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Re·FLECTIONS

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LETTER FROM THE EDITOR

The first article in this edition of *Re-flections* examines aspects of the dysfunction of the left myocardial venticle and its role in heart failure. The information in this article should provide guidance in the assessment of venticular dysfunction and explain its significance for underwriters. This issue also features Dr. Richard Rougeau discussing an underwriting approach to elevations in liver function tests. In this follow-up to a prior *Re-flections* article, he specifically deals with the issue of non-alcoholic fatty liver disease (NFLD). I hope you enjoy both of these articles.

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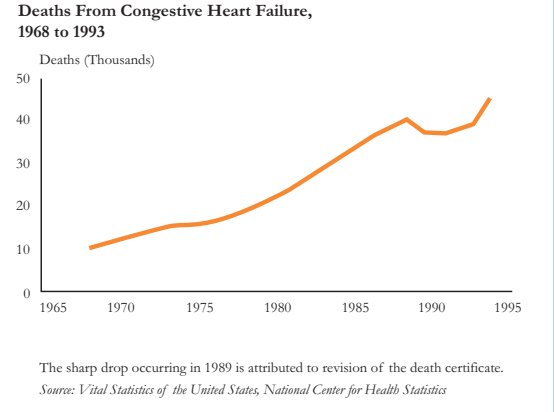
VENTRICULAR DYSFUNCTION AND CONGESTIVE HEART FAILURE

by J. Carl Holowaty, M.D.

Heart failure is the most frequent cause of hospitalization in persons aged 65 and older.[1] Approximately five million Americans have been diagnosed with this condition. The incidence of heart failure is about 380 per 100,000 persons for men, and about 315 per 100,000 persons in females — an incidence that has not declined during the last two decades. Although the five-year survival rate has improved from 43 percent in 1979–1984 to 52 percent in 1996–2000[1], heart failure is still generally poor from an insurability perspective.



The prevalence of congestive heart failure (CHF) varies with age. It is low at younger ages, gradually rising to an estimated 8 to 10 percent at ages greater than 75. Mean occurrence is age 73 in men and 79 in women, but CHF can, however, occur at any age. A general population study done in Minnesota[2], for example, revealed that 2.2 percent of adults over age 45 had validated congestive heart failure.

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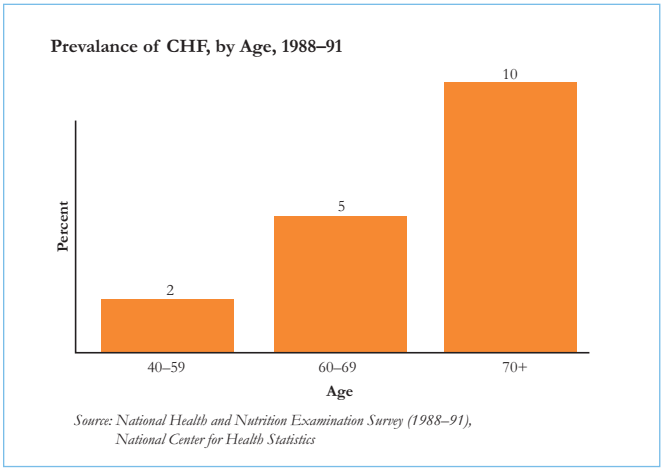
Unfortunately, heart failure is not always easy to diagnose (with exception of the most overt forms), and is not always clearly presented on attending physician reports. All too often, the only reference to this condition is a terse comment referring to CHF at some point in the past. This reference is difficult to either ignore or validate. A thorough understanding of the nature of congestive heart failure as well as its many presentations can help in arriving at a reasonable mortality assessment.



Essentially, heart failure is an impairment or dysfunction of the myocardium whereby the cardiac output (CO) becomes inadequate to meet the oxygen and nutritional needs of the body. If the myocardium is only mildly impaired, the heart and other regulatory mechanisms in the body respond (compensate) in several ways to provide the necessary blood flow to the vital organs. Responses include:

- An increase in ventricular volume and pressure, which results in a more forceful ejection of blood from the ventricles during systole.
- An increase in ventricular mass (hypertrophy).
- An increase in sympathetic nervous activity, which increases the heart rate.
- Activation of the renal-angiotensin system, which increases blood volume by retaining body fluids.

The early stage of heart failure is referred to as ‘compensated heart failure’. Clinicians may not easily recognize people in this phase of heart failure, unless they have a high index of suspicion. Sometimes the only clues present may be a mild tachycardia and slight ankle edema. Although this ‘compensatory’ phase of heart failure helps to provide adequate blood flow to the body, the compensatory mechanisms are a double-edged sword, ultimately leading to cardiomegaly, ventricular hypertrophy, abnormal heart rhythms, peripheral edema and pulmonary congestion. Eventually the compensatory mechanisms fail, leading to a state called congestive — or decompensated — heart failure, which invariably leads the patient to seek medical care. Even with proper medical care, people with heart failure often alternate between states of compensated and decompensated failure. Ideally, the periods of decompensation are brief.

A common classification system for chronic heart failure is the American College of Cardiology/ American Heart Association (ACC/AHA) system.

Stage	Description
A: High risk for developing heart failure	History of hypertension, diabetes mellitus, CAD, family history of cardiomyopathy
B: Asymptomatic heart failure	Previous MI, left ventricular dysfunction, valvular disease
C: Symptomatic heart failure	Structural heart disease, dyspnea and fatigue, impaired exercise tolerance
D: Refractory end-stage heart failure	Marked symptoms at rest despite maximal medical therapy

The New York Heart Association (NYHA) Heart Failure Classification System, another common classification scheme, is based on symptoms.

NYHA Class	Level of Impairment
I	No symptom limitation with ordinary physical activity
II	Ordinary physical activity somewhat limited by dyspnea (i.e. long distance walking, climbing two flights of stairs)
III	Exercise limited by dyspnea at mild work loads (i.e. short distance walking, climbing one flight of stairs)
IV	Dyspnea at rest or with very little exertion

When considering whether an individual applicant may have heart failure, it is critical for life insurers to discriminate between people in the ACC/AHA Stages A, B and C. People in Stage D are usually easily identified by their clinical history. In order to make this discrimination it is necessary to be aware of the risk factors for heart failure, the different presentations of ventricular dysfunction, and the lab tests and drug treatments that may provide the clues.

When deciding whether a vague past single reference to possible CHF should be taken seriously, the first thing to consider is whether the applicant has any of the risk factors. The absence of these risk factors decreases the likelihood that the individual has actual heart failure.

Common Causes:

- Coronary heart disease
- Hypertension
- Valvular heart disease
- Aging (possibly)

Other Causes:

- Infections: viruses (including HIV), bacteria, parasites
- Pericardial diseases
- Drugs (e.g. cocaine, chemotherapeutic drugs)
- Alcohol
- Connective tissue disease
- Infiltrative disease (e.g. amyloidosis, sarcoidosis, hemochromatosis, malignancy)
- Tachycardia
- Obstructive cardiomyopathy
- Neuromuscular disease (e.g. muscular dystrophy)
- Metabolic disorders
- Nutritional disorders
- Pheochromocytoma
- Radiation
- Endomyocardial fibrosis
- Eosinophilic fibrosis
- High-output heart failure (e.g. intracardiac shunt, atrioventicular fistula, pregnancy, hyperthyroidism)
- Peripartum cardiomyopathy
- Dilated idiopathic cardiomyopathy

Another consideration is the presence or absence of the usual signs of symptoms of heart failure, whether in the past or currently. An attending physician's statement, medical examination, or paramedical examination may provide some of the needed information.

The Framingham Criteria for Heart Failure are as follows (Heart Failure is present with 2 major or 1 major and 2 minor criteria):

Major Criteria:

- Paroxysmal nocturnal dyspnea or orthopnea
- Neck vein distension (elevated jugular venous pressure)
- Rales in the chest
- Cardiomegaly
- Acute pulmonary edema
- S3 gallop noted on auscultation of the heart
- Increased venous pressure
- Circulation time greater than 25 seconds
- Hepatomegaly

Minor Criteria:

- Ankle edema
- Night cough
- Dyspnea on exertion
- Hepatomegaly
- Pleural effusion
- Vital capacity decreased one-third from maximum
- Tachycardia rate > 120 bpm

Major or Minor Criteria:

- Weight loss > 10 pounds in 5 days in response to treatment

The next step in determining CHF is considering whether any laboratory investigations can help establish the presence of heart failure. There are no specific EKG features diagnostic of heart failure, but atrial and ventricular arrhythmias are common findings. Atrial fibrillation is present in many patients with cardiomyopathies associated with heart failure. The EKG findings associated with CAD or left ventricular hypertrophy will also increase the likelihood that heart failure may exist either currently or in the past.

Exercise testing can also be a useful assessment tool. Tachycardia at rest, poor exercise tolerance, rapid escalation in heart rate with exercise and slow return to baseline heart rate may point to the existence of heart failure.

Chest X-Rays are also helpful. Cardiomegaly may suggest the presence of heart failure, but some forms of heart failure do not manifest ventricular enlargement, at least in the early phase. More details will be provided later in this article.

Echocardiography is quite useful, when available. Unfortunately its expense can be limiting, especially as a screening tool in the elderly. Enlargement of heart chambers, left ventricular mass measurements, wall motion abnormalities and often ejection fraction abnormalities will be present.

Occasionally, angiography or MRI testing will be used to evaluate heart failure, but this is less common.

A simple blood test called BNP (brain natriuretic peptide) has also been used in the evaluation of heart failure. BNP is released from cardiac ventricles and has been used to monitor the status of people with known CHF, as well as those at risk of failure or displaying some signs and symptoms of this condition. A precursor of this peptide called NT ProBNP is assayed for similar purposes.

An individual's medication profile may also help in determining the presence of heart failure. Some of the more common drugs or drug families to look for are:

- Angiotensin Converting Enzyme (ACE) inhibitors. Reduce the afterload of the heart.
- Angiotensin receptor blockers. Used when ACE inhibitors are not tolerated.
- Beta-blockers. Exact mechanism uncertain, but shown to improve mortality.
- Digoxin. Provides symptomatic relief, but may not improve mortality.
- Diureteics. Reduce volume overload and relieve symptoms.
- Hydralzazine and nitrates. Reduce afterload of heart.

It is important to understand that all cases of heart failure are not alike. The primary mechanism of heart failure is ventricular dysfunction. Although it is common to think of myocardial function as that of contraction (occurring during systole), another important function of the myocardium is to relax properly following a contraction (during diastole). Failure to contract normally is referred to as systolic dysfunction, and failure to relax properly is termed diastolic dysfunction. While systolic dysfunction is a well-recognized cause of heart failure, diastolic dysfunction is present in approximately 30 to 40 percent of people admitted to the hospital with a diagnosis of heart failure.[4] Its prevalence increases with age. Although the mortality from this entity is not quite as severe as that of systolic ventricular dysfunction, it is still high. The annual mortality for patients with systolic heart failure ranges from 10 to 15 percent, while that of diastolic heart failure ranges from 5 to 8 percent. It is also not uncommon for these two forms of ventricular dysfunction to co-exist.[3]

Condition	% of studied population (adults > 45 yrs old)
Mild diastolic dysfunction	20.8
Moderate diastolic dysfunction	6.6
Severe diastolic dysfunction	0.7
Any degree of systolic dysfunction	6.0
Moderate or severe systolic dysfunction	2.0

Some degree of diastolic dysfunction appears to be a common entity, as determined by a study done in Minnesota.[2] Interestingly, less than half of those indi-

viduals with moderate or severe systolic dysfunction had recognized congestive heart failure.

While the most common precursor for systolic dysfunction is CAD, the most common precursors for diastolic dysfunction are the conditions that lead to alterations of myocardial relaxation such as cardiac hypertrophy and restrictive cardiomyopathies secondary to prolonged hypertension, sarcoidosis and hemochromatosis.

Some of the key differentiators between these two forms of ventricular dysfunction are:

Systolic Dysfunction	Diastolic Dysfunction
Ejection Fraction < 35–40%	Ejection Fraction > 40–45%
Presents at ages < 65 years	Usually presents at ages 65 and older
Progressive shortness of breath	Acute pulmonary edema
S3 gallop heard on auscultation of heart	S4 gallop heard on auscultation of the heart
Pulmonary congestion and cardiomegaly noted on CXR	Normal heart size on CXR
ECG shows Q waves	EKG may show evidence of left ventricular hypertrophy with strain
Ventricular wall thickness decreased	Ventricular wall thickness increased
End diastolic volume is increased	End diastolic volume is normal

The key differentiators are the Ejection Fraction (E.F.) and size of the heart. Characteristics of diastolic dysfunction illustrate that serious heart failure may be present even with a normal E.F. and in the absence of cardiomegaly.

Heart failure is primarily, but not exclusively, a disease of the elderly. An aging North American population as well as the life insurance industry's focus on the elderly make it essential to recognize the subtle clues that may indicate the early presence of this serious health condition. Failure to do so will likely result in early death claims.

I hope the information in this article will allow the reader to determine if heart failure is present, but the absence of reliable, inexpensive, non-invasive effective screening for this common condition in the elderly makes errors inevitable. While the echocardiogram and clinical history are currently the best available tools for determining CHF, they are expensive and not always reliable. Hopefully future advances in directly measuring the force of ventricular contraction and relaxation will enable us to selectively screen for this important condition in the population at risk. In the meantime, maintain a high index of suspicion for this condition in the elderly with poor exercise tolerance, shortness of breath and edema. ■

NON-ALCOHOLIC FATTY LIVER DISEASE (NFLD)

by Richard Rougeau, M.D.

In a previous edition of *Re-flections* (Vol. 12, Nov. 2003) I outlined an underwriting approach to elevated liver function tests (LFT). In this discussion I will further address mortality issues arising from "fatty liver" disease. In fact, after thorough investigation to rule out other causes of asymptomatic LFT elevations have been undertaken, it is estimated that primary fatty liver disease accounts for 90 percent of the remaining total. This would make it the most common cause of asympotmatic LFT elevations in the U.S.

A wide variety of medical terms are used to describe this disease entity: fatty liver hepatitis, diabetic hepatitis, alcohol-like liver disease, Laënnec's disease, and non-alcoholic steatohepatitis (NASH). More recent medical literature, however, prefers the term non-alcoholic fatty liver disease (NFLD). Accordingly, the remainder of this article will use NFLD to refer to a range of liver disorders from simple steatosis to steatohepatitis to advanced fibrosis up to and including cirrhosis. Each subset, however, will be highlighted in an attempt to further risk stratify as appropriate.

To elucidate the natural history of NFLD, mention must be made of three very significant clinically associated conditions. Studies of NFLD patients estimate the prevalence of obesity at 30 to 100 percent, type 2 diabetes mellitus at 10 to 75 percent, and hypercholesterolemia at 20 to 92 percent. Further to hypercholesterolemia, some studies have found hypertriglyceridemia to be a more significant risk factor in the development of NFLD. Other risk

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factors include a positive family history for NASH or cryptogenic cirrhosis with no consistently discernable race or sex-based predilection.

Regarding the epidemiology of NFLD, general population prevalence estimates from various countries range from 10 to 20 percent. One study estimates that NFLD affects 2.6 percent of children. Steatohepatitis is believed to affect 3 percent of lean individuals (weighing <110 percent of ideal body weight) and 19 percent of the obese population. Based on the U.S. population in 2000 it is estimated there are 30.1 million obese adults with steatosis and 8.6 million with steatohepatitis. These are likely significant underestimates of true prevalence, as many affected individuals are neither obese nor diabetic. Further, it is felt that the severity of NFLD may be synergistically enhanced by the occurrence of two or more of the following conditions in the same individual: obesity, diabetes, or hyperlipidemia. In any event, the magnitude of the NFLD epidemic appears to be much larger than hepatitis C, where it is believed that 1.8 percent of the U.S. population is chronically infected.

Clinical manifestations of NFLD are largely absent in the majority of individuals with the condition, although some will complain of fatigue, malaise or upper abdominal discomfort. An enlarged liver is often the only finding upon physical exam. Aminotransferase enzyme elevations (ASL/ALT) are commonly in a mild to moderate range. The AST/ALT ratio is usually less than 1.0 but can exceed this level where NFLD cirrhosis has become established. Other liver enzyme elevations such as Alkaline Phosphatase (AP) and Gamma-glutamyl-transferase (GGT) are often mildly elevated along with serum ferritin levels in approximately half of affected individuals. Both ultrasound (U/S) and computed tomography (CT) can be used to aid in diagnosis. With U/S, NFLD produces a diffuse increase in echogenicity of the liver as compared to the kidneys, but cirrhosis can have a similar appearance. CT scanning usually reveals a diffuse low density liver but NFLD can occasionally present as focally infiltrative and liver metastases therefore need to be ruled out.

Biopsy studies have shown that NFLD is histologically indistinguishable from alcohol-induced liver damage. The presence of features such as steatosis, mixed inflammatory cell infiltration, hepatocyte

TABLE 2: Grading and Staging the Histopathological Lesions of Nonalcoholic Fatty Liver Disease*

GRADING FOR STEATOSIS

Grade 1: <33% of hepatocytes affected

Grade 2: 33% to 66% of hepatocytes affected

Grade 3: >66% of hepatocytes affected

GRADING FOR STEATOHEPATITIS

Grade 1, mild

Steatosis: predominantly macrovesicular, involves up to 66% of lobules

Ballooning: occasionally observed; zone 3 hepatocytes

Lobular inflammation: scattered and mild acute inflamation (polymorphonucular cells) and occasional chronic inflammation (mononuclear cells)

Portal inflammation: none or mild

Grade 2, moderate

Steatosis: any degree; usually mixed macrovescular and microvesicular

Ballooning: obvious and present in zone 3

Lobular inflammation: polymorphonuculear cells may be noted in association with ballooned hepatocytes; pericellular fibrosis; mild chronic inflammation may be seen

Portal inflammation: mild to moderate

Grade 3, severe

Steatosis: typically involves >66% of lobules (panacinar); commonly mixed steatosis

Ballooning: predominantly zone 3; marked

Lobular inflammation: scattered acute and chronic inflammation; polymorphonuclear cells may be concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis

Portal inflammation: mild to moderate

STAGING FOR FIBROSIS

Stage 1: zone 3 perivenular, perisinusoidal, or pericellular fibrosis; focal or extensive

Stage 2: as above, with focal or extensive periportal fibrosis

Stage 3: bridging fibrosis, focal or extensive

Stage 4: cirrhosis

*Adapted from Brunt et al.

ballooning and/or necrosis, glycogen nuclei, Mallory's hyaline and fibrosis alone or in combination provides for a wide spectrum of histologic findings. The presence of fibrosis in any specimen tends to suggest more advanced liver injury. A biopsy-proven diagnosis of NASH is suggested by the presence of steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and spotty necrosis. A fairly recent development in this area concerns a proposed system of classification for NFLD based on stratifying the lesions of steatosis and necroinflammation into a grade, and extent of fibrosis into a stage (see Table 2).

The pathogenesis of NFLD remains hypothetical. The mechanisms that promote the transition from steatosis to NASH appear to involve multiple cellular adaptations to oxidative stress that arise from disordered fatty acid metabolism secondary to insulin resistance. Lipid retention (primarily triglycerides) within hepatocytes is considered essential for NFLD to develop. Why the disease remains limited to steatosis in the majority of NFLD affected individuals, while progressing to more serious conditions in others, remains a source of vigorous debate.

The clinical diagnosis of NFLD usually arises from asymptomatic elevations of hepatocellular enzyme levels, imaging studies suggestive of fatty liver, and — not infrequently — hepatomegaly. The clinical diagnosis and liver tests, however, have a poor predictive value with respect to gauging liver injury severity. This can only be accomplished by obtaining a liver biopsy. Individuals most likely to benefit from biopsy (and hence a more accurate prognosis) include those age 45 or older, obese, type 2 diabetic and with an AST/ALT ratio greater than 1.0. Other causes for the histologic findings — alcohol abuse, viruses, autoimmune responses, metabolic, genetic factors — need to be ruled out.

The natural history of NFLD, although not fully understood, appears related to the degree of histologic damage obtained from biopsy. In five series, 54 of 257 individuals with NFLD underwent serial liver biopsy during an average follow-up of 3.5 to 11 years. Within this group, 28 percent showed liver damage progression, 59 percent were considered stable and 13 percent showed improvement or resolution of histologic findings. Of note, progression through stages from steatosis to NASH to fibrosis and eventually cirrhosis has been documented in several instances. The likelihood of liver-related death appears to vary across the spectrum of severe liver injury as well. Poorer outcomes are associated with higher degrees of ballooning degeneration of hepatocytes, Mallory hyaline, fibrosis and the coexistence of hepatitis C.

It should be mentioned that the majority of studies examining the aspect of the natural history of NFLD have arisen from highly selected tertiary care referral centers where liver biopsy is frequently undertaken. It could be argued that large-scale population-based studies are likely to reveal a more benign course for the majority of affected individuals, as noted above.

In terms of clinical management of this condition, adherence to a program of lifestyle modification designed to promote good metabolic control and weight loss is recommended for those with metabolic syndrome X, diabetes mellitus or hyperlipidemia. As yet, no medications have proven beneficial independent of results achieved through weight loss. Medications such as gemfibrozil, vitamin E, metformin and ursodial have been shown to lead to reduction in liver enzyme levels and, in the case of ursodial, some histologic improvement as well. For those individuals who progress to end-stage liver disease and decompensated cirrhosis, liver transplant provides the only remaining therapeutic option.

NFLD constitutes a variety of liver-related illness throughout the world. Although its pathogenesis remains somewhat obscure, most individuals run a relatively benign course restricted to simple steatosis. A minority progress to steatohepatitis (NASH), to more advanced fibrosis and eventually decompensated cirrhosis. Liver biopsy remains the only valid means to gauge prognosis and base treatment decisions. Treatment remains limited with respect to lifestyle, and drug treatment may prove more beneficial in the future. For those who fail to respond to these more conservative measures, liver transplant may be necessary. ■

INFORMATION

Find current and past issues of *Re-flections* at www.rgare.com/media/re_flections.asp

REFERENCES

1 Roger, Veronique L, Weston, S, et al. “Trends in Heart Failure Incidence and Survival in a Community-Based Population.” *Journal of the American Medical Association* 21 Jul. 2004: 344–50.

2 Redfield, MM, Jacobsen, SJ, et al. “Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic.” *Journal of the American Medical Association* 8 Jan. 2003: 194–202.

3 Stainback, RF. “Congestive Heart Failure Arising From Diastolic Dysfunctino in the Left-Ventricular Systolic Function.” *Texas Heart Institute Journal* 1999; 26 (10): 34–41.

4 Gheorghiade, M, Bonow, R. “Chronic Heart Failure in the United States.” *Circulation* 1998; 97: 282–89.

Additional Reference

Zile, M, Brutsaert, Dirk. “New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part 1.” *Circulation* 2002; 105: 1387.