Dysfunction

Table II lists the mechanisms associated with LV dysfunction. These mechanisms have been investigated both in experimental diabetic and non-diabetic animals as noted in table II. Cellular adaptations include alterations in myocardial blood flow that may be matched to myocardial oxygen consumption. In the hypertrophied failing myocardium, there are increased intercapillary distances, raising the question of ischaemia. This may be of even greater importance in the scarred ventricle in patients with coronary disease and/or diabetes. Mitochondrial function may be normal or impaired depending on the experimental model used and the stage of CHF in the model. Adenosine triphosphate (ATP) content, production and turnover may be normal or variably decreased in patients with CHF. Alteration of contractile proteins with reduced ATPase activity has been seen in the rat, as a result of a change in the myosin isoform which is induced by diabetes. Similar changes have not been noted in the human heart.

In patients with increasing LV dysfunction and CHF there is stimulation of the sympathetic nervous system and elevation of catecholamine levels leading to alterations in adrenergic modulation of myocardial function. Consequently, there is desensitisation to adrenergic drive and a resultant down regulation of the myocardial β_1-adrenergic receptor. Furthermore, there is a preponderance of inhibitory G proteins in the failing heart reducing cyclic adenosine monophosphate (cAMP) generation from adrenergic receptor stimulation.[20,21] In addition, altered myofibrillar calcium responsiveness may be responsible for altered contraction coupled with inadequate calcium removal. Reduced calcium uptake by the sarcoplasmic reticulum may lead to reduced calcium release.[22,23]

Alterations in LV chamber and myocardial function have been well studied, especially with regard to volume or pressure overload stress. Examination of a family of Frank Starling curves (figure 2) demonstrates that with reduced LV contractility and compensatory LV dilatation, systolic wall

Table II. Mechanisms associated with left ventricular dysfunction

Cellular and Molecular
Nutritive blood flow[a]
Mitochondrial function[a,b]
Energy reserve[a,b,c]
Myofibrils[a,c]
Adrenergic receptors[a,b,c]
G Proteins[a,b,c]
Calcium[a,b,c]
Remodelling[a,b]
Neurohormonal[a,b]
Heightened sympathetic nervous activity
Renin angiotensin system and aldosterone
Vasodilatory, natiuretic, antimitogenic peptides
atrial and brain natiuretic factors
nitric oxide
Vasoconstrictive, antinatiuretic, mitogenic peptides
angiotensin II
endothelin
cytokines (tumour necrosis factor)
Other - arginine vasopressin, adrenomedullin, growth hormone
Abnormal reflex control[a,b]
Disturbances in sodium and water balance[a,b]

a Animal data, nondiabetes.
b Human data, nondiabetes.
c Animal data, diabetes.

stress increases, which serves as a positive feedback loop leading to a further decline in LV systolic performance. Over time, a process of chamber remodelling occurs with resultant chamber dilatation, hypertrophy, increased collagen, and interstitial and myocardial fibrous deposition. Myocardial cell slippage, myocyte necrosis, myocyte apoptosis (programmed cell death) and other ultrastructural changes occur associated with remodelling.

Neurohormonal changes with progressive LV dysfunction are both a marker and a contributor to the LV dysfunction and CHF process. Peripheral noradrenaline (norepinephrine) levels in patients with CHF are elevated and the level of elevation correlate with survival.[24] Catecholamines support the circulation during acute CHF by increasing heart rate, blood pressure, and both arterial and venous tone. These processes may become deleterious if chronic as they increase myocardial oxygen demand, result in myocyte necrosis, produce arrhythmias and increase mortality. The renin angiotensin system is also activated early in the course of progressive LV dysfunction. Elevated angiotensin levels lead to myocardial hypertrophy, interstitial fibrosis, LV dilatation, increased arterial resistance and are a major contributor to progressive LV dysfunction after MI.[25-28] Because of elevation of angiotensin, aldosterone is also elevated, which contributes to interstitial fibrosis, and potassium excretion and depletion. Other peptides (table II) are activated during progressive LV dysfunction and can be categorised as vasodilatory, natiuretic and antimitogenic, or vasoconstrictor, antinatiuretic and mitogenic.[29-37]

With chronic CHF, there is abnormal reflex control of the circulation. Blunting of cardiac and arterial baroreceptor responsiveness and its inhibition results in increased sympathetic output and increased angiotensin levels.[38] Abnormalities in atrial stretch receptors and abnormalities in neurotransmitter synthesis, storage and release are also present. Sodium and fluid retention in patients with

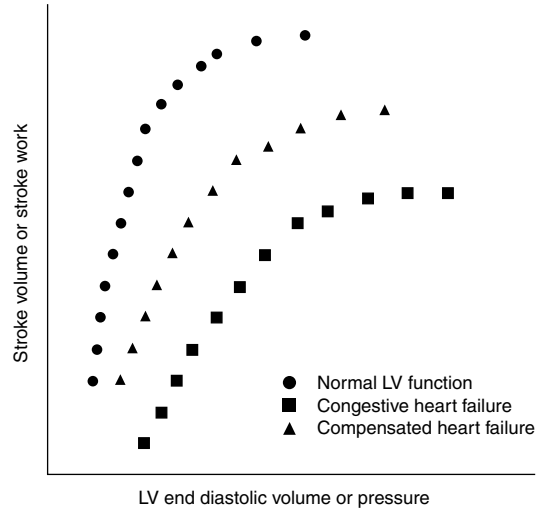

Fig. 2. A family of Frank Starling curves are depicted. The y axis can be represented by stroke volume, stroke work, or other ventricular output variables. The x axis can be represented by end diastolic fibre length, end diastolic volume or pressure, or other input variables.

CHF is well known, and therapeutic efforts are aimed at maintaining fluid balance. Reductions in glomerular filtration and renal blood flow result in vasoconstriction and sodium retention.[39] Compensatory mechanisms to maintain the glomerular filtration rate include angiotensin II and aldosterone production resulting in vasoconstriction and sodium retention. Long-term, renal blood flow will remain depressed and with marked neurohormonal stimulation will lead to more water retention as a result of arginine vasopressin excretion.[29] The release of these vasoconstrictor peptides results in some production of the vasodilatory peptides but the vasoconstrictor influences overwhelm the vasodilatory factors.

1.3 Precipitants of CHF

Table 3 outlines common precipitants of CHF and causes of acute decompensation in patients with pre-existing chronic CHF. An often overlooked cause of decompensation is noncompliance with a prescribed medical regimen. These include salt restriction, medication use and use of alcohol and drugs (e.g. cocaine) that depress LV systolic function. Inappropriate medications that promote fluid retention (e.g. nonsteroidal anti-inflammatory agents) or with overt negative inotropic properties (e.g. profanenone, calcium channel antagonists) are important precipitants. Efforts should be made to exclude systemic diseases including anaemia, thyroid disease and infection. In patients with diabetes, declining renal function may lead to fluid retention and pulmonary congestion. Silent myocardial ischaemic events and rapid atrial fibrillation may be important precipitants in the patient with diabetes. Haemodynamic factors including excessive tachycardia, bradycardia and severe hypertension should be sought.

Table III. Precipitants of congestive heart failure

Pharmacological
Negative inotropic agents
antiarrthymics
calcium channel antagonists
β-blockers
Sodium retaining drugs
Systemic diseases
Anaemia
Thyroid disease
Systemic infection
Ischaemia
Nephropathy
Hemodynamic stresses
Tachycardia; (e.g. atrial fibrillation)
Bradycardia
Hypertension
Patient noncompliance
Medication
Salt restriction
Alcohol or other toxin use

2. Diagnosis and Evaluation of Patients with CHF

The presenting history, physical examination and diagnostic testing in patients with symptoms and signs suggesting heart failure are similar in both patients with and those without diabetes.

2.1 History

Left-sided symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and nocturia. Right-sided symptoms include leg oedema, fatigue, and abdominal pain and bloating. Each of these symptoms are not specific for CHF and can be found in other disease states that can complicate the diagnosis and care of patients by being important comorbid conditions. The extent of each of these symptoms may depend on whether right- or left-sided CHF is predominant. Symptoms of fatigue are common and may be caused by low output, but can also be caused by fluid and electrolyte disturbances from diuretic therapy. Most symptoms are related to low cardiac output, and pulmonary or systemic venous congestion.

2.2 Physical Examination

Findings can be categorised into left-sided findings [presence of an S3, displaced point of maximal impulse (PMI), mitral regurgitant murmur and pulmonary crackles on auscultation, or peripheral hypoperfusion] or right-sided findings (elevated

jugular venous pressure, tricuspid regurgitant murmur, hepatomegaly, ascites or oedema). Some physical findings may be related to the underlying aetiology of CHF. The vital signs may provide information in that the heart rate may be excessively fast with decompensation or slow because of atrioventricular block or another cause. Blood pressure may be excessively elevated with uncontrolled hypertension or low with overdiuresis or excessive use of vasodilators. However, oedema can be secondary to venous insufficiency, liver failure and nephrotic syndrome (in diabetes) related to albuminuria in the nephrotic range.

2.3 Diagnostic Testing

Laboratory testing should include complete blood count, serum electrolytes and magnesium, assessment of renal and hepatic function and, if indicated, thyroid testing. Assessment of risk factors for coronary artery disease, including lipids and glycaemic control in patients with diabetes should also be performed. A chest radiograph should be reviewed for cardiac silhouette size, assessment of pulmonary vasculature and for pleural effusions or other lung disease. An electrocardiogram should be performed assessing LV hypertrophy, infarction, myocardial ischaemia, conduction system disease and arrythymias. Assessment of LV systolic and diastolic function and valvular or pericardial disease can be evaluated by two-dimensional echocardiography and Doppler or radioventriculography (to assess LV function).

Table IV outlines the causes of LV dysfunction. Ischaemic disease is the predominant cause (>50%) with idiopathic dilated cardiomyopathy being the cause in an additional 15 to 20% of patients. It is important to remember that systolic measurements of LV function may only loosely correlate with symptoms of dyspnea or exercise tolerance. A full one-third of patients with CHF have normal systolic function[40] and are assumed to have diastolic dysfunction with slowed relaxation. The actual mechanisms involved have been poorly elucidated. More severe diastolic dysfunction, consisting of the pseudonormal and restrictive filling pattern, may be associated with systolic dysfunction and has been correlated with elevated LV filling pressures, low output and a poor prognostic finding.[20] Cardiac catheterisation may need to be performed to assess valvular or ischaemic disease with an view to correction. Critical aortic stenosis, severe mitral stenosis and ischaemic LV dysfunction are important reversible causes of CHF, which can be identified and eliminated.

Individual clinical criteria alone may not be sufficient to make the diagnosis of CHF. Framingham, Boston and Duke criteria[41,42] have been developed which combine history, physical examination and chest radiography into an index to make the diagnosis of CHF.

3. Cardiomyopathy and CHF in Patients with Diabetes

Cardiomyopathy has been classified by the World Health Organization as dilated, hypertrophied, restrictive (amyloid), arrhythmogenic right ventricular dysplasia, and unclassified. Dilated cardiomyopathy has multiple aetiologies but these aetiologies can be conveniently categorised into ischaemic and nonischaemic. Dilated cardiomyopathy is associated with left and/or right ventricular dilatation, elevated LV filling pressures and systolic dysfunction. Diastolic abnormalities (figure 1) are common and can run the gamut from abnormalities of relaxation to abnormalities of chamber compliance with variable diastolic filling patterns

Table IV. Aetiologies of left ventricular dysfunction and heart failure

Ischaemic
Valvular
Hypertension
Myocarditis
Viral
Nonviral
HIV
Tachycardia
Alcohol
Diabetes mellitus
Metabolic
Amyloidosis and other infiltrative diseases

(abnormal relaxation, pseudonormal or restrictive).

Cardiomyopathy in patients with diabetes can present in a variable fashion. As hypertension often coexists with diabetes, presentations may have elements of dilated, hypertrophied or even restrictive types of cardiomyopathy depending on the extent of LV hypertrophy, fibrosis, dilatation and systolic dysfunction. Unusual causes of CHF associated with diabetes include acromegaly and haemochromatosis (cardiomyopathy).

3.1 Diabetes, Hypertension and Cardiovascular Morbidity and Mortality

The combination of hypertension and diabetes clinically presents additive risks to patients. The incidence of CHF is substantial in patients over the age of 65 years, being at least 40%. As hypertension and MI are important additional causes of CHF in patients with diabetes, the value of calcium channel antagonists and ACE inhibitors has been studied in four trials. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial[43] demonstrated fewer moderate or severe events with ACE inhibitors compared with calcium channel antagonists. The importance of addressing blood pressure lowering in patients with diabetes is well illustrated in the Systolic Hypertension in Europe (SYSEUR) study[44,45] where patients with diabetes demonstrated a 55% and 73% reduction in mortality and total events (including MI and CHF) compared with 26% and 38% in patients without diabetes. Similarly, in the Hypertension Optimal Treatment (HOT) study,[46] blood pressure lowering demonstrated reduced mortality in a subgroup of patients with diabetes. In the UK Prospective Diabetes Study (UKPDS),[47] more intensive blood pressure lowering resulted in fewer morbid events (24%) and lower mortality (32%).

3.2 Independent LV Dysfunction in Patients with Diabetes

Clinically, independent LV dysfunction associated with diabetes has been termed 'diabetic cardiomyopathy'. Clinical and subclinical evidence of LV systolic and diastolic dysfunction have been noted in patients with type 1 (insulin-dependent) diabetes mellitus and to a lesser extent in type 2 (noninsulin-dependent) diabetes mellitus, as characterised by a subnormal ejection fraction[48] and stroke volume,[49] responses to exercise, abnormal systolic time intervals[50,51] and resting ejection fractions, and abnormal diastolic function as characterised by an abnormal relaxation filling pattern.[52-55] Diastolic dysfunction (abnormal relaxation) is more common and occurs earlier than systolic dysfunction.[56] Exercise-induced LV dysfunction early in the course of diabetes may be as a result of the defective and blunted recruitment of the SNS and impaired sympathetic nervous system stimulation. This has been demonstrated by PET (positron emission tomography) scanning with reduced MIBG (I-meta-iodobenylguanidine) uptake.

Diabetes has also been implicated in the development of significant clinical LV dysfunction in the absence of coexisting disease processes that may result in LV dysfunction. Evidence of myocardial hypertrophy, focal areas of fibrosis, capillary microaneurysms and deposition of interstitial glycoprotein have been reported in patients with diabetes and CHF without coexisting hypertension or coronary artery disease.[10,57]

Evidence of systolic or diastolic dysfunction appears to be related to the duration of diabetes,[54] the presence of microvascular disease,[53-55] and autonomic dysfunction.[58] In children with diabetes for an average duration of 5.9 years, prolongation of LV relaxation was associated with a longer disease duration and poor control of diabetes.[59] Conversely, in a study of patients with type 1 and type 2 diabetes, there was an inverse relationship between late diastolic filling and glycolated haemoglobin, and a direct relation between glycolated haemoglobin, age and early diastolic filling. However, early diastolic filling was depressed in patients with type 2 diabetes. Many patients in this study had autonomic neuropathy.[60] The influence of autonomic neuropathy was addressed in a study of 36 patients (24 with type 1 diabetes) of which 12 had neuropathy, 12 did not and 12 were aged-

matched controls. The patients with autonomic neuropathy had reduced exercise tolerance and reduced early diastolic filling.[61] Mechanisms experimentally that have been cited to be responsible for the abnormal systolic and diastolic function include abnormalities of glucose and fatty acid transport, intracellular calcium overload, coronary microangiopathy, interstitial and perivascular fibrosis, and autonomic neuropathy. In addition, endothelial dysfunction, advanced end-stage glycation products, decreased nitric oxide, reduced autoregulation and diffuse atherosclerosis all lead to reduced myocardial contraction efficiency.

3.3 Experimental Evidence of Diabetes-Induced LV Dysfunction

Experimental diabetes mellitus has been induced by sequential injections of alloxan or streptozotocin into dogs, rats, rabbits and pigs.

Regan[62,63] evaluated LV functional responses to afterload (angiotensin infusion) and preload (volume) challenges in dogs 9 to 11 months after diabetes was induced. These diabetic dogs demonstrated a marked increase in LV end diastolic pressure for small volume or systolic pressure increments suggesting abnormal LV chamber stiffness despite normal systolic function. These functional responses were associated with an altered composition of the myocardium consisting of increased triglycerides, cholesterol and interstitial glycoprotein [periodic acid-Schiff (PAS)+].

Data from streptozotocin-induced diabetes mellitus in rats demonstrated abnormal relaxation, stiffness and abnormal systolic function in the papillary muscles of diabetic rats.[64-67] These functional alterations were associated with a predominance of the myosin subtype V3 which has reduced calcium ATPase activity,[66-68] reduced calcium uptake by the sarcoplasmic reticulum (ATPase-dependent) and increased calcium content of the cytoplasm.

Experimental diabetes has also been produced in pigs where decreased catecholamine responsiveness has been noted. β-receptor density was normal but receptor-dependent and G protein-dependent stimulation of adenyl cyclase was reduced.[69] Diabetic (rat) hearts have a decreased ability to regulate ATP synthesis, which was associated with decreased relaxation.[70]

3.4 The Issue of Calcium Overload

These functional alterations in the rat were associated with alterations in intracellular calcium homeostasis. In addition, the sarcolemmal and the sarcoplasmic reticular calcium transporters have been found to be depressed.[71] Consequently, cytoplasmic calcium content may be increased and the calcium outward current altered resulting in prolonged action potential duration and increased myocardial stiffness.[72] However, work in isolated diabetic myocytes have noted that resting intracellular calcium may not be increased. Although responses to isoproterenol were abnormal in resting and electrically-stimulated diabetic myocytes, direct calcium activators produced a normal twitch response.[73,74] Although there may be some controversy as to whether intracellular calcium was increased, there was a reduction in calcium sensitivity as a result of shifts in myosin light chains and troponin I sensitivity.[71]

The importance of calcium overload as a cause of cardiac muscle dysfunction has been evaluated in diabetic (rat) hearts without addressing insulin deficiency and hyperglycaemia. Inhibition of aldose reductase, which blocks the over-utilised polyol pathway, improved relaxation rates in diabetic papillary muscles. The mechanisms of action may be related to improvement in defective calcium handling by the sarcoplasmic reticulum[67] and a reduction in protease (which damage myocardial cells) release. Hyperglycaemic diabetic rats treated with verapamil demonstrated improved indices of LV contraction and relaxation, increased myosin ATPase levels and reduced ultrastructural distortion compared with untreated diabetic rats.[75]

Microvascular spasm has been suspected as an aetiological factor in the interstitial, arteriolar and capillary alterations seen in diabetes and in cardiomyopathy.[11,12,76,77] Verapamil has been demonstrated to slow the rate of cardiomyopathy and

myocytolysis in the Syrian hamster, presumably by reducing microvascular spasm.[76] The hypertensive diabetic rat also demonstrates histological focal areas of spasm and patchy interstitial fibrosis suggesting that widespread microvascular spasm plays an important role in the pathogenesis of the hypertensive diabetic cardiomyopathy seen in rats.[11-12]

3.5 Ischaemia and Diabetes

Experimentally, diabetes also sensitises the myocardium to ischaemic insults. Diabetic rats without ketosis demonstrated a greater reduction in systolic function with coronary hypoperfusion than nondiabetic rats.[52] Similarly, coronary ischaemia produced by balloon inflation of the left anterior descending artery in dogs with induced diabetes resulted in reduced LV compliance compared with nondiabetic dogs. Stroke volume and stroke work were also reduced in the diabetic dogs. These abnormalities in diastolic function may be related to the interstitial glycoprotein deposition which probably contributes to increased diastolic stiffness.[78] In experimental diabetes in the rat, morphologic changes were often absent but heart weight as a function of bodyweight was increased. The volume of extracellular components increased three-fold and the volume of capillaries fell, resulting in increased oxygen diffusion distance to mitochondria, increasing the potential for ischaemia.[79] Myofibril volume also fell[80] and advanced glycosylation end products of collagen increased resulting in a stiff ventricle.[81]

Clinically, there is excess mortality with coronary artery disease, MI and CHF in patients with diabetes. Noninfarcted myocardium appears to have reduced compensatory ability, which may be related to coronary artery disease, reduced vasodilatory reserve and abnormal metabolism of myocardial substrate. Reinfarction and recurrent events are more common in patients with diabetes. Finally, ischaemia is less well tolerated. Overt systolic dysfunction occurs late in the course of diabetes and is associated with advanced microvascular complications and hypertension.

3.6 Insulin Reversibility

Prevention or partial prevention of systolic and diastolic dysfunction can be demonstrated with insulin therapy in experimental diabetes in the rat. Prevention of these functional changes are associated with near normalisation of the levels of myosin calcium ATPase, normalisation of the myosin subtype, and a near normal collagen content of the myocardium and arterioles.[66,82-84] These changes appear to correlate with the plasma glucose level.[85] Insulin also influences calcium homeostasis with normalisation of sarcolemmal and sarcoplasmic reticulum-dependant calcium uptake,[18] and normalised glucose transport rates.[86,87] Using isolated myocytes from severely diabetic rats, Ren and Davidoff[88] demonstrated prolongation of contraction and relaxation as early as 4 to 6 days after induction of diabetes, which was reproduced in normal cultured rat myocytes exposed to a diabetes-like serum.[89] These isolated myocyte findings suggest rapid onset of myocardial dysfunction which may be amenable to reversibility with normalisation of glucose levels.

Compositional changes can also be reversed with insulin therapy. The increased interstitial and perivascular deposition of extracellular matrix can be prevented when insulin therapy is begun within 3 days after the induction of diabetes in the rat and only partially reversed (33% improvement) if insulin therapy is delayed 12 weeks.[80] Finally, diabetes also increases the presence of free radicals, which may contribute to myocardial damage and dysfunction. This increase was reversed with an antioxidant, which improved LV performance in the diabetic rat.[90]

Reversibility of abnormal LV function in diabetic dogs was somewhat less complete. Pogatsa et al.[64] demonstrated that induced diabetes mellitus in the dog resulted in an increased thermostability of collagen without other histologic changes. Insulin-treated diabetic dogs still demonstrated some increase in diastolic stiffness which was intermediate in level between healthy control dogs and untreated dogs with diabetes. However, the degree of revers-

ibility of systolic and diastolic functional changes may be related to the extent of histologic changes.

3.7 Glycaemic Control and LV Dysfunction

Although the role of glycaemic control in the healthy left ventricle has importance, patients with diabetes often have concomitant hypertension, coronary artery disease and LV dysfunction. There are no clinical studies to date that can answer this important question. An animal model of both type 1 diabetes and LV dysfunction was used to examine the relationship between glycaemic control and LV function. In our animal laboratory, we have used a canine model of chronic ischaemic LV dysfunction. In this model, 50 micron occlusive microspheres were injected in sequential dosages into the left main coronary artery resulting in diffuse microvascular ischaemia and LV infarction. Eight weeks after embolisation, dogs have a dilated left ventricle with moderate LV dysfunction, increased LV mass and increased LVEDP. Histopathology (figure 3) revealed diffuse but patchy fibrosis (replacement-fibrosis) emanating from microsphere occluded arterioles in the perivascular interstitial areas are found in all levels of the myocardium.[91]

As this model of LV dysfunction shares some histological characteristics of human diabetic cardiomyopathy, we combined this model of LV dysfunction with the canine model of diabetes of Regan et al.[62,63] We determined the effect of experimentally induced diabetes mellitus at different levels of glycaemic control on LV systolic and diastolic function by inducing diabetes in 7 dogs (with previously induced LV dysfunction) and ad-

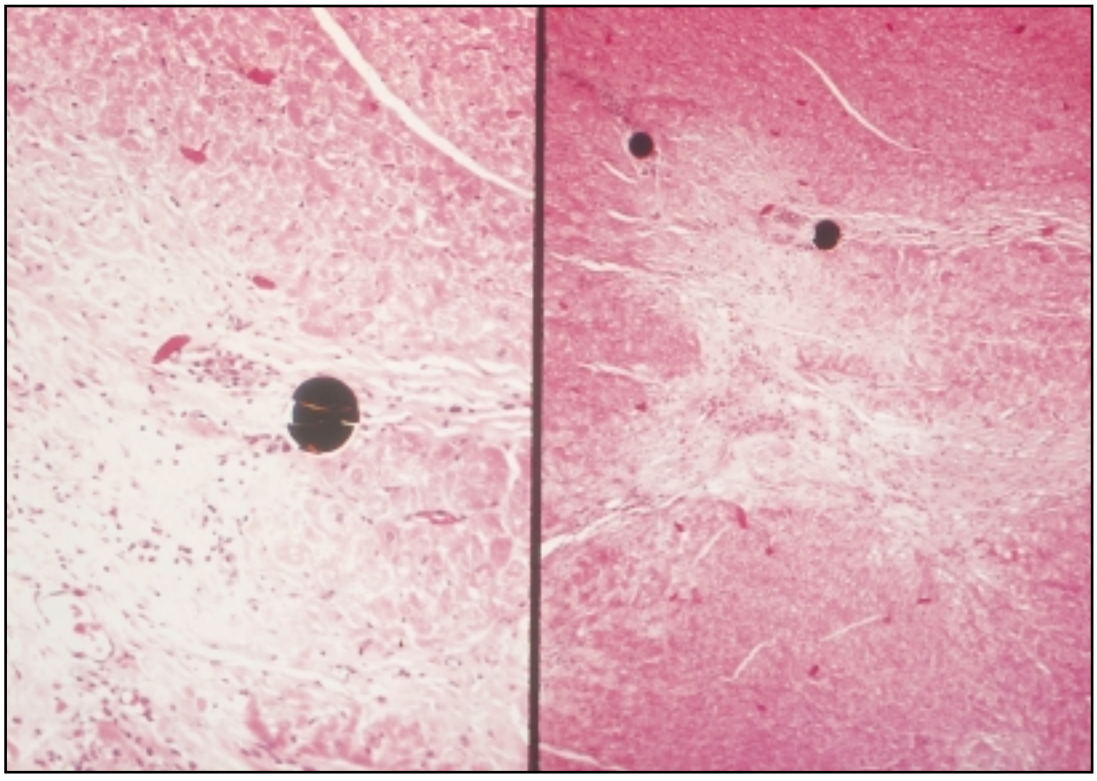

Fig. 3. A haematoxylin and eosin (low and high power) stain of myocardium with a microsphere in the field with interstitial and myocardial fibrosis (pale area) distributed in a patchy fashion throughout the myocardium.

justing daily insulin dosages to achieve 'poor glycaemic control' (250 mg/dl to 400 mg/dl; 6.5 to 10.3 mmol/L) for 3 months followed by 'good glycaemic control' (100 mg/dl to 150 mg/dl; 2.6 to 3.9 mmol/L) for the next 3 months. After 3 months of 'poor glycaemic control' (figure 4), LV size and LV end diastolic pressure increased and LV systolic performance declined. After three additional months of good control (figure 5), LV function reverted to the baseline level of LV dysfunction. *In summary*, this data suggests that glycaemic control has a modulating influence on LV systolic function and LV filling pressures.[92]

There had been limited clinical information and primarily observational studies regarding the influence of glycaemic control on LV systolic and diastolic function, and has exclusively focused on type 1 diabetes. Hausdorf et al.[93] demonstrated that levels of glycosylated haemoglobin correlated directly with the isovolumic relaxation period and inversely with systolic function in asymptomatic children with diabetes over a 2 year period. In patients with type 2 diabetes, insulin improved resting measure of LV systolic function and increased ejection fraction with exercise. The change in fasting glucose levels and glycosylated haemoglobin correlated with changes in the PEP/LVET (pre-ejection period/LV ejection time).[94] However, the effect of glycaemic control in a patient group with type 2 diabetes demonstrated improvement in non-invasive indices of relaxation and early diastolic filling only in patients where retinopathy was not present.[95]

These observational studies suggest that histological and microvascular changes are associated with long standing diabetes as are disturbances of LV systolic and possibly diastolic function. Additional information can be gleaned from randomised clinical trials investigating the role of glycaemic control. The Diabetes Control and Complications Trial (DCCT) indicated that intensive glycaemic control reduced the onset and progression of retinopathy, nephropathy and neuropathy (microvascular complications) in patients with type 1 diabetes. Although not powered to address these endpoints, the DCCT demonstrated a 41% reduction (nonsignificant) in the combined endpoint of peripheral vascular and cardiovascular events with intensive insulin therapy.[96] The influence of glycaemic control on cardiovascular morbidity and mortality has not been clearly determined. The University Group Diabetes Program in a post hoc subgroup analysis noted a 35% cardiovascular mortality in the placebo group and a 17% (variable insulin dose) and a 21% (fixed insulin dose) mortality in the groups who received insulin (nonsignificant).[97]

The applicability of the implications of glycaemic control to patients with type 2 diabetes seems reasonable except that insulin (insulin resistance) may be an atherosclerotic promoting factor. Preliminary data from two studies have yielded conflicting results. The Veteran Affairs Cooperative Study on glycaemic control and complications (VACSDM) demonstrated a 32% cardiovascular event rate in patients who received intensive treatment versus a 20% event rate in patients who re-

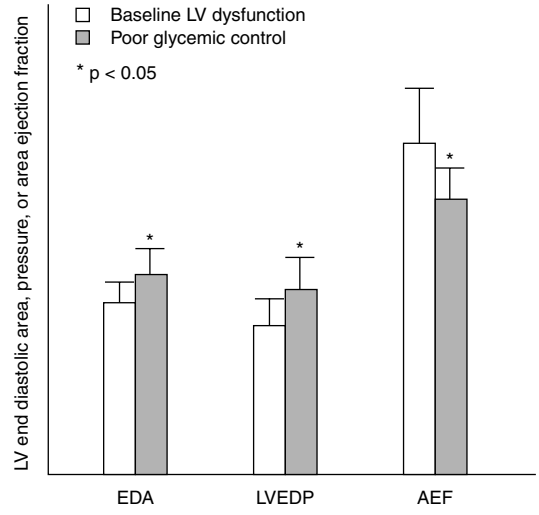

Fig. 4. The effect of poor glycaemic control on left ventricular (LV) size (EDA), LV end diastolic pressure (LVEDP) and systolic function (AEF-area ejection fraction) are shown at baseline LV dysfunction and after 3 months of poor glycaemic control. (Units for y axis are cm^2, mmHg and %).

ceived usual care (p = 0.1).[98] However, the incidence of pre-existing coronary disease was greater in the group who received intensive treatment. The Finnish studies demonstrated that cardiovascular mortality (coronary) is linearly related to glycaemic control irrespective of the mode (insulin therapy) of glycaemic control.[99] In the presence of acute MI, insulin-glucose infusion followed by strict glycaemic control was a predictor of reduced mortality in the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study.[100]

4. Management of CHF in Patients with Diabetes

4.1 Goals of Therapy

Therapy of patients with CHF in part is related to the underlying pathophysiology. Of prime consideration is the treatment of the underlying cause of LV dysfunction and the removal of all precipitating factors. The goals of therapy include the short-term relief of both pulmonary and systemic congestion, and the long-term slowing of the progression and potentially reversing the course of LV dysfunction and prolonging survival. Short term relief of symptoms can be accomplished by nonpharmacological approaches (relief of ischaemia and salt restriction) and pharmacological therapy. Similarly both nonpharmacological and pharmacological approaches can be employed for long-term therapy. Attention should directed at reducing the standard coronary risk factors (hypercholesterolaemia, hypertension, smoking, etc.). The transition between LV dysfunction and CHF is being vigorously investigated at the present time. Efforts to influence remodelling processes are being pursued. Reduced progression to overt CHF and reduced hospitalisation for CHF have been demonstrated in the prevention arm of the Studies of Left Ventricular Dysfunction Prevention (SOLVD) trial with the use of ACE inhibitors.[101] At the present time no other pharmacologic agent has been demonstrated to halt the transition from LV dysfunction to CHF.

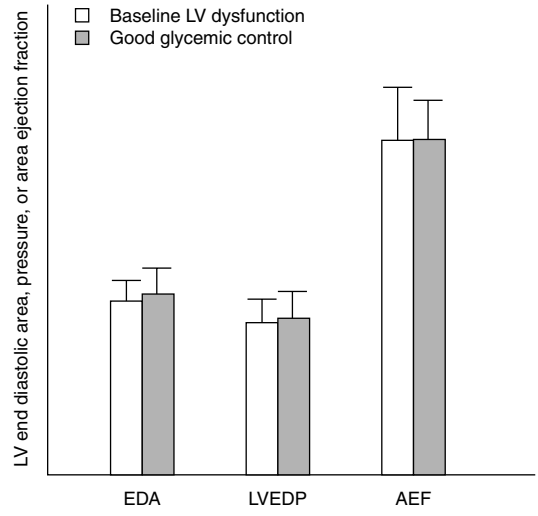

Fig. 5. The influence of good glycaemic control on left ventricular (LV) size (EDA), LV end diastolic pressure (LVEDP) and systolic function (AEF-area ejection fraction) are shown at baseline LV dysfunction and after 3 months of poor followed by 3 additional months of good glycaemic control. (Units for y axis are cm^2, mmHg and %).

The presence of diabetes adds an additional factor that has been recognised as an adverse prognostic indicator in general for cardiovascular disease. The incidence and extent of coronary disease are increased as is the incidence of LV dysfunction. Vigorous attention to glycaemic control and hypertension may be beneficial with regard to coronary disease and CHF, but randomised clinical trials have been underpowered and not designed to address these issues. In the UKPDS study, intensive treatment resulted in a reduced risk of MI (p = 0.052).[102] Many trials demonstrating symptomatic and survival benefit with either ACE inhibitors or β-blockers do not have predefined subgroups of patients with diabetes. However, as it is this subgroup who has the highest risk profile for CHF and mortality, interventions designed to reduce risk in the CHF population as a whole may very well have their greatest benefit in the patient with diabetes and LV dysfunction.

4.2 Pharmacological Therapy of CHF

The majority of therapeutic agents for CHF have similar or better efficacy in patients with diabetes as in those without. As a general principle, patients with diabetes and especially those with concomitant hypertension represent a subgroup with a high incidence of coronary artery disease and greater degree of LV dysfunction. Efficacious agents may be especially useful in this important subgroup (tables V and VI).

4.2.1 Inotropic Agents

Digoxin has been used as an inotropic agent for over 30 years. Its efficacy has only been recently established. Its action involves inhibition of monovalent cation transport resulting in increased availability of myocardial calcium. Neurohormonal modulation, amelioration of autonomic dysfunction with enhancement of parasympathetic stimulation and restoration of baroreceptor stimulation are some of its salutary actions. Therapeutic endpoints with digoxin have been difficult to achieve in the past because of digitalis intoxication. Attempts to optimise therapy based on digoxin concentrations will lead to increased toxicity without significant improvement in therapeutic effect.

In patients with New York Heart Association (NYHA) Class II to III CHF, digoxin increases ejection fraction, reduces symptoms of CHF, improves exercise capacity and decreases the number of CHF hospitalisations [Digitalis Investigation Group (DIG) trial].[108,119] Although there are few data in patients with NYHA Class IV CHF, digoxin appears to work across the spectrum and in patients with diabetes (a specified subgroup in this study).[108] However, it has a neutral effect on mortality.[108] Digoxin may be of particular use in patients with CHF and atrial fibrillation when its effects on the AV node can be used to control the heart rate. Sensitivity to the toxic effects of digoxin are more likely to manifest themselves with volume depletion, and potassium and magnesium depletion, which may occur with diuresis.

Sympathomimetic agents have been used to support the circulation acutely and for acute decompensated CHF. Dobutamine, dopamine and epinephrine (adrenaline) are primarily intravenous agents. Phosphodiesterase type III inhibitors have been used intravenously for similar purposes. However, oral milrinone was found to increase mortality and has been withdrawn [Prospective randomised milrinone survival evaluation (PROMISE) study] from clinical use,[109] although intravenous milrinone continues to be used.

Table V. Heart failure and mortality prevention trials[a]

Trial	Drug treatments	Mortality	MI	CHF	Adverse events	Stroke
Appropriate Blood Pressure Control in Diabetes (ABCD)[43]b	Enalapril *vs* nisoldipine		Reduced		Reduced	
Heart Outcomes Prevention Evaluation (HOPE)[103]c	Ramipril *vs* placebo	Reduced	Reduced	Reduced		Reduced
Hypertension Optimal Treatment (HOT)[46]c	Felodipine *vs* ACE inhibitors + β-blockers	Reduced	Reduced		Reduced	Reduced
Studies Of Left Ventricular Dysfunction Prevention (SOLVD)[101]	Enalapril *vs* nisoldipine			Reduced		
University Group Diabetes Program (UDGP)[97]b	Insulin *vs* placebo	Reduced				
Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI)[100]b	Insulin-glucose infusion *vs* placebo	Reduced				

a Results are for patients with diabetes, but were also true for patients without diabetes.

b Diabetes study.

c Diabetes subgroup.

CHF = congestive heart failure; **MI** = myocardial infarction.

Table VI. Heart failure and therapeutic trials

Trial	Mortality	CHF	Hospitalisations	Exercise Capacity
Angiotensin converting enzyme inhibitors				
Survival and Ventricular Enlargement (SAVE)[104]	Reduced	Reduced		
Studies of Left Ventricular Dysfunction Treatment (SOLVD)[101]	Reduced	Reduced	Reduced	
Cooperative North Scandinavian Enalapril Survival (CONSENSUS)[105]	Reduced	Reduced		
Vasodilator Heart Failure Trial (V-HEFT II)[106]	Reduced			
Trandolapril Cardiac Evaluation (TRACE)[107]a	Reduced	Reduced		
Inotropes				
Digitalis Investigation Group (DIG)[108]a		Reduced	Reduced	Increased
Prospective Randomised Milrinone Survival Evaluation (PROMISE)[109]	Increased		Increased	
Aldosterone antagonists				
Randomised Aldactone Evaluation Study (RALES)[110]	Reduced		Reduced	
β-Blockers				
Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)[111]	Reduced		Reduced	
Metoprolol in Dilated Cardiomyopathy (MDC)[112]	Reduced			
The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[113]	Reduced		Reduced	
Prospective Randomised Evaluation of Carvedilol on Symptoms and Exercise (PRECISE)[114]	Reduced		Reduced	Increased
Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)[115]	Reduced		Reduced	Increased
Calcium channel antagonists				
Prospective Randomised Amlodipine Survival Evaluation[116]	Neutral			
The Danish Verapamil Infarction Trial II (DAVIT-II)[117]	Reduced if no CHF			
Multicenter Diltiazem Post Infarction Trial (MDIPIT)[118]	Increased if CHF			

a Diabetes subgroup.

CHF = congestive heart failure.

4.2.2 Diuretics

In patients with CHF, renal adaptations to the reduced cardiac output occur mediated by the many neurohormonal changes. Glomerular filtration may be reduced when CHF is associated with renovascular disease. Glomerular filtration may be dependent on the the relative vasoconstriction of the afferent vs the efferent arterioles. There is no long-term data on the use of diuretics in CHF. Diuretics have been used in CHF as background therapy in clinical trials along with digoxin. Diuretics are a mainstay of therapy for volume overload and act by blocking ion transport in the loop of Henle or distal tubule. The activity of diuretics in the proximal tubule and collecting duct is usually less.

Loop diuretics are perhaps the most commonly used diuretics resulting in a prompt and brisk diuresis. Furosemide (20 to 80mg as a single dose) and bumetanide (1 to 3mg as a single dose) are two examples of loop diuretics. Their actions are in the ascending limb of the loop of Henle where they inhibit transport of sodium and chloride. Potassium depletion is common. Other diuretic classes (e.g. thiazides) inhibit sodium and chloride transport in the distal tubule. Their diuretic effect is more modest and less effective in patients with renal dysfunction. Their use may augment the effects of furosemide but at the expense of marked potassium depletion. Potassium sparing diuretics include triamterene and spironolactone, which is an inhibitor of type I mineralocorticoid and glucocorticoid receptors. Secondary hyperaldosteronism occurs in the setting of CHF, especially with loop diuretic use. Spironolactone is useful in re-

storing diuresis when secondary hyperaldosteronism occurs with loop diuretic use. More recently, spironolactone at low nondiuretic doses (25mg) demonstrated a salutary effect on CHF, hospitalisations and survival in the Randomized Aldactone Evaluation Study (RALES).[110] Metolazone, a thiazide-like diuretic, with some proximal tubule effect has been used at a dose of 2.5 to 10 mg/day to augment the effect of loop diuretics.

Diuretics are helpful in avoiding volume overload, but can lead to potassium depletion, prerenal azotemia and other electrolyte disorders which can become more acute in the setting of renal insufficiency (especially in patients with diabetes). Diffuse oedema or anasarca can result in diuretic resistance as a result of nonabsorption secondary to bowel oedema. Diuretics can also impair glucose tolerance (thiazides) and in the presence of renal insufficiency (loop diuretics) may lead to hyperkalaemia and renal insufficiency with volume depletion secondary to distal tubular renal acidosis.

4.2.3 Vasodilators

Although vasodilators were popular at one time for the treatment of CHF, they have been largely supplanted by ACE inhibitors. α-Blockers including prazosin have early impressive haemodynamic effects that wane as a result of tachyphylaxis. They demonstrate no survival effect [Vasodilator Heart Failure Trial (V-HEFT)] and their use has largely been abandoned.[120] The nonspecific vasodilator, hydralazine (approximately 300 mg/day) when combined with isosorbide dinitrate, improved survival, increased ejection fraction and reduced symptoms of CHF.[120]

However, the effects were not as salutary as those seen with ACE inhibitors in VHEFT-II.[106] The use of nitrates alone may assist with symptoms of pulmonary congestion and angina in patients with LV dysfunction and coronary disease.

4.2.4 Angiotensin Converting Enzyme Inhibitors

ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II. Bradykinin degradation is also inhibited resulting in increased levels which may be responsible for the cough sometimes seen with their use. They are now used for the treatment of hypertension, CHF and diabetic nephropathy. Their cardiovascular and renal actions are targeted at reversing the effects of angiotensin II. These include antagonising the increased sympathetic outflow, vascular and smooth muscle cell hypertrophy, endothelial dysfunction, increased oxidative stress, atherosclerotic and thrombotic effects, and aldosterone production. Renal function may be adversely impacted by their use as 10% of patients will have an increase of serum creatinine by 0.3 units. Renal atherosclerosis and efferent arteriole constriction contribute to the decrease in renal function.[39] This class of drugs are excreted by the kidney and may accumulate in patients with renal insufficiency made worse by hypotension and reduced glomerular filtration.

SOLVD, Survival and Ventricular Enlargement (SAVE), the Cooperative North Scandinavian Enalopril Survival Study (CONSENSUS) and VHEFT-II are clinical trials that have demonstrated improved survival in patients with CHF with ACE inhibitors.[101,104-106,120] Subdivisions into patient groups with and without diabetes were not systematically performed in these trials. However, the Heart Outcomes Prevention Evaluation (HOPE) study of patients at high risk for cardiovascular events but with ejection fractions >40% and no CHF, demonstrated a marked risk reduction in MI, death and stroke, and a 22% reduction in the incidence of new CHF.[103,121] The effects were more marked in patients with diabetes. Similarly, in the Trandolapril Cardiac Evaluation (TRACE) study, patients receiving trandolapril who had a previous MI and had LV dysfunction with and without CHF demonstrated a 27% increase in life expectancy. Patients with diabetes after infarction are a high risk group with ≥50% mortality over 6 months in the TRACE study. These salutary findings on mortality were more marked in the subgroup with diabetes. In patients with diabetes, there was a reduction in cardiovascular death (44%), sudden death (54%) and progression to CHF (62%) with trandolapril.[107] Very clearly, patients with diabetes (irrespective of type and insulin use) and LV dysfunction secondary to coronary artery disease

derive an ant-ischaemic effect and an effect on progression to CHF (anti-remodelling) that appear to be interrelated. The effects on mortality, reinfarction, stroke and CHF appear to be a class effect. It is important to administer maximal tolerated doses of the ACE inhibitor as most trials uptitrate the specific drug.

4.2.5 Angiotensin II Receptor Antagonists

These agents block the angiotensin II type 1 receptor (AT_1) but do not influence the unopposed angiotensin II type 2 receptor (AT_2) stimulation. AT_2 receptor stimulation results in vasodilatation, an antigrowth and antiproliferative effect but an increase in apoptosis.[122] In CHF, glomerular filtration is under the control of both the afferent and efferent arteriole constriction and a low ultrafiltration coefficient.[123] The renal vasculature arborises so the arterial pressure needs to be 65 mmHg at entry into the glomerulus with 35 mmHg needed to transport across the glomerular basement membrane. When the effects of angiotensin I are blocked with ACE inhibitors, glomerular filtration rate improves as a result of increased perfusion, reduced afferent tone and adequate efferent tone. AT_1-receptor antagonists affect the glomerular efferent tone to a lesser extent than ACE inhibitors, which reduces renal problems.[124,125] However, patients who have ACE inhibitor renal intolerance may also have intolerance to AT_1-receptor antagonists. In the Evaluation of Losartan in the Elderly (ELITE) trial, <10% of patients had a 0.3 unit increase in their serum creatinine.[126]

Monotherapy with an AT_1-receptor antagonist decreased the mean pulmonary capillary pressure by 6.3 mmHg. Higher doses added no further haemodynamic benefit acutely, but resulted in less mortality and chronic CHF.[127-130] Both drug classes have been used in combination in the treatment of CHF and have resulted in additive decreases in the mean pulmonary capillary pressure with little hypotension.[131] The ELITE trial demonstrated that losartan had a lower mortality associated with its use compared with captopril,[126] which were not confirmed in the ELITE II trial.[132] Although ACE inhibitors improve survival in patients with CHF, LV dysfunction and coronary disease, the data for AT_1-receptor antagonists are limited. At the present time, patients unable to tolerate ACE inhibitors should receive isosorbide dinitrate and hydralazine, a combination with a positive effect on mortality.[120]

4.2.6 Aldosterone Antagonists

Aldosterone stimulation in patients with CHF results in increased sodium and water retention, increased potassium and magnesium loss, increased sympathetic and reduced parasympathetic nervous system stimulation, and increased collagen synthesis. ACE inhibitor therapy does not antagonise aldosterone production. Angiotensin II production can occur through the chymase pathway despite ACE inhibitor therapy.[133,134] To test the influence of aldosterone on CHF symptoms and mortality (RALES study), patients with CHF were randomised to spironolactone 12.5 to 25mg or placebo in addition to maintenance therapy (ACE inhibitor, diuretic, digoxin, but a low use of β-blocker). Mortality was reduced from 46% to 35% in the treatment group and CHF hospitalisations were reduced 35%.[110]

4.2.7 β-Blockers

β-Blockers have progressed from being contraindicated in patients with CHF to being important agents that have symptomatic and survival benefits. Multiple trials performed have demonstrated efficacy and safety in patients with Class II to III CHF.[111-115,135-140] Ejection fraction generally improves over 3 months with variable improvements in exercise tolerance.[135,136] In most trials of symptomatic patients with ejection fractions <40%, background therapy consisted of an ACE inhibitor, a diuretic and digoxin. Both selective and nonselective agents have been used.

Metoprolol demonstrated a 34% decrease in risk of transplant in the Metoprolol in Dilated Cardiomyopathy (MDC) trial[141] and 34% decrease in mortality in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study.[111,137] Bisoprolol use resulted in a 34% decrease in hospitalisation [the Cardiac Insufficiency Bisoprolol Study (CIBIS)] and a

34% decrease in mortality in CIBIS-II, which was similar whether LV dysfunction was caused by ischaemic or nonischaemic aetiologies.[113,137] Carvedilol use demonstrated a 65% decrease in mortality and hospitalisation with a 38% reduction in death.[140] Both the Prospective Randomised Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) and Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trials demonstrated a reduction in the combined endpoint of mortality and hospitalisation of 39-49%. The MOCHA trial demonstrated that higher dosages were more advantageous.[114,140] With regard to patients in Class IV CHF, there is no data for efficacy and there is a concern regarding decompensation. Subgroup analysis of some of these trials demonstrated similar efficacy in patients with diabetes as those without.

The general rule is to start at very low doses (metoprolol 6.25mg or carvedilol 3.125mg) and to uptitrate. Careful scrutiny for symptoms of fatigue, bodyweight gain, decreased exercise tolerance and hypotension is required. Alteration of diuretic dose can address hypotension and bodyweight gain. Continued deterioration should prompt a search for the precipitants of CHF including noncompliance of medication, ischaemia, arrhythmias and infection. Efforts should be made not to discontinue the β-blocker since their proven efficacy with regard to CHF hospitalisation and mortality is sizeable.[140] The presence of diabetes does not pose a relative contraindication to the use of β-blockers. On the contrary, β-blockers may be even more important in this subgroup of patients.

4.2.8 Calcium Channel Antagonists

Enthusiasm for the use of calcium channel antagonists in patients with CHF has largely waned. Trials have demonstrated efficacy, no benefit, or even harm in subgroups of patients with CHF after MI. The earliest trial was the Multicenter Diltiazem Post Infarction Trial (MDIPIT) which used diltiazem after MI and demonstrated increased mortality post infarction in patients with CHF.[118] Verapamil in the Danish Verapamil Infarction Trial II (DAVIT-II) did show benefit in patients with CHF using a combined endpoint.[117] Amlodipine showed no adverse effects when used in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study.[116] This is important because amlodipine is a commonly-used agent in the therapy of hypertension in patients with CHF.

4.3 Therapy of CHF in Patients with Diabetes

There are no specific trials that address this issue. In fact, subgroup analysis of patients with diabetes are rarely addressed unless the trial involves patients with ischaemic disease or after MI. Diabetes and hypertension are important adverse risk factors in ischaemic heart disease and CHF. Efforts to address ischaemia in this high risk group with therapies that are efficacious for CHF and are antiischaemic, antithrombotic and improve endothelial and vasodilator function are likely to make great impact on the morbidity and mortality of patients with diabetes. Other clinical trials have demonstrated that effective therapies generate the greatest impact on subgroups with the highest risk: patients with diabetes and hypertension. Antidiabetic therapies that produce tight glycaemic control may improve the microvascular complications associated with diabetes, but have uncertain impact on macrovascular complications and LV systolic and diastolic function. It is these issues that require more investigation to maximise the impact of CHF therapy in patients with diabetes.

4.4 Pitfalls in Therapy of CHF

The most important pitfall is not recognising the presence of CHF. Not all patients will present with classic symptoms and signs. The presence of LV dysfunction is an important clue. However, diastolic dysfunction can be an important cause of congestive symptoms. The presence of coronary artery disease, hypertension with LV hypertrophy, or even infiltrative diseases including amyloidosis can produce congestive symptoms with preserved LV systolic function.

Although the cornerstone of CHF therapy are ACE inhibitors, diuretics are commonly employed

to treat pulmonary congestion and may produce either symptoms of fatigue with overuse or congestion with underuse. ACE inhibitor dose administration needs to be maximised based on clinical trials. Use of dosages that are too low is common and prevents the full effect from these agents being gained. Not all patients will tolerate ACE inhibitor therapy because of adverse effects, primarily coughing. Although AT_1-receptor antagonists are possible alternatives to ACE inhibitors, clinical trials do not yet support their widespread use. However, the combination of isosorbide dinitrate and hydralazine does improve symptoms and mortality, as shown in the V-HEFT trial.[107]

Therapy for CHF should include an assessment of the quality of life and long term goals of patients. Very simply, therapies aimed at reducing long term mortality are paramount. Not all these therapies will reduce symptoms, nor will all therapies aimed at reducing symptoms improve mortality. However, all therapies aimed at reducing congestion should be mortality neutral.

5. Conclusions

The diagnosis of CHF in patients with diabetes is no different than in patients without diabetes. However, diastolic dysfunction is common early on in patients with diabetes. The clinician should be alerted to this possibility and investigate symptoms of dyspnea realising that they may represent pulmonary congestion. As patients with type 2 diabetes often have concomitant hypertension, the increased incidence of fibrosis, abnormal relaxation, and reduced myocardial and chamber compliance often results in pulmonary congestion on exertion. Rapid atrial fibrillation may exacerbate diastolic dysfunction by producing episodes of pulmonary congestion and haemodynamic decompensation.

The presence of diabetes in patients with CHF provides some unique considerations. Glycaemic control reduces the progression of microvascular complications, but whether it has salutary effects on vascular disease, coronary artery disease, and systolic and diastolic function is unclear. The role of hyperinsulinaemia, which may result from increased efforts to control glycaemia, may have atherosclerotic and growth promoting potential on vascular lesions. Little if any data exist with regard to agents (metformin or thiazolidinediones) that improve insulin sensitivity. Nevertheless, glycaemic control is important to the overall health of patients. Experimental data may suggest that hyperglycaemia can be responsible for exacerbating LV dysfunction. Furthermore, CHF is a state where high levels of catecholamines exist that can adversely effect glycaemic control.

Exacerbation of CHF in patients with diabetes has many potential causes. The presence of poorly controlled atrial fibrillation, hypertension, infection and ischaemia are examples. Nephropathy associated with diabetes can result in fluid retention, hypertension and increased symptoms of pulmonary congestion. Efforts to treat these symptoms may be hampered by a lack of response to diuretics and worsening renal function produced by ACE inhibitors, resulting a in dosage reduction in or cessation of this latter drug.

Management of patients with diabetes and CHF is similar to patients without diabetes. As patients with diabetes represent a high risk subset of patients with CHF, efforts to maximise therapy will have a substantially greater impact on hospitalisation and mortality than other subsets of patients. Dosages of ACE inhibitors should be maximised to achieve the greatest benefit. For those patients who are unable to tolerate this class of drug, hydralazine and nitrates according to the dose administration of the V-HEFT trial should be used. To date, there is insufficient data on the effects of AT_1-receptor antagonists on CHF hospitalisation and mortality to recommend them as alternative therapy. β-blockers should also be employed in patients with class II to III CHF to reduce long-term mortality. Although there has been previous concern in patients with diabetes that β-blockers may mask hypoglycaemic episodes and worsen glycaemic control, the benefits in patients with diabetes and CHF with this class of drug are substantial. As concomitant coronary artery disease is often pres-

ent in patients with diabetes, β-blockers offer additional benefits in reducing ischaemic episodes and MI.

Patients with diabetes, LV dysfunction, CHF and coronary artery disease represent one of the highest risk subset of patients. It is this group where maximised therapy is likely to achieve its greatest relative benefit. However, the prognosis despite these efforts is still not as good as for the patient without diabetes.

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Correspondence and offprints: Dr *Steven J. Lavine*, Cardiovascular Center, University of Florida-Jacksonville, 655 West 8th Street, Jacksonville, Florida 32209, USA.
E-mail: Steven.Lvine@jax.ufl.edu