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Review Article

Heart Failure Management - Evolution Over The Ages

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"The longer you look back, the further you can look forward". - Sir Winston Churchill

The simplest definition of heart failure is "A condition in which the heart fails to discharge its contents adequately"[1]. Even though the prevalence is quoted at 4 - 20 / 1000 population, in the elderly above 65 years, the figures may exceed 100/1000. After the age of 45, it is found that the relative incidence of heart failure which is approximately 1 - 5 /1000, double for each decade of life. As modernization increases and healthcare improves over the years, the prevalence of heart failure also increases due to the increase in longevity of individuals.

The oldest case of heart failure in a mummy has been identified in the remains of an Egyptian mummy - Nebiri, who lived 3500 years ago in Egypt [2]. Atherosclerosis also has been described in ancient Egyptian mummies that lived 3500 years ago. One study where 52 mummies had whole body multislice computed tomography done showed definite evidence of atherosclerosis or calcification of the coronary arteries. These mummies belonged to the BC 1550 - 1580 period [3].

Some of the cardiac glosses of the Ebers papyrus (1536-1550 BC) seem to have described one of the earliest documented observations of the syndrome of heart failure [4].

Hippocrates (460-370 BC) also had described cases of heart failure as dropsy and dyspnea. Though this was not specific for heart failure, his description of heart failure with cardiac cirrhosis is classical [5].

A twelfth century description of heart failure from "The Alexiad", a biography of the Byzantine Emperor Alexis I Comnenus written by his daughter Anna Comnena describes the symptoms of heart failure lucidly - "Every day it grew worse, attacking him no longer at intervals, but relentlessly, with no interruptions. He was unable to lie on either side, so weak that every breath involved great effort. His condition was serious, for never for one moment could he breathe freely he was forced to sit upright in order to breathe at all: if by chance, he did lie on his back or side, the suffocation was awful to breathe in or exhale even a tiny stream of air became impossible" [6].

Blood letting, either by venesection or leeches (hirudinotherapy) was a popular treatment to alleviate the symptoms from dropsy associated with heart failure [7]. The medicinal leech *Hirudo medicinalis*

was used for this. This type of treatment with leeches for bloodletting is said to be known to ancient Egyptians and Greeks. It was also popular during the middle ages.

In the early 19th century, Reginald Southey who was an English physician introduced the Southey's tubes or cannula for draining edema of the limbs. [8].

It was in the year 1785 that William Withering published his account of 158 patients whom he treated with foxglove. Withering had noticed that an old woman in Shropsire was using the drug as a concoction to treat dropsy in some patients. Withering soon zeroed in on the active ingredient in the concoction and found that it was the foxglove plant. Thus was born the era of digitalis treatment of heart failure, revolutionizing the management of the disease [9].

The treatment of heart failure took a leap forward with the introduction of organomercuial diuretics in 1920 and Thiazide diuretics in 1958 [1]. Prior to 1980's the "Non pharmacological Era" of heart failure management stressed mainly on lifestyle modification like bed rest, positioning, restriction of fluids, digitalis and diuretics which were just coming in to the practice of managing heart failure.

Pharmacological Era of Heart Failure Management

In 1975, beta blockers, Alprenolol and Practolol were reported to be tried in heart failure [10] ushering in an "Era of Pharmacological Interventions" in the management of heart failure. The initial observation of survival with the use of beta blockers in heart failure was recorded as early as 1979 [11]. But it was only after the publication of the multicenter randomized trial regarding the benefit of Metoprolol in 1993 were beta blockers officially approved for the management of chronic congestive heart failure [12]. Soon trials established the fact that Carvedilol, Metoprolol and Bisoprolol are the three beta blockers which are effective in reducing mortality in chronic congestive heart failure.

Concurrently, other studies also were ongoing and the Vasodilator Heart Failure (ValHeft) trial published in 1986 heralded a new "Era of Neurohumoral interventions" when beta blockers, Angiotensin Converting Enzyme inhibitors (ACEI) and mineralocorticoid inhibitors changed the scenario in the management of heart failure [13]. The publication of the CONSENSUS study in 1987 was a landmark in the treatment of heart failure where the emphasis shifted from symptomatic management to a more rational management based on pathophysiology.

Soon to follow were the use of Angiotensin Receptor Blockers (ARB) in the management of heart failure after the publication of the trial in 2001 [15]. Valsartan, Candesartan, Losartan, Irbesartan and Telmisartan soon were alternate drugs available. Though they were superior to placebo, they were not better than ACE inhibitors in the management of congestive heart failure. Studies have shown that the use of betablockers with mineralocorticoid receptor antagonists when added to ACEI resulted in incremental decreases in the risk of death by 30-35%.

The latest addition to the pharmacological therapy of heart failure has been the introduction of Angiotensin-Neprilysin inhibitors (ARNI) in heart failure [16]. The benefit of this combination was excellent leading to premature stopping of this trial.

Simultaneously, developments with other inotropic and vasodilator therapy also occurred with the use in intravenous Dobutamine [17], Milrinone [18], Nitroglycerine, Sodium Nitroprusside and Nesiritide [19]. But intravenous inotropes, unlike vasodilators, fell into disrepute owing to their increasing side effects like arrhythmogenesis and are hardly of use today.

A novel mechanism to tackle the heart rate in chronic heart failure was discovered with the introduction of the I_f or "funny channel" inhibitor Ivabradine [22]. It reduced the risk of hospitalization and worsening of heart failure in patients with stable symptomatic chronic heart

failure with left ventricular ejection fraction of 35% or less who are in sinus rhythm with a resting heart rate of 70 bpm or more and either are on maximally tolerated doses of beta blockers or have a contraindication for beta blocker therapy.

Device Therapies in Heart Failure

The turn of the century saw the dawn of the "Device Era" in the management of heart failure. Also known as "Electrophysiologic Intervention" of heart failure, it includes, pacemakers, Cardiac Resynchronization Therapy devices (CRT) and Implantable Cardioverter Defibrillators (ICD).

Cardiac Resynchronisation Therapy (CRT)

The development of mechanical asynchrony as a consequence of electrical and conduction defects in a failing heart decreases contractile cardiac performance, prolongs mitral regurgitation thereby resulting in wasted cardiac work [21]. Restoration of electrical synchrony could hence restore mechanical synchrony and reduce mitral regurgitation. This was the basis of CRT. Cazeau et al in 1994 performed the first biventricular pacing in a case of dilated cardiomyopathy, successfully increasing cardiac output and reducing pulmonary artery wedge pressure [22]. Soon to follow were a series of observational studies (without a control group) endorsing the improvement in exercise capacity and quality of life [23]. The MIRACLE Trial was a randomized double blind trial which showed improvement in symptoms, quality of life and exercise capacity in the treated arm of the study [24]. The left ventricular size was reduced and the ejection fraction reduced.

In 2010, the Heart Failure Society of America (HFSA) laid down guidelines for CRT therapy in heart failure [25]. The European Society of Cardiology and the ACC/AHA also emphasized the importance of devices in the management of heart failure and published guidelines for the same in 2010 and 2012 respectively.

Implantable Cardiac Defibrillator (ICD)

It was in the 1970's that the first ICD use was reported [26]. The ICD was developed by Dr. Michel Mirowski and Dr. Morton Mower. Initially, as has happened with most inventions and discoveries in the past, they were widely criticized by the medical fraternity for their impractical ideas. But undeterred, the duo proceeded to develop the ICD and reported the first implantation in 1973. The initial ICD was very large needing thoracotomies to implant them. The advances in technology have miniaturized them so much so that they can now be implanted like a pacemaker and have an assortment of sophisticated functions like atrial and ventricular defibrillation, pacing for tachycardia and bradycardia, storage of electrograms and biventricular pacing.

The landmark MADIT I and II trials published in 1996 and 2002 showed a remarkable decrease in risk of death in patients with coronary disease and low ejection fraction [27,28]. Studies of implantation of ICD in heart failure also showed a substantial benefit in survival compared to treatment with anti arrhythmic drugs for the prevention of sudden death due to arrhythmias. Bardy et al showed that ICD implantation reduced the risk of death by 23% whereas Amiodarone had no benefit in prolonging survival in patients with heart failure [29]. Soon guidelines on device therapy in heart failure were published by the European Society of Cardiology [30] and the ACC/AHA [31]. Both the introduction of CRT and ICD has to a great extent revolutionized the modern management of heart failure.

Emerging Therapies in Heart Failure

Other newer devices in the management of chronic heart failure are Ventricular Assist devices like

Left, Right and Biventricular assist devices. Surgical options in the management of heart failure are revascularization procedures like Coronary Artery Bypass Surgery, Valvular surgery, Ventricular restoration and heart transplantation. A total artificial heart for orthotopic transplantation is being intensely investigated and offers promises for the future.

Questions arise as to what the future holds for the management of heart failure. It is well known that the heart is one of the organs in the body with the minimum chances of regeneration. The future holds plenty of scope for the use of stem cells in the management of heart disease and chronic heart failure. [32]. Improved left ventricular performance and better exercise tolerance has been shown by intracoronary stem cell infusion. Also the long term mortality was shown to be decreased in a non randomized study [33]. However, the use of stem cells in the treatment of heart failure has not received widespread acceptance yet.

Gene therapy focuses on improving the function of the existing myocytes in the heart by altering or influencing the expression of specific genes and holds promises for the future. Gene therapy is evolving a viable adjunct to the treatment of heart failure using mechanical or pharmacological methods. There are ongoing trials targeting various pathways for rescuing the failing myocardium. The results have been encouraging. [34]. The next decade may see the dawn of a new era of stem cell and gene therapy in the management of chronic heart failure.

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