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Heart Failure in the 21st Century: Is it a Coronary Artery Disease Problem or Hypertension Problem?

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Synopis

Hypertension and coronary disease are major risk factors for the incidence and progression of heart failure. These two risk factors frequently coexist, and have additive/synergistic effects that promote both left ventricular remodeling and heart failure in the general population. The relative contributions of these two risk factors to heart failure burden in the community may vary based on age, gender and race. In general, attribution of heart failure in the community to solely one of these two risk factors would be inappropriate. Prevention of both hypertension and coronary disease is important for preventing heart failure in the 21st century.

Keywords

Hypertension; Coronary Artery Disease; Heart Failure; Epidemiology

Introduction

The heart failure syndrome is characterized by high morbidity, mortality, reduced quality of life and substantial economic burden (1). The American Heart Association (AHA)/American College of Cardiology (ACC) Task Force defines heart failure as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" (2). It is manifested by fatigue and dyspnea, a decreased exercise capacity and is associated with episodic or chronic fluid retention.

Heart failure is the third most prevalent cardiovascular disease in the United States. An estimated 5 million people in the United States have heart failure, and the prevalence of the condition is estimated to increase to 10 million by the year 2040 (3). The prevalence of heart failure increases with age: from less than 1% in the 20–39 age-group to over 20% in people age 80 year or older (4). The lifetime risk of developing heart failure is estimated at about 20% in both men and women (4). Even without antecedent coronary artery disease (CAD), the lifetime risk of developing heart failure at age 40 is estimated at 11.4% for men, and 15.4% for women (4). In addition to overt heart failure, an estimated 74 million people are living with risk factors for heart failure, i.e. are in Stage A of heart failure (2;3). More than half a million

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new cases of heart failure are diagnosed each year, and this incidence is expected to rise to 772,000 new cases per year by 2040 (5). Heart failure also accounts for 12–15 million office visits and 6.5 million days of hospital stay each year (6). The number of hospitalizations for heart failure has risen to over a million per year over the past decade. The estimated economic burden of caring for patients with overt heart failure is $27–38 billion, with 10% of this amount being spent on drugs alone (2)(6).

As noted above, heart failure is also characterized by substantial morbidity and mortality. Nearly 50,000 people die annually of heart failure (3). Despite major advances in treatment, the prognosis after a diagnosis of heart failure is still dire and comparable to that of several forms of cancer (7). Even though the case-fatality rate associated with heart failure has been declining (8), the crude number of deaths attributed to the condition has been increasing, primarily due to increasing prevalence of the condition. The aging of the population, and an improved survival and 'salvage' of patients with myocardial infarction (with subsequent progression to pump failure) are believed to be some factors contributing to the growing burden of heart failure.

Several epidemiological investigations have identified risk factors for heart failure (9). Increasing age, hypertension, coronary artery disease, diabetes, obesity, valvular heart disease, and the metabolic syndrome are key risk factors for heart failure (9;10). In recent years, many genetic risk factors have also been identified (11). The relative contribution of risk factors to the occurrence of heart failure in the community may be changing over time. Data from the Framingham Heart Study demonstrate that from the 1950s onwards there has been a steady decline in the contribution of valvular disease to the burden of heart failure, whereas the role of myocardial infarction has increased substantially (4;8).

Given the sizeable public health burden posed by heart failure, and limited health care resources, it is critical to identify the primary 'drivers' of this problem. Identification of the key risk factors in order of their relative importance will help guide health policy and resource allocation, and aid the formulation of efficient preventive and therapeutic approaches to target heart failure. Also, a majority of people with the 'pre-heart failure' phenotype (Stages A and B) and overt heart failure will be 'cared for' by primary care physicians, underscoring the importance of providing clear guidance on risk factors that warrant a primary focus to prevent the future burden of heart failure. Given that hypertension and coronary artery disease (CAD) are the major modifiable risk factors for heart failure (12;13), we appraise the relative contributions of these two conditions to heart failure burden in this review. provides the context for our debate.

A. Is heart failure primarily a CAD problem?

A1. Biological Plausibility and Mechanistic Insights

Coronary atherosclerosis is the critical determinant of the clinical manifestations of CAD. The role of myocardial infarction as a major antecedent of heart failure has been established by several studies (9;14–16). It is noteworthy that clinically silent coronary disease is widely prevalent both in the general population and in heart failure patients, as evidenced by the demonstration of coronary plaques both in children and young adults in autopsy series (17), and in angiographic studies of healthy heart transplant donors (18). In addition to epicardial disease, microvascular coronary disease is also both widespread and often under-recognized (19). These data suggest that coronary artery disease (epicardial or microvascular; clinically overt or silent) can lead to decreased perfusion of the myocardium (both acutely and chronically), thereby predisposing to myocardial damage with its sequel of decreased myocardial function.

CAD can lead to heart failure by several mechanisms:

1. Acute myocardial infarction (MI) frequently leads to permanent death of cardiac muscle. The infarcted segment is akinetic/dyskinetic, thus leading to inadequate relaxation in diastole and impaired contraction in systole. It has been shown that diastolic dysfunction is present early in MI, and may be related to the development of in-hospital heart failure, and death (20). The impairment of ventricular function after MI is usually improved with the early restoration of coronary blood flow in the culprit vessel, with either thrombolysis, angioplasty or with bypass surgery (21;22). The area of the infarct heals with scar formation, and there may be associated formation of an aneurysm, which can further impair contractile performance and relaxation. A third mechanism by which MI can result in heart failure is the dyssynchronous contraction of the infarcted segment that can decrease the efficiency of pump function. A fourth mechanism for heart failure occurs in the context of rupture of the mitral/submitral apparatus as a result of ischemic injury (papillary muscle rupture or flail leaflet), which can result in acute severe mitral regurgitation and acute onset of heart failure (23;24).

2. Changes in the ventricle away from site of myocardial insult or injury can also contribute to heart failure risk. Whereas the initial myocardial injury and scarring can result in regional dysfunction at the site of injury, subsequent remodeling of the ventricle can occur in myocardial segments that are remote from the site of infarction. Such regional remodeling frequently results in a distortion of ventricular structure and geometry, and can contribute to a further decline in ventricular function (25). Ventricular dilatation can promote annular dilation, with consequent mitral regurgitation, which can predispose to heart failure.

3. Chronic dysfunction of the myocardium resulting from hypoperfusion and/or hibernation may also enhance the risk of heart failure (26;27). Patients with both epicardial and endocardial coronary artery disease may have chronic hypoperfusion, which leads to increased myocardial stiffness secondary to chronic inflammation and fibrosis. Patients with episodic decreases in coronary perfusion may demonstrate impairment of myocardial function for hours or days(myocardial stunning) (28). Studies with positron emission tomography (PET; (29)) and single photon emission computed tomography (30) demonstrate decreased blood flow and glucose uptake in myocardial regions that can simultaneously be shown to have decreased systolic function. Ventricular diastolic function has been shown to be decreased in both experimental (31) and clinical ischemia (32). Also, the coronary vasodilator reserve decreases in proportion to degree of luminal stenosis of the coronary arteries (33; 34). Consequently, areas of the myocardium with normal blood flow at rest may have reduced myocardial blood flow during exercise, and may demonstrate reduced glucose metabolism on PET during exercise, with a concomitant decrease in ventricular function.

A2. Epidemiological Studies Identifying CAD as a major contributor to heart failure burden

Epicardial CAD has been demonstrated as an etiological factor in a third of patients with heart failure in some reports (35). Across several studies, coronary artery disease has been reported to account for 23–73 % of the heart failure in the patients evaluated. Some investigators have argued that the most common cause of heart failure is CAD (36). Framingham data indicate a differential contribute of CAD to heart failure burden in men versus women. The population attributable risk (PAR) for heart failure associated with CAD is 39% in men, but only 18% in women (37). In heart failure series that focused on patients with a reduced left ventricular ejection fraction, CAD is usually the major cause.(35) Autopsy series indicate that a third of patients with heart failure have prevalent but undetected major coronary artery disease (38).

Thus, even in heart failure patients classified clinically as 'non-ischemic cardiomyopathy,' up to a fourth may have evidence of CAD at autopsy (39). Also, ischemic changes have been demonstrated on endomyocardial biopsies (40) in such patients. Indeed, such patients with so-called 'non-ischemic cardiomyopathy' may develop clinical ischemic events on subsequent follow-up, an observation that suggests that coronary disease may not be just a 'bystander' in these patients (41). The frequent presence if microvascular disease detected with PET scanning 42) or with Doppler flow velocimetry (43) in response to stress in such patients further incriminates CAD as a potential contributor to the ventricular dysfunction.

The presence of underlying CAD also contributes to the morbidity and mortality of patients with heart failure (44). Angiographic evidence of CAD has been shown to be a marker of a worse prognosis in heart failure patients (45), with the mortality risk being increased by 250% in some reports (46).

In summary, perfusion abnormalities are likely present in the vast majority of patients with heart failure (including those categorized as 'non-ischemic'), rendering coronary disease as the predominant determinant of heart failure.

A3. Evidence linking CAD to Heart Failure from Clinical trials

Clinical trials of post-MI patients suggest that prompt and appropriately targeted therapy can lower the risk of development of ventricular dysfunction and overt heart failure after ischemic injury, thereby further suggesting a causal relationship between CAD (47–49). In the last decade, several large trials of MI patients have evaluated the incidence of new-onset heart failure as an endpoint(in addition to decrease in death, non-fatal MI and need for revascularization), and have shown a reduction in heart failure incidence with several treatment strategies (50–52). It is also well established that acute coronary events can precipitate the decompensation of patients with chronic compensated heart failure. It has been argued that the benefit of ACE inhibitors and beta blockers in heart failure trials lags behind the immediate hemodynamic improvement seen with these agents, raising the possibility that the accrual of benefits over time may be due to amelioration of coronary disease in some patients (36). Coronary revascularization in selected patients has been shown to ameliorate diastolic function abnormalities, reduce morbidity and mortality (53–56), and may improve systolic function (57), likely by 'recruitment' of hibernating myocardium.

In summary, extensive data from a basic science perspective, epidemiological studies and clinical trials suggest that CAD is a principal contributor to heart failure burden. As more and more 'high-risk' patients survive after CAD events due to accruing improvements in management strategies, it is conceivable that the burden of heart failure due to CAD may increase in the future. Indeed CAD may be the key risk factor for heart failure in the new millennium.

B. Is heart failure primarily a hypertension problem?

B1. Biological Plausibility and Mechanistic Insights

Systemic blood pressure is determined by peripheral vascular resistance and conduit artery stiffness. The myocardium has to pump blood against the afterload posed by the resistance of peripheral vasculature and the stiffness of the large and medium-sized arteries. An elevated blood pressure places greater hemodynamic burden on the myocardium.

Elevated blood pressure leads to compensatory increase in myocardial muscle mass in order to maintain normal cardiac output (58;59). In both hypertensive and pre-hypertensive states, there is slow but steady hypertrophy of the left ventricle (60;61). This is associated initially with myocardial stiffness and a decreased ability to relax and fill, initially during exercise and

subsequently at rest also (62–65). Ventricular diastolic dysfunction due to high blood pressure is an important contributor to the development of overt heart failure. Indeed, the prognosis of heart failure patients has been related to ventricular filling abnormalities regardless of ventricular ejection fraction (66). In addition, left ventricular mass increases disproportionately in hypertension, relative to the ability of the microvasculature (67) to perfuse the hypertrophied myocardium both at rest and during exercise, thereby proving to be a 'set up' for chronic subendocardial hypoperfusion.

The progression from chronic hypertension to structural ventricular changes, and then to asymptomatic systolic and diastolic ventricular dysfunction is well established by natural history investigations from longitudinal epidemiological cohort studies such as the Framingham Heart Study (37). Acute hypertensive crises can also cause heart failure. Experimental data as well as human studies have also demonstrated that sudden acute increases in blood pressure (such as in hypertensive emergencies) can lead to acute LV strain and manifest as hypertensive heart failure (68). It is also noteworthy that an acute elevation of blood pressure is a common precipitating cause for the decompensation of a patient with compensated chronic heart failure (69). Thus, both chronic and acute hypertension have been linked to the risk of heart failure.

B2. Epidemiological Studies identifying hypertension as a major contributor to heart failure burden

From an epidemiological perspective, hypertension is the most prevalent cardiovascular risk factor. An estimated 72 million Americans have high blood pressure, with millions more having a 'pre-hypertensive' state. Investigators have demonstrated that prehypertension also elevates the risk of developing heart disease (70).

Hypertension is an antecedent of the vast majority of individuals with heart failure in the community, as suggested by data from the Framingham Study (37). The PAR for heart failure associated with hypertension was 39% in men and 59% in women in a report from the Framingham Study (37). Although the PAR for hypertension is decreasing over the last five decades, the prevalence of hypertension is increasing and a substantial proportion of individuals with hypertension do not have their blood pressure controlled to recommended levels (71). Also, hypertension is frequently accompanied by metabolic risk factors and obesity, which themselves increase the risk of heart failure. With the rising societal burden of obesity and the metabolic syndrome (72), it is conceivable that the contribution of hypertension and prehypertension to ventricular remodeling and heart failure in the community may increase in this millennium, unless we can achieve better rates of control of cardiovascular risk factors (including elevated blood pressure).

B3. Evidence linking Hypertension to Heart Failure from Clinical trials

A number of clinical trials demonstrate the benefit of treating hypertension in the prevention and treatment of heart failure (73;74–75). Primary prevention trials demonstrate up to a 50% reduction in the incidence of heart failure in patients with hypertension who are treated with blood pressure lowering agents(76). In patients with established cardiovascular disease, treating blood pressure to targets advocated by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure reduced further incidence of recurrent events and also the progression to heart failure (77). In patients with left ventricular systolic dysfunction (78) or left ventricular hypertrophy, control of blood pressure prevents or retards ventricular remodeling and decreases the incidence of overt heart failure (79). In patients with established heart failure, further decreases of blood pressure with therapy may improve the mortality, the progression of disease, hospitalizations, exacerbations, and enhance the quality of life and the functional capacity (14).

The pivotal role of high blood pressure in the pathophysiology of heart failure may be inferred by the profound benefits of afterload reducing agents in reducing clinical outcomes in patients, relative to a lesser magnitude of benefit achieved by using inotropic agents. Angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers ARBs, hydralazine (in combination with nitroglycerine) and dihydropyridine calcium channel blockers all reduce morbidity and mortality in heart failure, as opposed to a lack of survival benefits with the use of diuretics, digoxin, phosphodiesterase inhibitors, and inotropes (2). Thus, clinical data support the contention that higher systemic blood pressure is a dominant determinant of heart failure risk.

Not only is chronic hypertension a problem, but acute elevations in blood pressure can also precipitate episodes of heart failure (68). Also, recurrent catecholamine surges as seen in sleep apnea and the blunting of the daily nocturnal declines in blood pressure have been linked to hear failure risk (80). It is also important to recall that hypertension is a very common condition in the community. As such, the PAR associated with a common condition is likely to be higher, even if the relative risk of heart failure is higher for CAD (or MI).

In summary, considerable evidence from experimental and clinical studies and epidemiological investigations indicate the critical role of hypertension in the pathogenesis of heart failure. The lifetime risk of hypertension is estimated to be 90% (81). Thus, a compelling argument can be made that hypertension may be a key contributor to heart failure risk in the new millennium. Clearly, if we are able to prevent hypertension and control blood pressure in those with established hypertension effectively, the risks associated with hypertension may diminish in this millennium.

Discussion: Is this a reasonable debate?

As we see from the above section, persuasive arguments can be made to substantiate the claims that either CAD (atherosclerotic coronary disease?) or hypertension may be key etiological risk factors for heart failure in the new millennium. But it is worth pondering if this is, in reality, a reasonable debate. Several issues have to be considered to ascertain the primacy of one risk factor over other. Hypertension and CAD frequently coexist. The two conditions also interact synergistically with each other as risk factors for heart failure (see below). Also, the relative impact of the two conditions may differ according to age, gender, race and other factors. It is well established that blacks face a higher burden of blood-pressure related conditions including heart failure, compared to whites in whom CAD is more often a culprit (3;37). And lastly we outlined above some of the ascertainment bias in the adjudication of a particular risk factor as the primary etiological factor for heart failure.

High blood pressure is a powerful risk factor for CAD, with a continuous gradient of risk that starts at levels below what is recognized as hypertension(82;83). Hypertension is also a risk factor for left ventricular hypertrophy (LVH), which itself has been shown to be associated with a 2 to 5 fold increase in MI on long-term follow-up (76). Also, hypertension can contribute to ischemia by increasing myocardial oxygen demand through increased workload imposed on the heart, and due to a diminished subendocardial blood supply in concentric hypertrophy (84). Experimental data demonstrate that hypertrophied hearts demonstrate subendocardial ischemia during pacing-induced tachycardia, and during exercise even in the absence of epicardial coronary disease (85;86). In addition, hypertension can precipitate acute coronary syndromes via shear stress that can contribute to rupture of unstable plaques (87).

In this context, it is important to point out that widespread atherosclerosis has also been implicated in the pathogenesis of vascular stiffness and decreased vascular reactivity. Such atherosclerosis-related increased vascular stiffness and endothelial dysfunction may contribute

to higher peripheral vascular resistance and blood pressure (88;89). Also, renal artery atherosclerosis can lead to increased activation of RAAS pathway and cause hypertension. The impact of statins in effectively improving systemic (90) and coronary (91) vasoreactivity is consistent with the notion that atherosclerosis can be a cause, not just a consequence of elevated blood pressure (though other pleiotropic effects of statins may also contribute to these observations).

In addition a common set of biological pathways have been implicated in the pathogenesis of both hypertension and CAD. The most notable such pathway is the renin-angiotensin-aldosterone system(RAAS). It is well documented the activation of RAAS is a major mechanism in the development and establishment of both primary and secondary HT (92). Use of agents that block the RAAS (with aldosterone antagonists e.g., eplerenone; or renin inhibition e.g., aliskiren) is a key antihypertensive management strategy. Activation of RAAS is also implicated in CAD; biomarkers of RAAS activation (such as PRA (93) and aldosterone levels (94)) correlate vascular function (95) and with cardiovascular outcomes (96). Treatment with agents that interfere with the RAAS pathway (ACE-I's, ARB's and eplerenone) reduce the risk of cardiovascular outcomes, thereby definitively establishing the pivotal role of this pathway. RAAS is also instrumental in the progression of heart failure. ACE inhibition and aldosterone antagonism are the most well-established strategies to control blood pressure, restore endothelial function, stop or reverse LV hypertrophy, improve microcirculation, improve LV function, and improve survival in hypertension, CAD and heart failure. Thus, common underlying pathogenetic mechanisms preclude any attempts to simplify heart failure as a "one-major factor- related " condition. A majority of heart failure patients have both CAD and hypertension, thus further rendering the discussion of which factor to 'blame more' a moot point.

Conclusions

Both hypertension and CAD are major risk factors for the onset and the progression of heart failure. They have additive and synergistic effects in the pathogenesis of the syndrome, and frequently coexist. With the aging of the population in developed countries and with onset of epidemiological transition of developing countries (to the stage of chronic degenerative diseases) (97) the prevalence of hypertension, CAD and heart failure will likely rise world-wide over the next few decades. Fortunately, our understanding of these conditions and their treatments is robust, rendering this challenge as an opportunity to implement better preventive methods.

Obesity, atherogenic diet, sedentary lifestyle and smoking underlie adult development of metabolic syndrome, vascular risk factors (including hypertension), and CAD. As Dr. William Kannel pointed out 'overt heart failure is now better regarded as medical failure rather than indication for treatment' (98). Thus future endeavors to reduce heart failure burden must include primordial prevention (the prevention of risk factors themselves), not just management of existing risk factors or established disease.

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