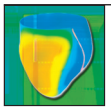

CHAPTER 1

The epidemiology of heart failure and commonly associated conduction disorders

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Introduction

Heart failure is a clinical syndrome resulting from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood commensurate with the needs of the body, or precludes it from doing so in the absence of increased filling pressures. This syndrome manifests primarily as dyspnea, fatigue, fluid retention, and decreased exercise tolerance. Heart failure may result from disorders of the pericardium, myocardium, endocardium or valvular structures, great vessels of the heart, or rhythm disturbances. However, because valvular disease, pericardial disorders, and rhythm disturbances are usually easily amenable to effective surgical correction or other definitive treatment, heart failure is usually discussed primarily in terms of myocardial dysfunction.

From a practical standpoint, it is useful to divide patients with heart failure into those with primarily systolic dysfunction and those with diastolic dysfunction, which usually involves an assessment of the patient's ejection fraction. Patients with a low left ventricular (LV) ejection fraction, usually < 40–45%, are classified as having systolic dysfunction. Such patients typically have dilatation of the LV cavity and a decreased cardiac output on the basis of diminished contractility of the myocardium. In contrast, patients with symptoms and exam findings consistent with heart failure but with a preserved ejection fraction are often said to have diastolic dysfunction, which is typically a disease of impaired ventricular filling.

Heart failure is a final common pathway of all diseases of the heart and is a major cause of morbidity and mortality. Approximately 4.9 million Americans carry the diagnosis of heart failure [1] and about 550 000 new cases occur each year in the USA [2]. Hospital discharges for heart failure in the USA have increased 155% between 1979 and 1999 to 962 000 per year [3]. Heart failure accounts for about 5% of annual hospital admissions, with more than 100 000 annual admissions in the UK and more than 2.5 million annual admissions in the USA [4, 5]. Reports from several countries suggest that approximately 1–2% of the total healthcare budget is spent on the management of heart failure [6]. Yet, despite recent advances in the treatment of heart failure, the prognosis remains poor, with mortality data that are comparable with data for the worst forms of malignant disease.

Epidemiology of heart failure

Prevalence of heart failure

Population-based studies in heart failure are difficult to compare because of a lack of agreement on the definition of the disease from study to study. Studies investigating the prevalence of heart failure can generally be divided into those population studies based on physician records and prescriptions, studies based on clinical criteria, and those based on

Cardiac Resynchronization Therapy, 2nd edition. Edited by Cheuk-Man Yu, David L. Hayes and Angelo Auricchio. © 2008 Blackwell Publishing, ISBN: 978-1-4051-7739-9.

echocardiographic surveys. Not surprisingly, prevalence data may differ depending on the method of identifying subjects with disease. Likewise, data can vary widely in inpatient and outpatient population studies. Nonetheless, efforts to identify prevalence have helped to shed light on the magnitude of the problem and elicited several trends in the etiology of the syndrome of heart failure.

Population studies based on physician records and prescriptions

Among the more recent reports, residents of Rochester, Minnesota were screened for the diagnosis of heart failure in January 1982, using the resources of the Rochester Epidemiology Project. The age- and sex-adjusted prevalence was reported at 265.8 per 100 000 person-years. The prevalence rate was higher in men vs. women (327.3 vs. 213.6 per 100 000 person-years) and tended to increase with age. For example, rates increased from 74.4 per 100 000 among men 45–49 years old to 2595.5 per 100 000 among those 65–69 years old and 2765 per 100 000 among those 70–74 years old. A similar trend was seen among women (72.6 per 100 000 in those 45–49 years, increasing to 2743.8 per 100 000 among those 70–74 years) [7].

The Resource Utilization Among Congestive Heart Failure (REACH) study derived the incidence and prevalence of heart failure among 29 686 patients who had acquired an International Classification of Diseases (ICD) code for heart failure during an inpatient or two outpatient encounters within the Henry Ford Health System in Detroit, Michigan. In 1999, the age-adjusted prevalence of heart failure was found to be 14.5 per 1000 in men and 14.3 per 1000 in women. The higher prevalence of heart failure in this population may be attributable to the higher proportion of inpatients included in this study [8].

More recently, an extensive survey of the incidence and prevalence of heart failure in Scotland was carried out between April 1999 and March 2000. Using the continuous morbidity recording (CMR) in general practice scheme, data were collected from every face-to-face doctor–patient encounter for a total of 307 741 patients from 53 medical practices. Patients were identified by diagnostic codes for heart failure. The prevalence of heart failure among men aged 45–64 years of age was 4.3 per 1000 and 134 per 1000 in those over 85 years, again confirming the strong link between heart failure and increasing age. A similar trend was seen in women, in whom the prevalence rose from 3.2 in those 45–64 years to 85.2 in those over 85 years [9].

Population studies based on clinical criteria

Additional population studies involved clinical encounters with each study subject. Heart failure was identified based on various historical, physical exam, and laboratory findings. Among the best-known population studies, the Framingham Heart Study, for example, was a landmark longitudinal effort that established strict clinical criteria for diagnosing heart failure; the natural history of the disease in a defined population has been reported and has now been followed for over 50 years. The Framingham Heart Study was initiated in 1948 for the purpose of eliciting the etiology and natural history of cardiovascular diseases. Initially, 5209 residents between the ages of 30 and 62 years from Framingham, Massachusetts were enrolled in the study and followed for the development of cardiovascular disease with medical histories, physical exams, and laboratory tests every 2 years. Children and spouses of children of the original cohort were added to the study in 1971. A total of 9405 participants (47% male) were followed from September 1948 to June 1988. Heart failure developed in a total of 652 patients. The prevalence of heart failure was found to dramatically increase with age, such that in men the prevalence jumped from 8 cases per 1000 patients in those aged 50–59 years to 66 cases per 1000 in those aged 80–89. Likewise in women, the prevalence increased from 8 cases per 1000 in those aged 50–59 to 79 cases per 1000 in those aged 80–89. During the 1980s, the age-adjusted prevalence of heart failure was 7.4 cases per 1000 men and 7.7 cases per 1000 women [10, 11].

Another study carried out between 1960 and 1962 looked at 3102 residents from Evans County, Georgia between the ages of 40 and 74 years for whom medical histories, physical exams, ECGs, and posterolateral chest X-rays were carried out as part of an epidemiologic survey. This study found a prevalence of 10 cases of heart failure per 1000 in residents aged 45–54 years, 28 cases per 1000 in those aged 55–64 years, and 35 cases per 1000 in those aged 65–74 years. The overall prevalence

among all residents aged 45–74 years was 21 cases per 1000 [12].

In 2004, an update of the Rotterdam Study was published, giving a current account of the prevalence of heart failure in this population. The Rotterdam Study was a prospective cohort study of various cardiovascular, neurological, and ophthalmologic diseases in the elderly. A total of 7983 inhabitants of Ommoord (a suburb of Rotterdam in the Netherlands) who were aged 55 years or older were enrolled between July 1989 and 1993 and followed clinically until January 2000. The 1998 point prevalence of heart failure was 0.9% in subjects aged 55–64 years, 4% in those aged 65–74 years, 9.7% in those aged 75–84 years, and 17.4% in those over the age of 85, again confirming the steep increase in the prevalence of heart failure with age [13].

Population studies based on clinical and echocardiographic criteria

To examine further the nature and prevalence of heart failure in the elderly population, the Helsinki Ageing Study examined a randomly selected population of 501 Helsinki residents (367 females) who were born in 1904, 1909, and 1914 (aged 75–86 years). Heart failure was diagnosed on the basis of clinical criteria obtained by cardiologic assessment, including history, physical exam, ECG, and posterolateral chest X-ray. Participants also had a transthoracic echocardiogram to assess systolic and diastolic dysfunction. Of those enrolled in the study, 41 (8.2%) were diagnosed with heart failure. However, only 28% of these patients were found to have systolic dysfunction (defined as fractional shortening $< 25\%$ and LV dilatation). The remainder had diastolic dysfunction or a preserved ejection fraction. The overall prevalence of LV systolic dysfunction in symptomatic and asymptomatic patients was 10.8% [14].

In 1997, a subset analysis of 1980 patients in the Rotterdam Study who had undergone echocardiographic study was published. Impaired LV function, defined as fractional shortening $< 25\%$ (comparable to a LV ejection fraction of 42.5%), was reported in 3% of these subjects. Consistent with previous studies, the prevalence of LV systolic dysfunction was higher in those aged over 70 years (4.2%) [15].

Later, the EPICA (EPidemiologia da Insuficiência Cardiaca e Aprendizagem – Epidemiology of Heart Failure and Learning) study was performed to estimate the prevalence of heart failure in mainland Portugal. Between April and October 1998, 551 patients (208 males, 343 females) out of a total 5434 subjects enrolled from various healthcare centers in the community were identified as having heart failure by a combination of clinical and echocardiographic criteria. Echocardiographic evidence of LV dysfunction was defined by LV fractional shortening below 28%, evidence of LV hypertrophy and/or chamber enlargement, moderate to severe valvular disease, or moderate to severe pericardial effusion. The estimated prevalence of all types of heart failure was 1.36% in those aged 25–49, 12.67% in ages 70–79, and 16.14% in those over 80 years of age. About 40% had preserved LV function, or a normal ejection fraction [16].

More recently, the residents of Olmstead County, Minnesota were studied to determine the prevalence of heart failure by American Heart Association/American College of Cardiology staging classification. Between January 1997 and September 2000, a total of 2029 residents ≥ 45 years of age were enrolled and underwent medical record review, symptom questionnaire, physical examination, and echocardiogram. Patients were then classified by heart failure stage, with normal patients being stage 0; patients in stage A having risk factors but no clinical evidence of heart failure; stage B consisting of asymptomatic patients with cardiac structural or functional abnormalities; stage C including patients with symptomatic heart failure; and stage D representing end-stage heart failure. A total of 640 persons (31.5%) were normal by these criteria. Another 454 (22.4%) were stage A, 691 (34.1%) were stage B, 239 (11.8%) were stage C, and 5 (0.2%) were stage D [17].

Table 1.1 summarizes the prevalence of heart failure as estimated from various population-based studies.

Over the past decade, there has been a significant rise in the prevalence of heart failure. In the REACH study, for example, the prevalence rose from 3.7 per 1000 and 4.0 per 1000 in women and men, respectively, to 14.3 and 14.5 per 1000 between 1989 and 1999 [8]. This is probably mainly attributable to the increasing proportion of elderly people in the population, as these individuals have the highest incidence of coronary artery disease and hypertension,

Table 1.1 Prevalence of heart failure

Study	*Location*	*Study date*	*Overall prevalence rate*	*Prevalence rate in older population*
Physician records/prescriptions				
Rodeheffer *et al.* [7]	Rochester, US	1981–1982	3/1000	–
REACH [8]	Southeast Michigan, US	1999	14.3/1000 (women) 14.5/1000 (men)	–
Murphy *et al.* [9]	Scotland	April 1999 to March 2000	7.1/1000	90.1/1000 (>85 years)
Clinical criteria				
Framingham [10, 11]	Framingham, US	1980–1989	7.7/1000 (women) 7.4/1000 (men)	79/1000 (80–89 years) 66/1000 (80–89 years)
Garrison *et al.* [12]	Georgia, US	1960–1962	21/1000	35/1000 (65–74 years)
Echocardiographic and clinical criteria				
Helsinki [14]	Helsinki, Finland	1990–1991	–	82/1000 (75–86 years)
Rotterdam [15]	Ommoord, Netherlands	1997	30/1000 (>55 years)	42/1000 (>70 years)
EPICA [16]	Portugal	1998	12.9/1000 (systolic dysfunction)	~30/1000 (>80 years)

which are strongly correlated with the development of heart failure. In addition, the survival in those patients with coronary artery disease is improving. As myocardial infarction is the most powerful risk factor for heart failure, it follows that increasing survival after myocardial infarction may lead to a higher prevalence of heart failure later in life. Improving mortality rates among patients with heart failure may also be playing a role [18].

Incidence of heart failure

Information on the incidence of heart failure and the change over time is much more limited than prevalence data. Results of some of the various studies on the incidence of heart failure are summarized in Table 1.2.

Similar to the prevalence data, several studies have documented the rising incidence of heart failure with age. The Framingham Heart Study, for example, showed that the annual incidence increased from 3 cases per 1000 in men aged 50–59 years to 27 cases per 1000 in men aged 80–89 years. A similar increase, from 2 to 22 cases per 1000 in the same age brackets, was seen among women. Furthermore, the incidence of heart failure was found to be one-third lower in women than men after adjustment for age. During the 1980s, the age-adjusted annual incidence of heart failure was 2.3 and 1.4 cases per 1000 in men and women, respectively [11].

Likewise, the Rotterdam study showed a jump in the incidence rate of heart failure from 1.4 cases per 1000 in those aged 50–59 to 47.4 per 1000 in those 90 years or older. The overall incidence of heart failure was 14.4 per 1000 person-years and was significantly higher in men (17.6 per 1000 man-years) compared with women (12.5 per 1000 woman-years) [13]. These age and gender trends were confirmed in a study of incident cases of heart failure in Olmstead County, Minnesota in 1991 [19] and another study of 696 884 people in a general practice population in the UK [20].

Of great debate recently is whether the incidence of heart failure is decreasing in response to advances in medical treatment for heart failure. Data from the Framingham Heart Study were published in 2002 and suggested that over the last 50 years the incidence of heart failure amidst a cohort of 10 311 subjects has declined among women but not among men. In men, for example, the age-adjusted incidence of heart failure from 1950 to 1969 was 627 cases/100 000 person-years (95% confidence interval (CI) 475 to 779), compared with 564 (95% CI 463 to 665) cases/100 000 person-years between 1990 and 1999 (rate ratio 0.93, 95% CI 0.71 to 1.23).

Table 1.2 Incidence of heart failure

Study	*Location*	*Study date*	*Overall incidence rate*	*Incidence rate in older population*
Framingham [10, 11]	Framingham, US	1980–1989	2.3/1000 (men)	27/1000 (men ≥80 years)
			1.4/1000 (women)	
			22/1000 (women ≥80 years)	
Rodeheffer *et al.* [7]	Minnesota, US	1981–1982	1.6/1000 (men)	9.4/1000 (men 70–74 years)
			0.7/1000 (women)	9.8/1000 (women 70–74 years)
Senni *et al.* [19]	Minnesota, US	1991	2/1000	
De Giuli *et al.* [20]	UK	1991	9.3/1000	45/1000 (≥85 years)
Rotterdam [13]	Ommoord, Netherlands	1997–1999	17.6/1000 (men ≥55 years)	47.4/1000 (≥90 years)
			12.5/1000 (women ≥55 years)	
Roger *et al.* [1]	Minnesota, US	1979–2000	3.8/1000 (men)	
			2.9/1000 (women)	

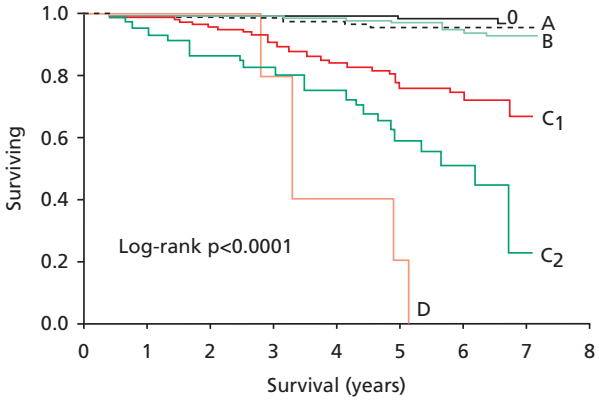
In contrast, for women the age-adjusted incidence of heart failure fell from 420 cases/100 000 person-years (95% CI 336 to 504) to 327 cases/100 000 person-years (95% CI 266 to 388, rate ratio 0.69 [95% CI 0.51 to 0.93]) over the same period [2]. However, a recent population-based cohort study conducted in Olmstead County, Minnesota was not able to corroborate these findings. Among 4537 residents (57% women, mean age 74 years) with a diagnosis of heart failure identified between 1979 and 2000, the incidence of heart failure did not change over time in either gender [1].

Mortality of heart failure

The mortality of heart failure is alarmingly high. Data derived from the Framingham cohort published in 1993, for example, suggested that the overall 1-year survival rates in men and women were 57% and 64%, respectively. The overall 5-year survival rates were 25% in men and 38% in women [21]. In comparison, 5-year survival for all cancers among men and women in the USA during that same period was about 50% [11]. Survival tends to be better in women. Furthermore, the mortality of heart failure seems to increase with age. For example, a Scottish study examining 66 547 patients admitted with heart failure between January 1986 and December 1995 reported the 30-day mortality rate in patients < 55 years of age to be 10.41% and the 5-year mortality rate to be 46.75%. In contrast, the 30-day and 5-year mortality in patients 75–84 years of age was 22.18% and 88%, respectively [22]. Recent data from Ammar *et al.* also stress the importance of heart failure stage as a powerful predictor of mortality, as 5-year survival decreased from 97% in stage A to 20% in stage D (see Fig. 1.1) [17].

Role of atrial fibrillation

Of increasing interest is the contribution of atrial fibrillation to outcomes in patients with heart failure. Both conditions are responsible for substantial economic cost, morbidity, and mortality. These conditions also tend to disproportionately affect the elderly, the incidence of each doubling for every successive decade of age [23]. Thus, the burden associated with these disorders is expected to increase as the population ages. An important feature of atrial fibrillation and heart failure is their propensity to coexist, in part because they share antecedent risk factors but also because one may directly predispose to the other. Various studies have estimated that the prevalence of atrial fibrillation in patients with heart failure is about 15–30% over the course of their disease. Data from the Framingham Heart

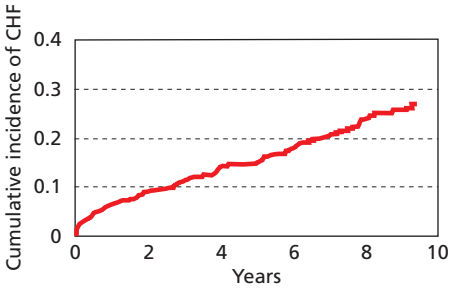


No. at risk	0	640	640	639	637	635	454	218	34
Stage	A	454	453	451	449	446	322	133	22
	B	691	687	685	677	673	475	239	29
	C_1	195	193	197	178	166	114	54	5
	C_2	44	42	38	36	33	18	8	1
	D	5	5	5	4	2	1	0	0

Figure 1.1 Survival curves according to heart failure stage. Reproduced from [17] with permission.

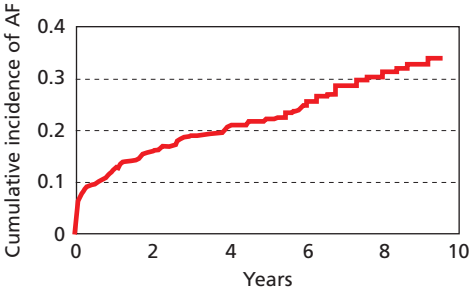
Study suggest that for those aged 40 years and older, the lifetime risk of atrial fibrillation is approximately one in four for both men and women. After exclusion of patients with pre-existing or concurrent heart failure, this risk was reduced by 5–6%. Analysis of only patients without antecedent or concurrent heart failure or myocardial infarction, reduced the lifetime risk of atrial fibrillation still further, to about 16% [24]. Of the participants in the Framingham Heart Study, 1470 developed atrial fibrillation, heart failure or both. Among 382 individuals with both conditions, 38% had atrial fibrillation first, 41% had heart failure first, and 21% had both diagnosed on the same day. The incidence of heart failure among atrial fibrillation subjects was 33 per 1000 person-years, and the incidence of atrial fibrillation among heart failure subjects was 54 per 1000 person-years (see Figs 1.2 and 1.3) [25].

It is widely perceived that the combination of these conditions carries a worse prognosis than either alone. The data on the joint prognosis of atrial fibrillation and heart failure are conflicting, however. For example, the Valsartan Heart Failure Trial (V-HeFT) investigators failed to show an increase in major morbidity or mortality among patients with mild–moderate heart failure and atrial fibrillation compared to those patients with sinus rhythm [26]. Likewise, Mahoney *et al.* concluded that atrial fibrillation in patients with advanced (NYHA class III or



No. at risk	683	454	360	250	171	120

Figure 1.2 Unadjusted cumulative incidence of first episode of heart failure in individuals with atrial fibrillation. Reproduced from [32] with permission.



No. at risk	708	323	230	146	92	62

Figure 1.3 Unadjusted cumulative incidence of first episode of atrial fibrillation in individuals with heart failure. Reproduced from [32] with permission.

IV) heart failure is not associated with decreased event-free survival in their study of 234 consecutive patients referred for heart transplant [27].

The majority of evidence, however, indicates that atrial fibrillation in patients with heart failure carries a poor prognosis, and recent efforts have focused on the identification of subsets of patients at greater risk. One study, for example, looked at 390 consecutive patients with advanced heart failure (45% ischemic, 55% non-ischemic) and a mean LV ejection fraction (LVEF) of 19% ± 7%. Of the 75 patients (19%) with paroxysmal or chronic atrial fibrillation, actuarial survival was significantly worse compared with those patients with sinus rhythm (52% vs. 71%, $P = 0.0013$). Sudden death-free survival was also lower in the atrial fibrillation group (69% vs. 82%, $P = 0.0013$) [28]. Among patients enrolled in the SOLVD Prevention Trial (mostly asymptomatic patients with LVEF ≤ 35%) and SOLVD Treatment Trials (symptomatic heart failure patients with LVEF ≤ 35%), atrial fibrillation was also associated with poorer prognosis. In a combined analysis of patients in both trials, patients with atrial fibrillation suffered greater all-cause mortality (34% vs. 23%, $P < 0.001$), death attributed to pump failure (16.7% vs. 9.4%, $P < 0.001$), and were more likely to reach the composite end-point of death or hospitalization for heart failure (45% vs. 33%, $P < 0.001$) [29] compared to those with sinus rhythm. Likewise, the Framingham Heart Study demonstrated increased mortality among patients with atrial fibrillation who developed heart failure and also among patients with heart failure who subsequently developed atrial fibrillation [24].

Patients with atrial fibrillation and heart failure seem to have a high mortality regardless of their underlying LV function. A retrospective study, for example, found that of 478 consecutive patients who presented to the emergency department with a diagnosis of atrial fibrillation and heart failure and had an assessment of LVEF, 218 (46%) had preserved LV function (LVEF ≥ 50%). At 5 years, mortality was similar between the preserved and depressed EF groups (50% vs. 48%, $P = 0.74$) [30]. Analysis of patients enrolled in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity (CHARM) program confirmed that atrial fibrillation carries an increased risk of adverse cardiovascular outcomes in patients with heart failure and either reduced (≤ 40%) or preserved (> 40%) LVEF. In fact, atrial fibrillation was associated with higher all-cause mortality in the group with preserved ejection fraction compared to those with low ejection fraction (HR 1.8, 95% CI 1.46 to 2.21 compared with HR 1.38, CI 1.21 to 1.59) [31]. As more data on the prognostic significance of atrial fibrillation in heart failure continue to amass, efforts to reduce the mortality of heart failure are increasingly focusing on medical and mechanical therapies to treat or prevent atrial fibrillation in such patients.

On other fronts, there is evidence to suggest that with the advent of improved medical therapies, survival in patients with heart failure may be improving. Among subjects in the Framingham Heart Study cohort, for example, the 30-day, 1-year, and 5-year age-adjusted mortality rates among men declined from 12%, 30%, and 70%, respectively, in the period from 1950 to 1969 to 11%, 28%, and 59%, respectively, in the period from 1990 to 1999. The corresponding rates among women were 18%, 28%, and 57% for the period from 1950 to 1969 and 10%, 24%, and 45% for the period from 1990 to 1999. Overall, there was an improvement in the survival rate after the onset of heart failure of 12% per decade [2]. These data were corroborated by a study conducted in Olmsted County, Minnesota in which the 5-year age-adjusted survival was found to be 43% during the period from 1979 to 1984 compared with 52% in the period from 1996 to 2000 [1]. Data from Owan *et al.* suggest that this reduction in mortality over time may apply only to patients with reduced ejection fraction, for although the prevalence of heart failure with preserved ejection fraction increased over the 15-year period studied, the rate of death in those with preserved LV function remained unchanged [32].

Though the reasons for the decline in heart failure mortality over time are not completely understood, the advent of improved medical therapies has almost certainly played a central role. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and aldosterone antagonists, for example, have significantly reduced mortality and morbidity in New York Heart Association (NYHA) class II–IV patients while improving their quality of life [31, 33, 34]. The benefits of drug therapy are limited, however, and despite

aggressive medical treatment for heart failure many are left with grave debilitation. This has engendered great interest in a variety of non-pharmacologic treatments for patients with drug-refractory heart failure. Heart transplant remains the best solution, but it can only be applied to a restricted number of patients and the supply of donor hearts is limited. Thus investigation has continued, searching for other therapies to improve symptoms and/or survival in patients with end-stage cardiomyopathies.

Role of pacing-induced dyssynchrony

When first introduced, pacemakers were simply life-saving devices. With the advance in our understanding of cardiac physiology during artificial pacing, there is an appreciation that inappropriate right ventricular (RV) pacing may not only have a mechanical deleterious effect but may also ultimately increase morbidity and mortality.

In 1925, Wiggers [35] first demonstrated acute LV dysfunction from RVA pacing in animals, subsequently shown to result from slower transmyocardial conduction as opposed to the normally rapid ventricular activation seen during sinus rhythm or atrial pacing in the setting of intact atrioventricular (AV) nodal–Purkinje conduction [36]. Myofibrillar disarray [37] and increases in intramyocardial catecholamine concentrations [38] have also been observed in association with RV apical pacing.

Early studies in humans demonstrated pacing-induced cardiac dyssynchrony as assessed by radionuclide angiography, resulting in a deterioration in cardiac performance [39]. These findings have been substantiated by recent studies further examining the effects of RVA pacing on LV function. One study from 2001 looked at 24 patients ranging in age from 3.8 to 34.6 years (mean 19.5 ± 8.1 years) with normal LV function who were paced from the RV apex for heart block or sinus node dysfunction and compared them with 33 age-matched control subjects. Duration of RV apical pacing ranged from 0.7 to 18.9 years (median 10 years). Pacing was programmed as VVI in 15 patients and DDD in 9 patients. The majority (23 of 24) were 100% ventricularly paced at the time of evaluation. Assessment of LV function after a median follow-up of 10 years demonstrated impaired area- and Doppler flow-derived indexes of LV systolic and diastolic function compared with control patients. Paced QRS interval and age were found to significantly influence global LV contraction in these patients [40].

Another study examined 44 consecutive patients with symptomatic moderate–severe heart failure (ejection fraction $30 \pm 13\%$) who underwent dual-chamber defibrillator implant at a single institution. Mean age was 64 ± 11 years and 82% were men. Comparison was made between patients continuously RVA paced after implantation (DDD or VDD mode) and those that were not (intrinsic conduction). After implant, 25 patients (57%) were noted to be RVA paced whereas 19 (43%) were not. Preimplant QRS durations were normal (< 120 ms) in 12 of the 25 patients (48%) in the paced group and in 13 of 19 (68%) of the non-paced group ($P = 0.2$). After implant a wide QRS (≥ 120 ms) was present in 52% of the paced group and 32% of the non-paced group. Symptom worsening occurred in 11 of the 25 paced patients (44%) but only 1 of the 19 non-paced patients (5%). Three patients in the paced group (12%) experienced severe worsening of heart failure symptoms requiring hospitalization and intravenous inotropic support. This symptomatic deterioration was reversed after reprogramming the device to back-up VVI pacing mode, thus allowing intrinsic conduction. Patients with right bundle branch block (RBBB) or normal QRS at baseline who received RVA pacing after implantation had a higher incidence of worsening heart failure than those who were not paced ($P < 0.001$) [41].

In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial, 506 implantable cardioverter defibrillator (ICD) patients with depressed cardiac function were randomized to DDDR pacing at a relatively short AV interval vs. ventricular backup pacing at 40 beats per minute (bpm). Increased RVA pacing observed in the former group was associated with a significantly higher incidence of new or worsened heart failure. The 1-year survival, free of the composite end-point of death or first hospitalization for heart failure, was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard 1.61; 95% CI 1.06 to 2.44) [42]. Further analysis demonstrated that per cent RVA pacing was predictive of the outcome of death or heart failure hospitalization [43].

The Mode Selection Trial (MOST) randomized 2010 sinus node dysfunction patients to dual cham-

ber vs. RVA pacing and found a reduction in signs and symptoms of heart failure in the dual-chamber patients [44]. When Sweeney *et al.* subsequently examined a subset of 1339 MOST study patients with a normal baseline QRS duration, however, they found that a higher cumulative per cent RVA paced rhythm was strongly predictive of heart failure hospitalizations and atrial fibrillation, regardless of whether these patients were programmed to DDDR or VVIR pacing [45]. Subsequently, they reported that post-implantation QRS duration (QRSd) was also a strong predictor of heart failure hospitalizations (HFH). The risk of HFH increased incrementally with increasing QRSd, independent of whether the prolonged QRSd occurred spontaneously or as a result of RVA pacing [46]. The association of prolonged QRSd with worsening heart failure in paced patients is probably a reflection of electrical asynchrony and slow myocardial conduction which, in turn, leads to significant inter- and intraventricular dyssynchrony. Although RVA pacing results in a LV activation sequence resembling left bundle branch block (LBBB), the implications and prognosis are not necessarily the same. Sweeney *et al.*, for example, reported that the risk of HFH was always about twofold higher for any given value of prolonged QRSd that occurred spontaneously vs. that resulting from RVA pacing [44].

Indeed, a wide QRS complex is frequently observed in patients with chronic heart failure associated with LV systolic dysfunction and has been associated with a significantly higher mortality in this population. As with RVA pacing, this is probably partly owing to the deleterious effects that intraventricular conduction delay (IVCD) has on both systolic function and LV filling, as well as its propensity to aggravate functional mitral regurgitation. Together, these factors have made IVCD an attractive target for heart failure therapy.

Epidemiology of intraventricular conduction delay

Data on the prevalence and prognosis of IVCD, manifesting as either RBBB or LBBB, are difficult to compare, as patient populations (and associated comorbidities) vary widely from one study to another. Nevertheless, taken collectively, these studies suggest that IVCD in the general population becomes more common with advancing age and is often associated with hypertension, diabetes, coronary artery disease, or cardiomegaly; heart failure is also often found. As a frequent marker of underlying cardiovascular disease, both LBBB and RBBB have been shown to be associated with higher mortality, though the data on mortality with BBB in the general population are conflicting.

Intraventricular conduction delays are much more common in patients with heart failure, and in this setting carry a much more ominous prognosis. Several studies have documented the link between IVCD and symptomatic heart failure and have identified a trend between progressive widening of the QRS interval and higher mortality.

Prevalence of intraventricular conduction delay

Table 1.3 summarizes some of the various studies on the prevalence of IVCD.

The prevalence of IVCD in the general population is fairly low, but seems to increase with age. Both points are illustrated in a study of the community of Tecumseh, Michigan undertaken between 1959 and 1960. Subjects ranged in age from 16 to >80 years. In this cohort, the prevalence of BBB was found to be quite low. Of 8541 subjects, 18 (12 women, 6 men) were found to have LBBB (0.2%) and 18 (6 women, 12 men) were found to have RBBB (0.2%). Over 67% of those with BBB were older than 67 years [47]. The relatively low frequency of BBB in a healthy population was again seen in a study by Rotman *et al.*, looking at a series of over 237 000 ECGs on US Air Force flying personnel or training applicants. The prevalence of RBBB and LBBB was 0.16% (394 men) and 0.05% (125 men), respectively [48].

Edmands, who looked at BBB in a retirement community of residents over the age of 52 in Seal Beach, California found the prevalence of BBB to be 3.7% (57 out of 1560 patients). Nineteen residents (1.2%) had LBBB (8 men, 11 women) and another 38 residents (2.4%) had RBBB (24 men, 14 women). A total of 18 (94.7%) of those with LBBB and 32 (84%) of those with RBBB were 65 years or older, again confirming the association of IVCD with increasing age. About 50% of those with LBBB had cardiomegaly on chest X-ray compared with 16% of controls [49]. The prevalence of BBB was slightly

Table 1.3 Prevalence of intraventricular conduction delay

Study	*Location*	*Study date*	*Overall prevalence rate*	*Prevalence rate in older population*
In the general population:				
Ostrander [25]	Michigan, US	1959–1960	2/1000 (RBBB) 2/1000 (LBBB)	RBBB: 29/1000 (≥60 years) LBBB: 6/1000 (≥60 years)
Rotman and Triebwasser [26]	Texas, US	1957–1972	1.6/1000 (RBBB) 0.5/1000 (LBBB)	–
Edmands [27]	California, US	1962–1966	–	RBBB: 24/1000 (≥52 years) LBBB: 12/1000 (≥52 years)
Study of Men Born 1913 [28]	Goteborg, Sweden	1963–1993	7/1000 (RBBB) 4/1000 (LBBB)	RBBB: 113/1000 (80 years) LBBB: 57/1000 (80 years)
In patients with heart failure:				
Shanim *et al.* [32]	London, UK	1993–1996	369/1000 (QRS>120 ms)	–
IN-CHF [31]	Italy	1995–2000	61/1000 (RBBB) 252/1000 (LBBB)	–

LBBB, left bundle branch block; RBBB, right bundle branch block.

higher in another study of the population of men born in 1913. Of 855 men examined, 82 (9.6%) had BBB. The prevalence of BBB increased from 1% at age 50 years to 17% at age 80 [50].

In contrast, the prevalence of IVCD among patients with heart failure has been found to be markedly higher than in the general population. In a study of 34 patients with serial ECGs performed before death secondary to necropsy-proven idiopathic dilated cardiomyopathy, for example, 13 (38%) were found to have BBB. Of these 13 patients, 10 had LBBB [51]. Later, Xiao *et al.* examined the prevalence of IVCD in 58 patients with dilated cardiomyopathy. A QRS duration of >160 ms was seen in 19 (33%) of these patients [52]. Another study of 5517 patients with heart failure selected from the Italian Network on CHF (IN-CHF) registry between 1995 and January 2000 also demonstrated a high prevalence of IVCD in heart failure patients. A total of 1391 patients (25.2%) were found to have complete LBBB; 336 (6.1%) had complete RBBB. Other forms of IVCD were diagnosed in 339 (6.1%) of patients [53]. An additional study examined 241 patients with systolic heart failure admitted to the Royal Bromptom Hospital between July 1993 and March 1996. From these 241 patients, 89 (37%) were diagnosed with IVCD (defined as QRS duration >120 ms). Of these, 52 had a QRS duration of 120–160 ms, and the remaining 37 had a QRS >160 ms [54].

Prognosis of intraventricular conduction delay

The mortality data on IVCD among the general population is somewhat conflicting. Smith *et al.*, for example, who looked at 29 naval aviators whose ECGs changed from a normal pattern to that of a BBB, found no significant increase in mortality when compared with a control cohort of 666 men [55]. Likewise, in the study of men born in 1913, there was no correlation found between the development of BBB and either (1) risk factors for coronary artery disease at age 50 years, (2) incidence of myocardial infarction during follow-up, or (3) cardiovascular deaths [50].

The Framingham Study, however, found a significant correlation between LBBB and increased mortality and the development of heart disease. A total of 55 people (31 men, 24 women) who developed LBBB after the initial study examination were identified among the 5209 people enrolled. Before the onset of LBBB, case subjects had a statistically significant excess of most of the designated

cardiovascular abnormalities (65% had hypertension, 44% had cardiomegaly on chest X-ray, 20% had known coronary artery disease; only 27% had no cardiovascular disease). One-third of those case subjects who were free from clinical coronary disease before the onset of LBBB developed one of its manifestations coincident with or after the first appearance of LBBB. At each 2-year interval after the onset of LBBB the cumulative mortality rate from cardiovascular disease was approximately five times greater in the case subjects than in controls. About 50% of those with LBBB died of cardiovascular disease within 10 years of onset of LBBB, compared with only 11.6% of similar-aged controls. After correcting for the influence of diabetes, systolic blood pressure, age, coronary artery disease, and heart failure, the relationship between LBBB and risk of cardiovascular mortality was still statistically significant in men (but not women) [56].

Likewise, in a study of 146 patients with LBBB who had been admitted to the University of Kansas Medical Center or Kansas City Veterans Administration Hospital between 1954 and 1963, the average duration of survival after the conduction disturbance had been diagnosed was 36 months [57]. Similar survival data (3.3 years) were found in a study of 555 patients with LBBB who had been admitted to the Massachusetts General Hospital between 1937 and 1948. Almost one-half of the case subjects in this study whose QRS duration exceeded 160 ms had marked cardiac enlargement. Heart size correlated to survival; patients without cardiac enlargement survived 4.3 years compared with 2.5 years in those with marked cardiomegaly. A total of 429 patients (77%) had either hypertension, coronary artery disease, or both. Of the 357 deaths that had occurred at the end of the study, 255 (71%) were attributed to heart disease, with the majority having either heart failure or myocardial infarction [58]. The higher mortality and stronger association of LBBB with cardiovascular disease is perhaps a reflection of bias imposed by selecting an inpatient population with clinical indication for ECG.

In patients with cardiomyopathy, strong evidence exists to suggest that LBBB is associated with a significantly higher mortality. In the study by Xiao and his colleagues, for example, a QRS duration of >160 ms was found in 8 of 10 patients who died (80%), but only 5 of the 39 stable patients (12.8%). QRS duration tended to widen over time [52]. Another study by Shamim *et al.* took 241 heart failure patients and divided them into three groups: those with QRS <120 ms, those with QRS 120–160 ms, and those with QRS duration exceeding 160 ms. All patients were then followed to determine their 36-month mortality rates. Of the 141 patients with QRS <120 ms, 27 (20%) had died at 36 months, compared with 18 of 52 patients (36%) with QRS 120–160 ms and 19 of 37 patients (58.3%) with IVCD of >160 ms. Thus, IVCD was shown to have negative prognostic value in patients with heart failure, with a stepwise increase in mortality as a graded increase in the IVCD occurs [34]. The deleterious effect of LBBB was further demonstrated in a study of patients with heart failure from the IN-CHF registry. Of the 659 patients (from a total 5517 enrolled, 11.9%) who died during the 1-year follow-up period, the 1-year all-cause mortality rate for patients with LBBB was 16.1% (224 of 1391). This rate was 11.9% (40 of 336) for patients with RBBB. All-cause mortality and mortality rates as the result of sudden death were significantly greater among patients with LBBB. Increased mortality rates were not seen in patients with RBBB [53, 59].

In summary, LBBB results in significant intraventricular (LV) and interventricular dyssynchrony. Clinical consequences include significant impairment in systolic and diastolic function and functional mitral regurgitation. Dyssynchrony decreases cardiac efficiency and increases sympathetic activity. In patients with normal LV function, these changes are generally well tolerated. In patients with severe LV dysfunction and symptomatic heart failure, however, the results can be more profound and can contribute significantly to the increased morbidity and mortality observed in patients with IVCD and heart failure. These factors made IVCD a reasonable target for adjuvant therapy in this population. Biventricular pacing, by partially restoring intra- and interventricular synchrony, has the potential to mitigate the deleterious hemodynamic consequences of IVCD described above.

Summary

- Heart failure is a major public health problem in industrialized countries, the prevalence of which appears to have risen over the past decade.

- The incidence and prevalence of heart failure seem to increase with age.
- The prognosis in heart failure patients remains poor, with mortality data similar to the worse forms of malignant disease. Concurrent atrial fibrillation seems to worsen prognosis. Recent studies, however, suggest that survival in heart failure may be improving, concurrent with the advent of improved medical therapy.
- Chronic RVA pacing worsens outcomes in patients with heart failure, presumably by inducing intra- and interventricular dyssynchrony.
- IVCD is frequently seen in patients with heart failure and is a marker of higher mortality in this population. Thus IVCD, particularly LBBB, has become an attractive target for heart failure therapy.
- IVCD, particularly LBBB, results in significant intra- and interventricular dyssynchrony, with clinical consequences that include impairment of systolic and diastolic function and aggravation of functional mitral regurgitation.
- Biventricular pacing, by partially restoring intra- and interventricular synchrony, has the potential to mitigate the deleterious consequences imposed by IVCD.

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