The effects of β-blockers on exercise parameters in heart failure.

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List of Common Abbreviations

AI	angiotensin I
AII	angiotensin II
ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
BP	blood pressure
CO_2	carbon dioxide
HF	heart failure
HR	heart rate
K^+	potassium
LV	left ventricle
Na^+	sodium
NE	norepinephrine
NO	nitric oxide
NYHA	New York Heart Association
O_2	oxygen
PCWP	pulmonary capillary wedge pressure
Qc	cardiac output
RAP	right atrial pressure
RAS	renin-angiotensin system
RV	right ventricle
SWI	stroke work index
V_E	ventilation
VD	dead space ventilation
V_E/V_{CO_2}	ventilatory requirement for CO_2 removal
V_E/V_{O_2}	ventilatory requirement for O_2 uptake
VT	tidal volume

Abstract

Purpose: to examine the outcome of a 6-month treatment with carvedilol or metoprolol on peak and submaximal exercise performance and ventilatory efficiency in patients with heart failure (HF).

Methods: 27 patients with HF were randomized to receive either metoprolol or carvedilol for 6 months and compared with 12 healthy controls. Maximal exercise capacity was assessed at baseline and after 6 months with a symptom limited incremental treadmill protocol (RAMP). Submaximal exercise was determined to be the portion of exercise below a respiratory exchange ratio of 1.0. Peak heart rate (HR), oxygen uptake (VO_2), and ventilatory equivalent for O_2 and CO_2 were recorded. The slopes of the VE vs. VCO_2, VE vs. VO_2 and VE/VCO_2 vs. VO_2 relationships were calculated for each subject from submaximal values.

Results: Resting HR decreased to similar extent in both treatment groups. There were no other significant changes in resting hemodynamics or ventricular function. Peak VO_2 and HR decreased significantly in both treatment groups. Peak VE/VCO_2 and submaximal VCO_2 vs. VE slope were not changed significantly after therapy.

Conclusion: β-blocker treatment with either metoprolol or carvedilol does not decrease the slope of the VCO_2 vs. VE relationship. The present observations may suggest that the exaggerated ventilatory response of patients with moderate HF is not mediated by β-adrenergic receptors.

Résumé

Objectif : Les patients souffrant d'insuffisance cardiaque chronique démontrent une réponse ventilatoire à l'effort exagérée, dont le mécanisme n'est pas connu. Ce travail visait à évaluer les effets d'un traitement de six mois de carvédilol ou de métoprolol sur la réponse circulatoire et ventilatoire à l'effort de patients souffrant d'insuffisance cardiaque chronique (HF).

Méthologie : L'étude portait sur 27 patients assignés d'une façon aléatoire à recevoir le métoprolol ou le carvédilol pour une période de 6 mois ainsi que sur 12 sujets témoins asymptomatiques de même âge ne recevant aucun médicament. La capacité maximale d'effort a été évaluée par un test progressif incrémental (RAMP) sur tapis roulant, en période de pré-médication ainsi que 6 mois après le début de la prise de médicament. La réponse sous-maximale d'éffort a été évaluée en considérant la période du test incrémental compris entre le début de l'effort et l'obtention d'un rapport d'échanges gazeux respiratoire égal à 1.0. La fréquence cardiaque (HR), la consommation d'oxygène (V_{O_2}), ainsi que la ventilation minute (V_E) et les équivalents respiratoires de l'O_2 et du CO_2 ont été enregistrés en continu. Les pentes des relations en période sous-maximale entre V_E et V_{CO_2}, entre V_E et V_{O_2} ainsi qu'entre V_E/V_{CO_2} et V_{O_2} ont été calculées individuellement pour chaque sujet avant et après la période expérimentale.

Résultats : Les résultats témoignent d'une même diminution de la fréquence cardiaque de repos dans les 2 groupes de patients. Aucun autre paramètre circulatoire ou de la fonction cardiaque n'a été significativement modifié par le traitement. Une diminution de V_{O_2} pic ainsi que de la fréquence cardiaque maximale était observée dans les 2 groupes de patient. Ni le rapport V_E/V_{CO_2} , ni la relation sous-maximale du V_{CO_2} vs V_E n'ont été significativement modifiés par le traitement pour aucun des groupes expérimentaux.

Conclusions :

L'administration de béta-bloqueur ne modifie par le rapport entre V_{CO_2} et V_E à l'effort dynamique chez le patient insuffisant cardiaque, peu importe qu'il soit de type sélectif β_1 sans action sympathicomimétique spécifique comme le métoprolol ou de type partiellement sélectif β_1 , mais avec action α-bloquant, comme le carvédilol. Ces

observations suggèrent que la réponse ventilatoire exagérée de l'insuffisant cardiaque au cours de l'effort dynamique n'est pas médiée pas une stimulation β –adrénergique.

1.0 Definition and Pathophysiology of Heart failure

Although, commonly used, there is still not a clear definition for the term " heart failure". While the standard definition referred to "The inability of the heart to perfuse metabolizing tissue adequately" or its ability to do so only in light of elevated filling pressure, recent experimental evidence suggest that this definition is no longer valid. Revised guidelines for practice now acknowledge "heart failure" as a clinical syndrome characterized by signs and symptoms of intravascular and interstitial volume overload, associated with shortness of breath and edema as well as manifestations of inadequate tissue perfusion such as fatigue or poor exercise tolerance" [1]. Moreover, the disease is now considered to be highly complex involving neuroendocrine activation and cytokine release [2]. Heart failure is a progressive disorder with deterioration of cardiac structure and function and increasing severity of symptoms over time. This progression leads to a recurrent need for medical care and hospitalization and inevitably death [3]. There is confirmed epidemic of HF in the U.S. population manifested primarily as an increasing prevalence in both men and women over the past decade [4].

The clinical syndrome of HF results from changes in skeletal muscle, peripheral vasculature and the lungs that are a consequence of chronically decreased cardiac output [5] and resultant overactivity of the neurohormonal system. Ventricular dysfunction is accompanied by exertional symptoms of dyspnea and fatigue. The New York Heart Association (NYHA) classification system is commonly used to quantify the degree of functional limitation imposed by HF [6]. This system assigns patients to functional classes depending on the degree of effort needed to elicit symptoms.

Class 1: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class 2: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class 3: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class 4: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

1.2 Pathophysiology of Heart Failure

Heart failure is now recognized as a progressive disease of left ventricular (LV) remodelling that occurs after an index event. A non-failing heart sustains an initial injury that leads to some degree of systolic and/or diastolic LV dysfunction. This initial injury may be genetic or acquired, sudden or progressive. Acquired acute events can be a myocardial infarction or myocarditis resulting in myocardial inflammation. Heart failure can also result from progressive overload on the heart, such as pressure overload in long-standing hypertension, volume overload in valvular heart disease, or from congenital heart disease, severe chronic obstructive lung disease, untreated hyperthyroidism, toxic exposure (including ethanol), infectious disease, or idiopathic causes [2]. Less common causes of LV systolic dysfunction are listed in Table 1.

1.2.1 Acute Heart Failure

Acute heart failure, or cardiogenic shock, occurs with an acute insult to the heart, such as a large myocardial infarction or myocarditis. Its clinical presentation ranges from the sudden appearance of dyspnea to frank cardiogenic shock [7]. If cardiac output cannot be maintained there is impaired perfusion of vital organs [9]. The reduced stroke volume causes resetting of aortic baroreceptors leading to de-inhibition of sympathetic discharge to the heart and peripheral tissues [10]. There is altered loading of the heart with an increase in atrial and ventricular

stretch which also leads to activation of the adrenergic nervous system, as well as the renin-angiotensin system (RAS), vasopressin, endothelins, cytokines and atrial natriuretic factor [11, 12]. The RAS and sympathetic nervous system cross-activate each other. Physiologic adjustments are made to stabilize or increase myocardial performance. Cardiac output improves from an increase in heart rate (HR) and contractility via sympathetic nervous system stimulation. In order to maintain blood pressure (BP), there is exaggerated vasoconstriction and diversion of blood flow away from the skin, splanchnic bed and muscles[12].

Table 1. Less common causes of LV systolic dysfunction

Infectious	Viral, bacterial, fungal
Acute rheumatic fever	
Infiltrative disorders	Amyloid, hemochromatosis, sarcoid
Toxic	Heroin, cocaine, alcohol, amphetamines, adriamycin, cyclophosphamide, sulfonamides, lead, arsenic, cobalt, phosphorus, ethylene glycol
Nutritional deficiencies	Protein, thiamine, selenium
Electrolyte disorders	Hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia
Collagen vascular disorders	Lupus erythematosis, rheumatoid arthritis, systemic sclerosis, polyarteritis nodosa, hypersensitivity vasculitis, Takayasu's syndrome, polymyositis, Reiter's syndrome
Endocrine and metabolic diseases	Diabetes, thyroid disease, hypoparathyroidism with hypocalcemia, pheochromocytoma, acromegaly
Tachycardia induced	Incessant supraventricular arrhythmias or atrial fibrillation with rapid ventricular rates
Miscellaneous	Hypereosinophilic syndrome, peripartum cardiomyopathy, sleep apnea syndrome, Whipple's disease, L-carnitine deficiency

From Williams ACC/AHA 1995 [8]

Preload increases through activation of the RAS and adrenergic system and this increases end-diastolic volume and thus cardiac output via the Frank-Starling mechanism [12]. Angiotensin II (AII) mediates aldosterone secretion and causes salt and water retention at the kidney [12]. Vasopressin is released by non-osmotic mechanisms at the neurohypophysis through β-adrenergic and AT II receptors [13.14]. The salt and fluid retention acutely help to maintain BP and cardiac output (Qc) as the heart operates at higher volumes and filling pressures in the condition of reduced cardiac contractility. However, increased left and right

ventricular filling pressures may lead to transudation of fluid into the lungs causing pulmonary congestion and edema that leads to dyspnea.

Activation of the renin-angiotensin system

AII is the primary humoral mediator of the renin-angiotensin system (RAS). Angiotensinogen is produced in the liver and converted to the decapeptide angiotensin I (AI) by the action of renal renin (stored in the juxtaglomeruli cells surrounding the afferent arterioles of the glomeruli in the kidney) at both renal and extra renal sites. AI is essentially inactive itself but is converted by the action of converting enzyme (ACE or kininase II) in the kidneys, lungs, and other sites to the active effector, AII [15,16]. Angiotensin III and angiotensin 1-7 also have biological activity, but the principal effector of the RAS is AII [15, 16]. There is also non ACE-mediated AII production. Cathepsin-G, tissue plasminogen activator, chymase can generate AII from angiotensinogen or AI which has undetermined significance [16].

Renin release is controlled by four interdependent factors and is β_1-mediated [17]. In general, renin release is stimulated by a decrease in perfusion or circulating blood volume. First, a reduction in renal perfusion pressure is perceived by the juxtaglomerular cells as decreased stretch on the afferent arteriolar walls and stimulates renin release. Second, increased delivery of filtered sodium to the macula densa acts as a chemoreceptor in direct apposition to the juxtaglomerular cells and stimulates renin release. Third, the sympathetic nervous system can activate renin release in response to assuming an upright posture. Finally, circulating factors, such as increasing serum potassium (K^+), increase renin release, however, an increase in AII and atrial natriuretic peptide decrease renin release [5].

ACE is also the primary enzyme involved in the degradation of bradykinin, a nonapeptide produced in the kallikrein cascade, which stimulates prostaglandin synthesis and nitric oxide synthesis in blood vessels, kidneys, the heart and other

tissues. Both of these have vasodilatory effects. Exogenous bradykinin has been shown to cause vasodilatation in the forearm of patients with heart failure [18]. With increased degradation of bradykinins, there is less of its vasodilatory action. Bradykinin has been implicated as playing a direct role in myocardial remodelling and functional recovery from myocardial ischemia [19] and may impact positively on cardiac remodelling.

Short-term effects of AII

AII is the most potent pressor compound made in the body, and exerts its pressor action by a direct effect on arteriolar smooth muscle causing vasoconstriction. This results in increasing cardiac afterload and preload [15,16]. AII also has a positive inotropic and chronotropic effects on the heart [20]. AII receptor binding sites have been localized to the myocardium and cardiac adrenergic nerves and activation of these sites produces an increase in the rate of tension development in animal atria and papillary muscle. AII has been shown to retain its positive inotropic effect in the denervated heart and in the presence of β-blockade, thus a large proportion of the positive inotropic effect is likely to be direct. Angiotensin I (AI) does not suppress conversion of AI to AII in human hearts, thus AII formation in LV tissue occurs by an enzyme activity other than ACE and the inotropic effect is preserved [20].

AII affects renal function by constriction of renal arteries causing a reduction in renal blood flow. The constriction of efferent glomerular arteries enhances filtration fraction and in some patients, glomerular filtration rates. AII increases the reabsorption of sodium and water in the proximal convoluted tubule. AII also enhances renal sympathetic nerve transmission and suppresses renin release. Additionally, AII interacts with other neurohormonal systems. AII is a stimulus for production of aldosterone by the zona glomerulosa of the adrenal cortex, which enhances sodium (Na^+) reabsorption by the distal nephron and causes K^+ loss. AII stimulates secretion of arginine vasopressin and stimulates thirst, which may

cause hyponatremia. All increases norepinephrine (NE) release from presynaptic nerves [5].

1.2.2 Chronic Heart Failure

The body compensates for the cardiac dysfunction in various ways. In acute heart failure, activation of neurohormonal systems is a compensatory mechanism to provide support for the cardiovascular system. In chronic heart failure, this activation continues and plasma NE, epinephrine (EPI), endothelin and renin concentrations are higher than in controls [21,22]. This is the basis for the "neurohormonal hypothesis" in HF [23]. In this theory, neurohormonal activation can exacerbate hemodynamic abnormalities of HF and lead to a direct toxic effect on the myocardium.

Progressive Left Ventricular Remodelling

End diastolic volume may be increased either by augmenting preload or by chamber dilation resulting from remodelling [24]. In remodelling, the LV chamber dilates, hypertrophies and becomes more spherical as a result of various mechanical, biochemical and molecular signals [2,12]. The mechanism by which LV remodelling takes place is highly complex and poorly understood. Increase in chamber size exacerbates the hemodynamic stresses on the walls of the heart, decreases mechanical performance and increases the amount of regurgitant flow through the mitral valve. All of these factors serve to perpetuate the remodelling process [3,25].

The major determinants of myocardial oxygen demand are heart rate, contractile state and wall stress [12]. Neurohormonal mediators increase the hemodynamic stresses on the ventricle by causing sodium retention and peripheral vasoconstriction[3]. For example, NE can cause peripheral vasoconstriction and increase intravascular volume by impairing salt and water excretion by the kidneys through its action on α-adrenergic receptors. This results in increased ventricular size and pressures, which affects contractility and thus increases

myocardial oxygen demand [26]. Subendocardial blood flow is impaired because of the compressive forces on the inner wall of the chamber that occur as a result of high filling pressures during diastole [25]. Increasing HR can also interfere with appropriate diastolic coronary flow and contractility changes will greatly affect myocardial oxygen needs [26]. Furthermore, in the failing heart, there is a depressed response to tachycardia with inadequate cardiac output during resting conditions and inadequate increase in cardiac output during physical activity in HF patients due to the abnormal force frequency relationship that occurs in the failing heart [27].

Neurohormonal mediators can also trigger a cascade of events that exert direct effects on the myocardium and act growth factors to increase the number of contractile elements in the heart and cause hypertrophy [12]. AII is a mitogen that stimulates the growth of smooth muscle and cardiac cells in culture and can act (directly or indirectly) with other mitogens to promote hypertrophy of cardiac tissue [16]. Myocyte hypertrophy and increased myocardial length [28] may lead to progressive LV dilation and alterations in myocardial interstitium that may play a role in LV remodelling and dysfunction (this may be a direct effect of AII or mediated by levels of aldosterone and catecholamines). Contractile units are added in series rather than in parallel [29,30] causing a normally elliptical heart to increase in volume and become more spherical. Wall stress and functional mitral regurgitation increase [30]. The increase in wall stress reduces further systolic and diastolic performance, further activating neurohormones [12].

As shown in Figure 1, cell death can occur in a number of ways. AII, NE, cytokines and endothelins activate pathways leading to abnormal growth of myocytes and fibroblasts, which result in pathologic growth and myocytes death. The activation of fibroblasts to produce collagen results in fibrosis [31]. Since AII also stimulates the growth of smooth muscle, vascular hypertrophy and endothelial dysfunction can ensue. Subendocardial ischemia may result in cell injury and necrosis. It is also thought that AII and NE may have direct effects on

myocytes leading to cell necrosis and fibrosis [32,33]. Apoptosis is mediated by tumour necrosis factor-alpha (TNFα) [34]. Progressive ventricular dysfunction results and the cycle continues.

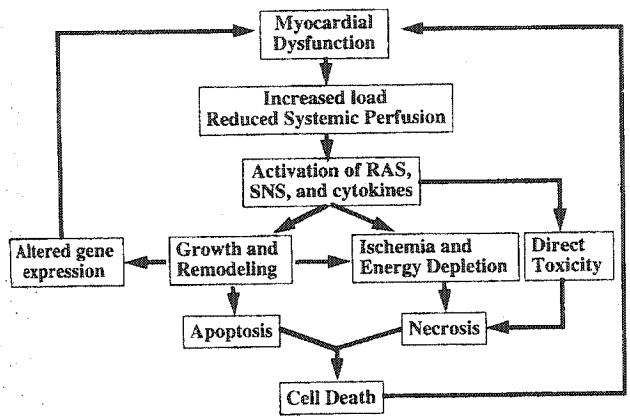

Figure 1. Mechanisms for heart failure progression. From Eichhorn[12]

Sympathetic Nervous System

Circulating levels of NE are an index of sympathetic tone and are elevated in HF [21, 22,35]. Increasing NE plasma levels are a strong predictor of outcome in HF [36], however plasma levels do not correlate with resting cardiac output [35]. In asymptomatic LV dysfunction, the increase in plasma levels is present before the onset of symptoms and therefore not only result of HF [37]. Prolonged activation of the sympathetic nervous system can decrease coronary blood flow [38] and may be linked to ventricular arrhythmias in heart failure [39].

There are at least three adrenergic receptors, β_1, β_2 and α_1, present in human cardiac myocytes that have positive inotropic response and contribute to cell growth [40,41]. In normal hearts, 70-80% of β-receptors are β_1, but in failing hearts, 35-40% of β-receptors are β_2 because the β_1 subtype is selectively down regulated [40,41]. β_2 receptors are present on the presynaptic nerve

terminals in the heart, where they facilitate NE release[40]. By acting through the β_1 and β_2 receptors, sympathetic stimulation can increase heart rate (HR) and contractility [26]. In the failing heart, there exists evidence of an increase in β_3 receptors, which may decrease cardiac inotropy [40, 41]. α_1 receptors are upregulated in the failing heart[40]. β_4 receptors may also exist [40].

Peripheral Vascular Changes

In normal vessels, the changes in shear stress on the endothelial cells that occur with changes in blood flow enhance vasodilation via release of nitric oxide (NO) and prostaglandins [42]. NO acts on smooth muscle and causes vascular relaxation as well as inhibiting platelet aggregation and smooth muscle proliferation [43]. In CHF, the response to endothelium-mediated vasodilation is blunted [21, 42]. The potential reasons for this reduced flow include the reduction in endothelial-derived relaxing factors, the most important one being NO [44], and increases in vasoconstrictive neurohormones such as endothelin-1 [45,46]. Endothelial cells release endothelin-1 and increased levels have been found in the circulation in patients with HF [35, 43]. Endothelin-1 plays an important role in cardiac function as high levels cause coronary vasoconstriction and increased afterload, which result in decreased cardiac output [43].

2.0 Treatment of Heart Failure

Acute HF and decompensation of chronic HF are cardiac emergencies and therapeutic interventions should be undertaken expeditiously to stabilize hemodynamics. This review will focus on the treatment of chronic and stabilized HF in adults. The aims of the treatment of heart failure are to improve the quality of life and slow the progression of cardiac disease. The first step to treatment of chronic HF is to identify and treat conditions or behaviours that are associated with an increased risk of HF. Steps are undertaken to control systolic and diastolic hypertension, diabetes mellitus and hyperlipidemia. Patients are encouraged to discontinue smoking, alcohol and illicit drug use. Moderate sodium restriction is indicated. Immunization with influenza and pneumococcal vaccines is useful to help prevent the risk of respiratory infections. Physical activity should be encouraged, except during periods of acute decompensation, to prevent deconditioning [7]. Since poor follow-up visitation has been identified as a significant predictor in hospital readmission for HF [47], compliance with treatment and monitoring should be urged in patients.

2.1 Conventional Pharmacological Therapy

Most patients with symptomatic LV dysfunction should be routinely managed with an ACE inhibitor, a diuretic and usually with digoxin. The value of these drugs has been established in numerous large-scale clinical trials [7]. More recently β-blockers have been shown to provide a central role in the treatment of HF.

2.1.1 Digoxin

Digoxin has been used in the treatment of HF for over 200 years. This cardiac glycoside, a steroid compound, inhibits Na-K ATPase and increases intracellular calcium, which results in positive inotropic and arrhythmogenic effects. Increased cardiac output and stroke work index [48] occur from an increase in intracavitary pressure during isovolumic systole at constant work rate and aortic pressure. The Frank-Starling curve shifts up and to the left so greater cardiac

output is generated at a given volume in both right and left ventricles [5] (see Figure 2).

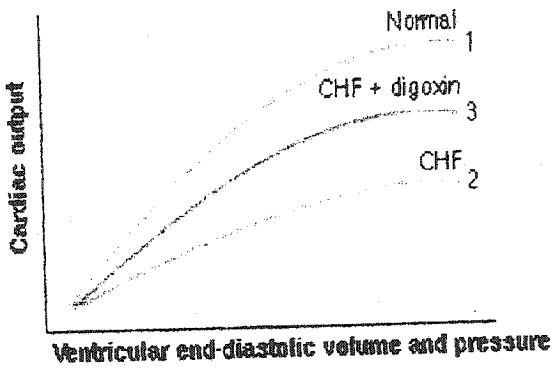

Figure 2. Effects of digoxin on the Frank-Starling curve. (From Sorrentino MJ.[49])

Digoxin also seems to reduce central sympathetic outflow in HF possibly via sensitization of high-pressure baroreceptors [50]. Plasma renin levels are lower which may be secondary to inhibition of sympathetic activity or a direct renal effect as digoxin inhibits Na-K ATPase in the kidney and thus decreases renal tubular reabsorption of Na, increasing delivery of Na to the distal tubules and suppressing renin excretion [5] (see Figure 3).

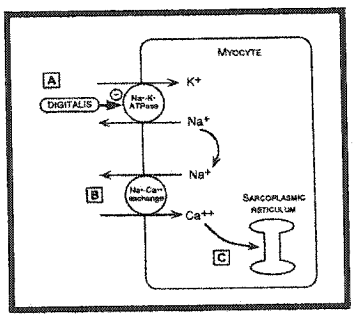

Figure 3. Mechanism of action of digoxin (from Hosenpud et al.[5])

Digoxin improves morbidity without effect on mortality. Lee et al. [51] examined the effects of digoxin in HF patients (average EF 29.4%) with normal sinus rhythm using a randomized, double-blind crossover protocol. Long-term use of digoxin produced clinical benefit in some HF patients who did not have atrial fibrillation. Greatest symptomatic improvements were seen in those patients with a third heart sound. No other variable contributed independently to

digoxin's effect. The Digitalis Investigation Group [52] published the largest clinical trial with digoxin in 1997. 6800 patients with HF (average EF 28.5%) were randomized to receive digoxin or placebo in addition to an ACEi and diuretic. There was no significant reduction in deaths due to progressive HF or all-cause mortality in the digoxin group compared to placebo, however, there was a significant decrease in hospitalizations for worsening of heart failure or cardiovascular events.

The Dutch Ibopamine Multicenter Trial investigators [53] examined the effects of ibopamine (an orally active dopamine agonist), digoxin or placebo on HF symptoms and neurohormonal activation in 161 patients with NYHA class II and III heart failure. There was no difference after treatment with digoxin in heart failure score or functional class; however, the digoxin group preserved exercise time whereas the placebo group had a mean decrease of 60 seconds during the incremental bicycle exercise protocol. Digoxin also produced a significant decrease in plasma NE levels at 3 and 6 months compared to placebo. Furthermore, in patients receiving long-term digoxin therapy, withdrawal of the drug produces a decrease in maximal and submaximal exercise tolerance, worsening of NYHA classification, and decreased LVEF [54].

Digoxin is recommended for those HF patients who continue to be symptomatic (NYHA class II-IV) on ACEi and diuretic and in all HF patients with NYHA class IV symptoms [50]. It is not used in patients with preserved LV systolic function, diastolic dysfunction (as the positive inotropy decreases LV relaxation), after an acute myocardial infarction (MI), or in treatable high cardiac output syndromes such as anemia and thyrotoxicosis. After an MI, digoxin may increase myocardial O_2 demand by increasing contractility and inducing peripheral or coronary vasoconstriction. In this situation, digoxin may potentially be arrythmogenic [5].

Lower doses (<0.25mg daily) produce mainly a neurohormonal effect with little inotropic activity. At higher doses (>0.25mg daily), there is an increase in contractility of the heart, however, increasing the dose of digoxin does not necessarily improve symptoms of HF [54].

2.1.2 Diuretics

Compensatory mechanisms of HF include salt and fluid retention to maintain BP and Qc; however, increased ventricular filling pressures may lead to transudation of fluid into the lungs. In the setting of acute heart failure, diuretics antagonize the sodium (Na^+) retention of HF by inhibiting the reabsorption of Na^+ or chloride at specific sites in the renal tubules [3]. This relieves congestion by decreasing intravascular volume and filling pressures (RV, LV, atrial and pulmonary). Decreased pulmonary edema may improve oxygenation and decrease dyspnea. Furthermore, venodilation increases within minutes of furosemide administration producing a net decrease in afterload and the lower filling pressures may limit ischemia. However, since contractility remains the same, Qc may decrease, fatigue and dizziness may occur [5]. Volume depletion may result in hypotension and renal hypoperfusion that can evolve into prerenal azotemia and renal failure [50].

With chronic use of diuretics, there is a decrease in intravascular volume and thus cardiac preload, with associated improvements in LV performance [50]. Fluid shifts lead to a decrease in peripheral edema reducing painful limb symptoms [5]. There is an increase in plasma NE, renin activity and angiotensin II concentrations, which contribute to the progression of HF [5, 50].

While all diuretics increase Na^+ excretion and urine volume, there are different types depending on where they act in the kidney as demonstrated in Figure 4.

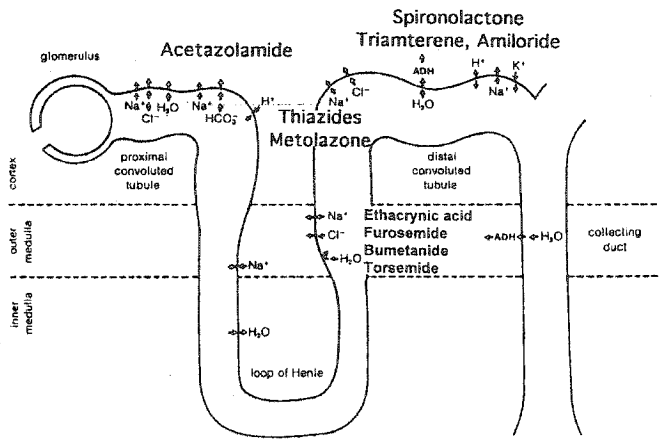

Figure 4. Effect of diuretics on fluid and electrolyte transport within the nephron (From Puschett et al. [55])

Loop diuretics (furosemide / bumetanide / torsemide)

Loop diuretics are absorbed intestinally and secreted in the proximal tubule by the organic secretory pathway. Thus they act from the luminal side of the thick ascending limb loop of Henle to inhibit the NaCl cotransporter. Since Na^+ reabsorption is inhibited, a larger amount of Na^+ is delivered to the distal tubule[5]. These diuretics are the most potent agents available as several times more NaCl is normally reabsorbed in the loop of Henle than the distal convoluted tubule and thus can be used more effectively in patients with advanced renal failure [50].

However, if renal function is severely impaired (creatinine clearance <5mL/min) loop diuretics become ineffective [3]. Patients may develop resistance by enhanced NaCl reabsorption in distal tubules due to hypertrophy of tubular cells from continuous use, or, in the case of renal failure, competition with endogenous acid may produce impaired proximal tubule secretion [5].

Thiazide diuretics

Thiazide diuretics inhibit sodium reabsorption in the distal tubule causing increased sodium and water excretion. Since they act proximal to the distal site

of K^+ secretion, they promote the active excretion of K^+, thus thiazide diuretics are classified as K^+ wasting. Significant loss of K^+ from plasma may contribute to fatal ventricular arrhythmias. They are generally reserved for patients with mild extracellular volume overload as they act at the distal tubule to inhibit urinary diluting capacity and are thus not as potent as loop diuretics. They become ineffective when glomerular filtration falls below 25-30mL/min and renal clearance may decrease with advancing HF [50].

Spironolactone

Spironolactone is an aldosterone-receptor blocker in the distal renal tubule [50]. Since aldosterone enhances Na^+ reabsorption, antagonizing its effects causes increase Na^+ loss in urine and is K^+ sparing [5]. Aldosterone may exert adverse effects on the structure and function of the heart and peripheral vessels independent to the deleterious effects produced by angiotensin II and may thus decrease the risk of progression of HF[3].

Pitt et al. [56] studied 1663 patients with HF randomized to spironolactone or placebo. Spironolactone reduced the risk of hospitalization from cardiovascular causes and decreased all cause mortality and death from cardiac causes. Spironolactone improved functional class compared to placebo. There was no significant difference between groups in serum Na^+ concentration, blood pressure or HR during the study. Increases in serum K^+ were seen but were not considered clinically important.

Treatment with spironolactone should be initiated at 12.5 mg per day and titrated up to 50 mg per day. Serum K^+ and creatinine levels should be monitored. Adverse effects include hyperkalemia and gynecomastia.

2.1.2.1 Risks of Treatment with Diuretic Therapy

Loss of electrolytes with diuretic therapy is due to enhanced delivery of Na^+ to the distal renal tubules and exchange of Na^+ for othe rcations. Depletion of K^+

and magnesium can predispose patients to serious arrhythmias, especially with concomitant treatment with digoxin[3]. Hypotension and azotemia can occur as a result of worsening HF due to redistribution of blood flow to the brain and heart. With excessive diuretic use, decrease in vascular volume can exacerbate the problem and further decrease peripheral perfusion [3]. During volume depletion, there is activation of endogenous neurohormonal systems, especially the renin-angiotensin system and a higher level of angiotensin II probably helps with renal function and blood pressure support, however, this contributes to disease progression in the long term [3, 8].

2.1.2.2 Initiation and Maintenance of Diuretic Therapy

In patients with fluid retention, a low dose of diuretic is started and slowly titrated up until urine output increases and weight decreases. The goal of treatment is to reduce symptoms and signs of fluid retention [8]. If electrolyte imbalances occur, they should be treated aggressively and the diuresis continued. If hypotension of azotemia occurs, one may slow the diuresis or, if fluid retention persists, positive inotropic agents or vasodilator drugs can be used to increase peripheral perfusion[3].

With long-term use of diuretics, patients may become unresponsive to their effects. As previously described, resistance may occur with impaired proximal tubule secretion or enhanced NaCl reabsorption in distal tubules due to hypertrophy of tubular cells after continuous use [3, 5]. Furthermore, the bioavailability of furosemide is usually 60%, but in decompensated CHF, edema in bowel walls or intestinal hypoperfusion inhibits absorption of the drug and increasing dose of the diuretic or intravenous administration may be required [3,5].

2.1.3 Angiotensin Converting Enzyme (ACE) inhibitors

ACE inhibitors (ACEi) inhibit the enzyme responsible for converting angiotensin I to angiotensin II. They reduce circulating and tissue concentrations of

angiotensin II, increase plasma concentrations of vasodilating substances such as prostaglandins, bradykinin and nitric oxide, and may diminish sympathetic nervous system activation thus influence hemodynamics in HF [50]. ACEi decrease symptoms of HF, improve exercise capacity, decrease hospitalization for HF and prolong survival [57-59].

ACEi improve symptoms of HF as per patients' subjective rankings [60] and improve NYHA functional classification [58,60,61]. Total mortality and hospitalizations for HF are reduced significantly with the use of ACEi in a broad range of patients [57-59,62]. Patients with the lowest ejection fractions appear to have the greatest benefits and the greatest effects are seen in the first 3 months, but additional benefit is observed with further treatment [62]. Packer et al. [63] reported long-term (39-58 months) treatment with lisinopril in high doses (32.5-35 mg) decreased all-cause mortality by 8% ($p=0.128$) and hospitalization for HF by 24% ($p=0.002$) than lower doses (2.5-5 mg).

The SOLVD Treatment trial [57] investigated 2,569 patients with mild-to-moderate HF who were randomized to either placebo or enalapril for an average of 41 months. Treatment with enalapril was associated with a 16% reduction ($p=0.0036$) in all-cause mortality and a 26% reduction ($p<0.0001$) in death or hospitalization for HF. In the V-HeFT II trial [59], 804 patients with mild-to-moderate HF were randomized to enalapril or hydralazine-isosorbide dinitrate. Treatment with enalapril was associated with a 33.6% reduction in all-cause mortality after one year and a 28.2% reduction after 2 years compared to vasodilator therapy. The reduction in mortality was due primarily to a decrease in sudden death in the enalapril treated patients. The CONSENSUS study [58] randomized 253 patients with severe HF (NYHA class IV) to either enalapril or placebo and found 27% reduction in all cause mortality with enalapril; however, there was no significant reduction in combined risk of death and hospitalization for HF. Enalapril has been found to decrease the persistence of baseline ventricular tachycardia at 3 months and the emergence of new ventricular

tachycardia at 1 and 2 years in patients with CHF. The reduction in ventricular tachycardia parallels a reduction in sudden death [64].

HR [65,66] and BP are reduced [59,65, 66,67] and LVEF is significantly increased [59- 61, 65] after ACEi therapy. Konstam et al. [65] for the SOLVD investigators found significant reduction in LVEDV and LVESV up to 3 years after withdrawal of enalapril, treatment. Two weeks after withdrawal of enalapril, LVESV and LVEDV returned to baseline levels, but not to the higher levels observed with placebo. However, Khattar at al. [61] and the RESOLVD pilot study investigators [66] did not find a significant reduction in LVESV after 3 months of captopril treatment, although a significant reduction in LV wall thickening, LV mass and reversion of the LV to a more spherical shape were observed. It is possible that the ACEi therapy does lead to a small decrease in LV mass and a more spherical geometry, but the available data suggests that ACEi's do not regress hypertrophy or reverse the remodelling process [12,68].

Gheorghiade et al. [48] measured HR and central hemodynamics during maximal chair cycle exercise with right heart catheterization. After acute intravenous administration of captopril, there was a significant reduction in systemic vascular resistance, an increase in systemic arterial pressure, an increase in cardiac index and an increase in maximal exercise time. No change in maximal HR, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) or stroke work index (SWI) was observed. Khattar et al [61] studied HF patients during maximal graded cycle exercise testing with a right heart catheter in place before and after 3 months of captopril therapy. Resting HR, SWI, and systolic and diastolic BP did not change at rest, but maximal exercise HR decreased after therapy, whereas BP and SWI did not change. PCWP was significantly reduced at rest and during maximal exercise after the 3 months of captopril.

In the V-HeFT II study [59], peak VO_2 did not change after 6 months of enalapril therapy and after one year, oxygen consumption declined progressively with treatment. Likewise, McConnell et al. [69] did not find an increase in peak VO_2 with captopril therapy. Increase in maximal exercise duration on a modified Naughton treadmill protocol has been observed over 3 months in captopril treated patients with HF [60]. As for submaximal exercise duration, the RESOLVD pilot study [66] did not observe an increase in 6 minute walk test duration after enalapril.

2.1.3.1 Mechanism of action of ACEi

With acute administration of ACEi to patients at rest, response varies from patient to patient and reflects the magnitude of renin angiotensin system (RAS) activation. In general, there are no changes in cardiac or stroke work indices, a decrease in RV and LV filling pressures, PCWP, arterial pressure and a modest decrease in HR (about 5bpm) [48]. Acutely, administration of ACEi causes a short-term decrease in renal function and a reduction in thirst via decreased secretion of arginine vasopressin. However, with long-term use, there is a natriuresis and improvement in K^+ balance by the blocking of AII mediated aldosterone secretion that decreases Na^+ reabsorption and K^+ loss [5].

ACEi block the RAS but also inhibit kininase II and thereby potentiate the action of bradykinin [70]. Bradykinin produces vasodilation and releases nitric oxide, endothelium-derived growth factor and prostacyclin, all of which are growth inhibitors [12]. The increase in bradykinin may be responsible for ACEi mediated improvement in endothelial function [71] and may play a role in anti-remodelling effects of ACEi (antihypertrophic and antiproliferative actions). The chronic administration of ACEi does not lead to complete suppression of AII, as it can be formed through alternate non-ACE pathways such as trypsin, cathepsin or chymase [70].

2.1.3.2 Risks of Treatment with ACEi Therapy

Due to the effects of angiotensin suppression, hypotension, worsening renal function and potassium retention can occur with ACEi therapy. Blood pressure decreases in almost every patient treated with ACEi but this is usually asymptomatic. Hypotension is primarily seen early on in therapy and is a concern if it is accompanied by worsening renal failure or syncope. Decreasing the dose of diuretic and starting with a low dose of ACEi and increasing slowly can manage this problem in most cases.

In patients with HF who are highly dependant on the renin-angiotensin system for support of renal homeostasis, a decrease in glomerular filtration due to ACEi may occur as angiotensin mediates efferent arteriolar vasoconstriction. Thus in patients with severe HF or hyponatremia, azotemia may occur. The risk of azotemia is increased with renal artery stenosis or concomitant non-steroidal anti-inflammatory drug (NSAID) therapy. Renal function usually improves with a decrease in diuretic therapy. Hyperkalemia may be associated with decreasing renal function or in patients taking K supplements or K-sparing diuretics.

Because ACEi's potentiate the effects of kinins, cough and angioedema can occur. Cough occurs in 5-15% of HF patients taking ACEi, and is usually non-productive. Patients should be encouraged to continue the therapy despite the cough, as the benefits are significant. Angioedema is a rare but life-threatening problem and ACEi should be avoided in patients suspected of having this problem[3].

2.1.3.3 Initiation and Maintenance of ACEi Therapy

All patients with HF due to LV dysfunction should be treated with an ACEi unless they have a contraindication, as they have been shown to prolong life [59]. ACEi should be given to all patients with LVEF less than 40% with NYHA class I symptoms that are asymptomatic or minimally symptomatic to prevent HF [72].

Patients with fluid retention should be prescribed an ACEi in combination with diuretic therapy to prevent peripheral and pulmonary edema and maintain Na^+ balance.

Absolute contraindications to ACEi therapy include prior angioedema or anuric renal failure with ACEi's and pregnancy. Relative contraindications include SBP < 80 mmHg, serum creatinine > 3mg/dL, bilateral renal artery stenosis and serum potassium > 5.5 mmol/L[3, 8]. The use of intravenous ACEi after acute myocardial infarction is not recommended [8].

Treatment should be started at a low dose and titrated up if tolerated to the amount shown to reduce mortality in clinical trials [57- 59, 68], which would be 20 mg enalapril or 150 mg of captopril daily [8]. Renal function and serum potassium should be assessed 1-2 weeks after initiation of therapy.

2.1.4 Angiotensin II receptor Blockers (ARB)

Although ACEi provided a major advance in the treatment of HF, they can be associated with significant side effects. In addition to blocking the formation of angiotensin II, ACEi prevent the breakdown of bradykinin. Also, the chronic administration of ACEi does not lead to complete suppression of AII, as it can be formed through alternate non-ACE pathways such as trypsin, cathepsin or chymase [70]. Angiotensin receptor blockers, or ARB's, were developed based on the belief that the benefits of ACEi were related to the suppression of angiotensin II formation and the side effects were related to accumulation of kinins. However, as the knowledge of HF advances, we now know that many of the benefits of ACEi may be related to this increase in kinins.

Most of the studies have been to compare the effects of treatment with ARB to ACEi. The first, larger-scale clinical trial of ARBs was the ELITE study [73]. In this multi-centre, randomized, double-blind trial, 722 patients with NYHA class II-IV HF and EF of 40% or less were randomized to losartan (ARB) or captopril

(ACEi). Treatment with losartan was associated with a 32% lower risk of death and/or admission for HF (p=0.075). There was no difference between drugs on the frequency of hospitalization or in all-cause mortality and sudden cardiac deaths, nor was there a difference between the 2 groups in renal function or NYHA functional class improvement. Discontinuation rates were higher for the captopril group. However, this study was not powered for mortality and the total number of events was small. As a result, a longer-term mortality trial, the ELITE II study, was undertaken and HF patients were followed for 555 days. There were no significant differences between ACEi and ARB in all-cause mortality or sudden death [74]. The RESOLVD study [66] randomized 768 patients with HF to candesartan, enalapril or the combination of both drugs. There was no significant changes in NYHA functional class or quality of life with ACEi, AII blockade or both; however, this study was prematurely terminated after concerns were voiced about the increased number of events in patients treated with candesartan, however, there was no statistically significant difference in mortality or hospitalizations among the three groups. Other investigators have found significant improvements in NYHA functional class [75, 76] or reduction in hospitalization for HF [76] when ARB was added to ACEi compared to placebo and ACEi. Granger et al. [77] studied candesartan therapy in patients with HF intolerant of ACEi. There was no difference in discontinuation of candesartan compared to placebo, but mortality and morbidity were similar in both groups. For the moment, the best available data does not confirm that ARBs are superior to ACEi in reducing mortality in HF. However, they may be considered an alternative to patients who are intolerant to ACEi [3].

In humans with heart failure on stable doses of ACEi, addition of losartan further reduces cardiac afterload as evidenced by decreased systolic BP [66,78]. An inhibition of the vasoconstrictive response of rabbit aortic smooth muscle has also been seen with losartan [15]. Improvements in ventricular function are variable in the literature. Lang et al. [79] found improvement in LVEF in patients treated with 50mg of losartan but not 25mg. In the RESOLVD trial [66], there was

a trend toward an increase in LVEF for combination therapy with candesartan plus enalapril compared to candesartan or enalapril alone, but it was not significant. This study also showed a significant increase in LVEDV and LVESV for the monotherapy groups, whereas the combination group taking 8mg of candesartan plus enalapril had a decline in LVESV. The ELITE ventricular function substudy [80] found both captopril and losartan significantly reduced LVEDV index. Captopril also reduced LVESV index whereas a non-significant trend was observed in the losartan group. After drug withdrawal, LVEDV index remained significantly lower than baseline in the captopril group.

Most investigators have found an increase in maximal exercise time with ARBs, but no improvement in submaximal exercise. The RESOLVD investigators [66] did not observe significant changes in 6 minute walk distance with ACEi, AII blockade or both. Lang et al. [79] withdrew ACEi therapy in clinically stable HF patients and introduced losartan (ARB) or enalapril (ACEi) for 12 weeks. There was no change after therapy in 6 minute walk distance, but the modified Naughton treadmill exercise test duration was increased from baseline in the enalapril group ($p=0.03$) and marginally increased in the losartan group ($p=0.06$). Hamroff et al. [75] found that adding losartan to patients with severely symptomatic heart failure on stable doses of ACEi improved peak Vo_2 and relieved symptoms. Candesartan has also been shown to produce a dose-related improvement in peak exercise time [81].

2.1.4.1 Mechanism of action of Angiotensin II receptor blockade

Assuming that the ACE independent pathways for AII production are clinically relevant, the nonpeptide antagonists, such as *losartan* or *candesartan*, make it possible to block the RAS at the angiotensin receptor without the confounding partial agonist effect of peptide AII receptor antagonists or the non-specific inhibition of the angiotensin converting enzyme with ACEi. These ARBs are selective to the AT_1 receptor, which mediates most of AII effects. When AT_1 receptors are blocked, AII levels increase [81] and there is a reduction in

vasoconstriction, aldosterone production, myocyte and smooth muscle hypertrophy, NE release and vasopressin release. ARB use results in increased and unopposed stimulation of AT_2 receptors, the significance of which is unknown. The increase in bradykinin and prostaglandins induced by ACEi are not found with AT_1 blockade, which may be important in the treatment of HF. Losartan blocks only the action of AII at its receptor [15, 16] and has been shown to have no effect on numerous receptor systems, such as vasopressin, serotonin, acetylcholine, histamine and bradykinin [15].

The benefit of ACEi in reducing preload and afterload would also be expected to reduce the inotropic effect of AII. However, the presence of a dual pathway for AII formation in the human heart represents a potential escape from complete inhibition of cardiac AII formation by ACEi [20]. In a study done by Spinale et al. [22] using pigs that had pacing-induced heart failure, ACEi alone reduced resting heart rate (HR), systemic vascular resistance, LV end diastolic dimension (LVEDD), LV peak wall stress, pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance and mean pulmonary artery pressure (PAP) compared to no therapy. LV fractional shortening was increased. More interesting was the increase in Qc despite the reduction in HR and LVEDD. With AII blockade alone, these effects were not seen, but when AII blockade was added to ACEi, there was a further reduction in HR, LVEDD, LV peak wall stress, PCWP, and PAP and systemic vascular resistance compared to ACEi alone or no therapy. There was also a further increase in fractional shortening of the LV and cardiac output compared with monotherapy alone. A contributory factor for the improved Qc might be a reduction in LV afterload and improvement in contractility as indicated by the increase in velocity of fractional shortening in the myocardium.

In heart failure, plasma norepinephrine (NE), epinephrine (EPI), endothelin and renin concentrations are higher than in controls [22]. Since bradykinin, which releases NE, is not increased with angiotensin II blockade but is increased with

ACEi [73], one would expect NE levels to increase with ACEi but not with ARB therapy. In the study by Spinale et al. [22], NE and EPI plasma levels are reduced and renin levels increased with the addition of ACEi or AII blockade, but the combination of both drugs does not significantly enhance the changes. In the ELITE trial [73], plasma NE levels increased in the ACEi group but decreased in the ARB group. In the RESOLVD trial [66], NE and EPI levels decreased and renin levels were shown to increase across all groups (candesartan, enalapril and combination) but the smallest increase in renin was in the candesartan group.

2.1.4.2 Initiation and Maintenance of ARB Therapy

ARB's are not generally approved for use in HF, however, they can be given to patients who are being treated with digoxin, diuretics and a β-blocker but who cannot take an ACEi because of cough or angioedema [7].

2.2 Treatment with β- Blockers

β-blockers have traditionally been contraindicated in heart failure patients because of the negative inotropic effects of β-blockade [82]. However, in the past few decades there have been a number of randomized control trials [83-89] showing improvement in morbidity and mortality when they are used in this patient population. There are three generations of β-blocking agents; an overview is presented in Table 2. β-blockers differ in the degree to which they antagonize the effects of the sympathetic nervous system in patients with HF. Acute administration of the first generation agents reduce cardiac index and increase systemic vascular resistance and therefore are poorly tolerated by patients with HF [40,90]. Metoprolol, because it does not antagonize β_2-receptor-mediated vasodilation or block cardiac β_2-receptors, produces less reduction in cardiac index and vasoconstriction and is therefore better tolerated [40, 90]. Carvedilol and bucindolol cause peripheral vasodilation via α_1-receptor blockade and thus do not generally lower cardiac index acutely because myocardial depression is offset by the reduction in systemic vascular resistance [40, 90]. Since the recent focus of

most HF studies has been on metoprolol and carvedilol, this review will focus on these two drugs.

Table 2. Properties of β-blockers

Generation	Tolerability	β_1	β_2	β_2-agonist §	α_1- blockade	ISA
First						
- propranolol	Poor	+	+		-	¶
- timolol		+	+			
Second						
- metoprolol	Good	++	-		-	-
- atenolol		+				
- bisoprolol	Good	++			-	
- betaxolol		+				
- ICI 118551			+			
Third						
- prazosin					+	
- labetalol		+	+		+	+
- carvedilol	Good	+	+		+	-
- pindolol		+	+	+	-	+
- celiprolol		+		+	?α_2 block	+
- dilevalol		+	+	+		
- bucindolol*	Good	+	+		- (but ↓PVR)	+
- nebivolol	Good	++	+		- (but ↓PVR)	-

* Not available in Canada
§ Peripheral vascular β_2 agonist activity resulting in less reflex vasoconstriction as unblocked peripheral vascular β_2 receptors can mediate vasodilation
ISA = Intrinsic sympathomimetic activity (antagonist activity yet partially activate β-receptors)
PVR = peripheral vascular resisitance
¶ Decrease contractile state, increase SVR, decrease cardiac output

2.2.1 Metoprolol and Carvedilol

Metoprolol is a second generation lipophilic, β_1 selective antagonist with no intrinsic sympathomimetic activity [83,91]. Carvedilol is a third generation β-blocker that also has α_1 blocking properties. It is mildly selective for $\beta_1$vs β_2 receptors and does not have ISA [91]. Table 3 presents an overview of the resting changes observed after carvedilol and metoprolol therapy.

When metoprolol is compared to carvedilol in clinical trials, no significant difference between groups has been found in reduction of resting HR after 12-16 weeks of therapy [97, 104]. Kukin et al. [100] compared the 2 drugs over 6 months, and found carvedilol to decrease resting HR significantly more than metoprolol. Metra et al. [96] and Maack et al. [101] studied the effect of metoprolol

or carvedilol over 13 to 15 months and did not find a significant difference between drugs in reduction of resting HR.

Table 3. Effects of β-blockers on resting cardiovascular and clinical parameters

Resting CV Effects	**Metoprolol**	**Carvedilol**
Heart rate	Decrease[82, 83,92-101]	Decrease[61, 89, 95-97, 100, 101,106-111]
Systolic BP	Increase[82,93] or N/C[94, 95, 97, 100]	Decrease[61,89, 95, 97,107,108, 110] or N/C[100]
Diastolic BP	N/C[83,92, 95]	Decrease[89, 97]
Mean AP	N/C[96] or increase[99]	N/C [96, 106, 109]
Pulmonary AP	Decrease[96]	Decrease[96, 106, 109]
PCWP	Decrease[93, 96, 99]	Decrease [61,96, 106, 109,112] or N/C[111]
Right atrial pressure	N/C [93, 96, 99]	N/C [96, 106, 111] or decrease[109]
PVR	N/C[96]	N/C [96, 106] or decrease [109]
Stroke volume index	Increase[93, 96, 99]	Increase [61,96, 106, 109]
Stroke work index	Increase[93, 96, 99]	Increase[96, 106, 109, 111]
LVEF	Increase[82,92-98, 100-104]	Increase[84, 85, 89, 95-97 100, 101, 104,107-112]
LV remodelling	Yes[82,]	Yes[84, 110]
LV end diastolic volume	Decrease[82, 96, 101] or N/C[97]	Decrease[96, 97,107,108,113]
LV end systolic volume	Decrease[82, 96] or N/C[97]	Decrease [61,96, 107,108, 110, 112, 113]
LV fractional shortening	Increase[97, 101]	Increase[97,101,106, 107, 113]
Resting clinical effects		
NYHA functional class	Improvement[93,95-97, 99-103,105] N/C[94]	Improvement [85,89,96,97, 100, 101,104,106,109,110,112] N/C [84,95]
Quality of life score	N/C[94- 97, 100,105]	Improvement[95-97, 100, 109] or N/C[84, 85, 89, 107,108]

N/C = no change, BP= blood pressure, AP= arterial pressure, PCWP= Pulmonary capillary wedge pressure, PVR = Pulmonary vascular resistance, LV= Left ventricular EF=ejection fraction

Increase in resting LVEF has been found when using metoprolol [82,92-98, 100-104] and carvedilol [84, 85, 89, 95-97, 100, 101, 104, 107-112] in trials on HF patients. The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial [84] was a dose-response investigation of carvedilol on LV function, morbidity and mortality in 376 subjects with mild-to-moderate HF. Carvedilol treatment was associated with a dose-related increase in EF, as well as a dose-related decrease in morbidity and mortality. The improvements in LVEF have been shown to continue over 18 months of therapy with metoprolol [82]. Results of a meta-analysis by Packer et al. [114] of 19 randomized controlled trials of metoprolol or carvedilol that measured LVEF before and after an average of 8.3 months of treatment showed a significantly greater increase in LVEF in

carvedilol vs. metoprolol groups. In 4 controlled trials that compared metoprolol directly with carvedilol, again the mean LVEF increased more in the carvedilol groups.

Even though carvedilol and metoprolol have been shown to decrease LVEDD [82, 96,97, 101,107,108, 113] and LVESV [61, 82, 96, 107,108, 110, 112,113] as well as induce LV remodelling [61, 82, 84, 110], variable results have been found on LVESV and LVEDV after treatment with β-blockers in carvedilol vs. metoprolol trials. Maack et al. [101] performed a cross-over study with metoprolol and carvedilol. After 12 months of treatment with either drug, only the metoprolol arm showed a decrease in LVEDD. The two groups were then crossed over to the other β-blocker for 6 months. Neither drug produced significant changes in LVEDD or LVESD. Metra et al. [96] found significant decreases in LVESV and LVEDV after 13-15 months of treatment with both carvedilol or metoprolol but the difference between groups was not significant. Gilbert et al. [104] did not find any significant change in LVEDD after 4 months of either drug and Sanderson et al. [97] found a significant decrease in LVEDD only in the carvedilol group and not the metoprolol group. Perhaps this can be explained by the duration of treatment with β-blockers. In one study by Hall et al. [82], metoprolol therapy for 3 months produced a significant decrease in LVESV only, whereas the control group on standard HF therapy and not β-blockers did not show a change in LVESV. However, after 18 months of metoprolol therapy, significant decreases were also seen in LVEDV. After 3 months of therapy with metoprolol, patients did not have a change in LV mass, but after 18 months, LV mass had regressed significantly and the LV had undergone remodelling and become less spherical and more elliptical. However, Khattar et al. [61] found a significant decrease in LVESV, LV wall thickness and LV mass as well as remodeling to a more elliptic shape after only 3 months of carvedilol treatment.

No change in resting mean arterial pressure has been reported in most studies with long-term administration of carvedilol [96, 106, 109] or metoprolol [96] therapy.

However, one study did find an increase in resting MAP with metoprolol treatment [99]. Metoprolol [93,96, 99] or carvedilol [96, 106, 111] have not been shown to decrease resting right atrial pressure (RAP). However, with carvedilol, significant decreases in resting pulmonary artery pressure are consistently reported [96, 106, 109]. Resting PCWP is decreased with metoprolol [93,96, 99] and carvedilol [96, 104, 106, 109, 112]. When the two drugs are compared in clinical trials, observations are inconsistent. Metra et al. [96] compared hemodynamic measurements at rest after 12 months of carvedilol or metoprolol and found that although both drugs decreased pulmonary artery pressure and PCWP, there was a significantly greater decrease in the carvedilol group probably because of the α-blockade with this drug. However, Gilbert et al. [104] reported that only carvedilol decreased resting PCWP from baseline.

Clinically, both metoprolol [93,95- 97,99-103,105], and carvedilol [85, 89, 96,97, 100, 101, 104, 106, 109, 110, 112] improve NYHA class and quality of life scores significantly, but neither drug has demonstrated a clear advantage over the other. When comparing metoprolol or carvedilol in studies, both drugs have been found to improve NYHA class equally [96,97, 100, 101]. However, Gilbert et al. [104] found an improvement in NYHA class in the carvedilol group only when metoprolol and carvediolol were given at doses to produce equivalent degrees of minimal and maximal HR [104]. Arumanayagam et al [95] found a mean decrease in NYHA functional class after 12 weeks of metoprolol therapy but no change in class after carvedilol therapy.

β-blockers have been shown in many multicenter randomized placebo-controlled trials to decrease morbidity and mortality [83- 89, 93,108] and are summarized in Table 4. These trials enrolled patients with LVEF <35-45% already treated with diuretics and an ACEi, with or without digoxin. Lechat et al.[115] performed a meta-analysis of 18 published double-blind, placebo-controlled, parallel-group trials of β-blockers in HF. β-blockade reduced all-cause mortality by 32% (p=0.003), and the reduction in mortality was greater for nonselective β-blockers than for β_1-selective agents (49% vs. 18%, p=0.049). However, more data are needed to

assess the efficacy of β-blockers in older people, women, racial subsets and patients with preserved systolic function or severely impaired renal function. Colucci et al. [85] did examine the effects of carvedilol on patients with mild symptoms of HF and found a 48% reduction in progression of HF (defined as death due to HF, hospitalization for HF or an increase in medications) but these patients had an EF < 35%.

Table 4 Morbidity and Mortality Outcomes in Heart Failure

Trial	Drug	# Patients	Mortality	Hospitalization for HF
CIBIS I (1994)	bisoprolol	641	20% decrease (p=0.22)	34% decrease (p<0.01)
CIBIS II (1999)	bisoprolol	2647	32% decrease (p<0.0001)	32% decrease (p<0.0001)
BEST (1995)	bucindolol	2708	12.5% decrease (p=0.04)	16.7% (p<0.001)
MDC (1993)	metoprolol	383	no decrease	no decrease
MERIT-HF (1999)	metoprolol	3991	34% decrease (p=0.00015)	35% decrease (p<0.001)
US Carvedilol HF (1996)	carvedilol	1094	65% reduction (p=0.0001)	27% decrease (p=0.036)
MOCHA (1996)	carvedilol	345	73% decrease (p<0.001)	45% decrease (p=0.03)
PRECISE (1996)	carvedilol	278	no decrease	46% decrease (p=0.029)
ANZ Carvedilol II (1997)	carvedilol	415	no decrease	non-significant decrease
COPERNICUS (2001)	carvedilol	2289	35% reduction (p=0.00014)	24% decrease (p<0.0001)
CAPRICORN (2001)	carvedilol	1959	23% decrease (p=0.03)	non-significant decrease

The Trial Data and Safety Monitoring Board terminated the US Carvedilol Heart Failure study Group [88] early because of a 65% reduction (p<0.0001) in mortality with carvedilol compared to placebo. This was a combination of 4 studies each with different randomization protocols and secondary endpoints, but the primary endpoint was total mortality for all trials. On the other hand, in the Metoprolol in Dilated Cardiomyopathy study [93], patients were randomized to placebo or metoprolol for 12-18 months. Treatment with metoprolol was associated with a 34% reduction (p=0.058) in the combined risk of death or transplant listing. However, most of the benefits of metoprolol were associated with a significant reduction in the risk of transplant listing (p=0.0001), because metoprolol did not decrease the risk of death or the frequency of hospitalizations. One of the mechanisms through which β-blockers may reduce mortality likely involves an antiarrhythmic effect as β-blockers consistently reduce the sudden death rate in trials [83,116,117].

2.2.1.2 Mechanisms

The mechanism by which β-blockade improves LV function is not clear. Down-regulation of β-receptors in HF probably occurs as a protective mechanism against the long-term sympathetic stimulation and its possible adverse effects [118]. When metoprolol is administered acutely to heart failure patients, there is an increase in systemic vascular resistance that results in an increase in LV afterload and LV volume [82, 91] and, aggravated by a decrease in HR, LVEF decreases [82], which is keeping with the known negative inotropic and chronotropic effects of β-blockade. On the other hand, when carvedilol, which is non-selective and blocks α_1-receptors causing peripheral vasodilation, is administered acutely to patients with HF, there is a significant decrease in resting HR, MAP and PCWP, but CI, SVI and SWI do not decrease since peripheral resistance is decreased [109].

After long term β-blockade with metoprolol, there is upregulation of β-adrenergic receptors, presumably due to upregulation of the β_1-subtype, which is downregulated in the failing heart [41, 104]. This upregulation would allow for renewed responsiveness to β-agonist stimulation which has been postulated to facilitate the myocardial contractile response to sympathetic stimulation and perhaps lead to improved exercise tolerance, reduction in metabolic stress, (lower HR) [118], improved myocardial energy balance and enhanced recovery of the failing myocardium [93]. However, carvedilol has no effect on the cardiac β_1-receptor density compared to baseline or placebo [104], yet significant improvements in LV function have been seen with carvedilol treatment [84, 85, 89, 95, 96, 100, 104, 107-112]. Furthermore, improvement of LVEF precedes any remodelling effect [82]. All β-blockers that prolong survival block the β_1-receptor but there must be other properties of the β-blocking agent that exert its effect on the sympathetic nervous system and provide clinical benefit. Thus, there must be other mechanisms working to improve LV function with β-blocker therapy, which probably include reduced autonomic activity [112], neuroendocrine deactivation and electrophysiologic adaptations that benefit the heart failure patient [83].

Carvedilol blocks all 3 adrenergic receptors (α_1, β_1, and β_2) that have been implicated in mediating the deleterious effects of catecholamines in the heart and blood vessels [26]. Carvedilol reduces coronary sinus and transmyocardial NE levels [104] perhaps because of a decrease in release of NE from presynaptic nerve terminals since β_2-receptors, present on the presynaptic nerve terminals in the heart, are blocked with carvedilol [40]. On the other hand, metoprolol tends to increase myocardial NE levels and enhance sensitivity of the heart to β-receptor stimulation [90, 104] since, unlike carvedilol, metoprolol up-regulates β-adrenergic receptors after long-term β-blockade [104]. Thus, the greater improvements with carvedilol in LV performance seen in many studies may be related to its ability to minimize transmyocardial NE levels.

Carvedilol differs from metoprolol in that it blocks α_1-receptors. Blockade of these receptors causes moderate arteriolar dilation and reduction in peripheral vascular resistance, which accounts for its vasodilator properties [91]. In clinical trials comparing carvedilol to metoprolol, carvedilol has been shown to lower SBP and DBP greater than metoprolol [95, 97]. Both of these trials were 12 weeks long, however, with longer use, the vasodilator activity is not prominent [61, 100, 106] and the importance of this effect clinically is uncertain as metoprolol and carvedilol produce similar changes in systemic vascular resistance after long-term treatment [96].

Carvedilol is also thought to have additional antioxidant effects. It has been found to suppress apoptosis of human umbilical endothelial cells exposed to plasma samples of patients with CHF [34]. In humans, carvedilol, but not metoprolol, decreases erythrocyte superoxide dismutase and glutathione peroxidase activity. Superoxide dismutase converts superoxide radicals into toxic hydrogen peroxide and glutathione peroxidase inactivates this free radical. A decrease in superoxide dismutase activity suggests a decrease in free radical production and attests to the antioxidant properties of carvedilol [95]. Carvedilol

has also been shown to reduce endothelin secretion invitro in human coronary endothelial cells and inhibits the proliferation of human coronary smooth muscle cells [119].

2.2.2 Risks of Treatment with β-Blocker Therapy

β-blockers may produce hypotension, especially those with α_1 receptor blockade. Carvedilol can produce excessive vessel dilation in the first few days of initiation of therapy or increasing dose of the drug which may lead to fluid shift and edema and possibly result in worsening of symptoms [120]. Patients should weigh themselves daily at the onset of treatment and increase the dose of diuretic if weight increases. β-blockers can also alter cardiac conduction and decrease HR that may lead to bradycardia or heart block [120]. The risk of these side effects increases with increasing doses of β-blocker. If HR <50 bpm or second or third degree heart block is seen, the dose of β-blocker should be decreased [3].

2.2.3 Initiation and Maintenance of β-Blocker Therapy

Treatment with a β-blocker should be added to diuretics and ACEi in patients with moderate-to-severe HF who have a LVEF <35-45%. Patients with bronchospastic disease, symptomatic bradycardia or advanced heart block should not receive a β-blocker. Patients with decompensated HF should not receive a β-blocker until they are clinically stable and fluid retention is adequately treated [40, 120].

Because of this initial negative inotropic effect of metoprolol administration, patients should have a low start dose and slow up-titration schedule if lower doses have been well tolerated [93]. Patients should be monitored for evidence of hypotension, bradycardia, fluid retention and worsening of HF during this period. The dose of diuretics should be optimized to prevent hypotension or fluid retention. During periods of clinical decompensation, patients with HF on

β-blockers should decrease the dose or discontinue the β-blocker until clinically stable [40, 120].

3.0 Exercise and Heart Failure

The severity of HF is usually graded according to the patients' symptoms and in particular to the amount of physical activity that is associated with dyspnea or fatigue (NYHA classification). The apparent severity of patients' symptoms may fluctuate widely according to mood and morale, although the patients' cardiac function may be unchanged and this functional classification provides no information on the mechanism of benefit. Exercise testing provides a more objective analysis and can assess the efficacy of therapeutic interventions. There exists a direct relationship between quality of life and exercise capacity [121] thus more and more studies looking at exercise responses in HF.

3.1 Response to acute dynamic exercise in heart failure

Exercise testing generally involves the use of dynamic protocols to measure the HR, BP, duration of exercise, and workload of patients with HF. Exercise responses have been assessed using both maximal incremental tests and submaximal protocols to examine functional capabilities. Maximal exercise responses can vary with the protocol used. It has been recommended that treadmill protocols with more gradual increments (such as the Naughton or ramp) are more appropriate for patients with cardiovascular disease as work increments that are large or rapid result in a tendency to overestimate exercise capacity, are less reliable for studying the effects of therapy and are less uniform and provide reproducible hemodynamic and gas exchange responses to exercise [122]. It must also be remembered that bicycle exercise may underestimate peak V_{O_2} values compared to the Bruce and modified Naughton treadmill exercise protocols [123].

Submaximal exercise testing can involve many protocols. The six minute walk test is used often in clinical studies involving HF patients as it is a simple, noninvasive, inexpensive and safe guide to disability and has good reproducibility

[121,124]. It is of particular value in assessing patients with severe HF, but is less useful in those with mild HF as little variation in the distance covered in 6 minutes has been found compared to normal controls, despite noticeable reduction in maximal exercise capacity [124]. Furthermore, it correlates with a specific activity scale [125] and it has been shown to strongly and independently predict morbidity and mortality in patients with HF [126]. It has been proposed that submaximal exercise testing may better reflect limitations in activities of daily living in patients with HF and is preferred by patients to the maximal treadmill test [124]; however, it is not well standardized, its use may be accompanied by inter-observer variability and it is difficult to control for patient motivation. Other testing procedures involve distance covered in nine minutes on a self powered treadmill and workloads on a treadmill or cycle ergometer that are a percentage of peak V_{O_2} or workload.

3.1.1 Peak exercise performance

Peak exercise capacity depends on the cardiac-output response to exercise and peak oxygen consumption (V_{O_2}). Patients with HF have reduced cardiac output at peak exercise proportional to the severity of disease [127,128] and, compared with age-matched controls, patients with HF have reduced peak V_{O_2} [129-134]. Peak V_{O_2} measurements are useful to determine functional capacity before and after an intervention [135], disease severity and prognosis and information derived from testing is valuable for the optimal timing of cardiac transplantation [136-138]. Peak V_{O_2} can be significantly lower than age matched controls even in patients who are totally asymptomatic [139]. However, there has been no correlation found between peak exercise capacity (peak V_{O_2}) and resting LVEF [129, 134, 138,140].

A V_E/V_{CO_2} ratio greater than 34 at peak exercise is characteristic of patients with more severe HF [141-144]. This is true even in patients whose exercise tolerance is well preserved [145,146] and is an independent prognostic marker of

mortality[144-147]. Furthermore, peak V_{O_2} in combination with peak V_E/V_{CO_2} has been proposed as a tool to prioritize transplant candidates [148].

3.1.2 Submaximal exercise performance

During submaximal exercise testing, patients with HF have significantly higher HR and reduced oxygen uptake (V_{O_2}) compared to normal subjects at matched workloads [149,150]. This is sometimes called oxygen uptake lag and is thought to be due to the relative inability of the cardiopulmonary system to adapt to the demands of the 8[illegible]. In a number of patients with HF, the ratio of ventilation to CO_2 output (V_E-V_{CO_2} slope) at any given submaximal exercise load is greater than that of healthy controls [129, 140, 143, 144, 146,151]. That is, minute ventilation is increased at any given level of CO_2 production.

The slope of the regression line relating CO_2 output and minute ventilation (V_E-V_{CO_2} slope) can be used to describe the ventilatory response to exercise [140]. Myers et al [129] compared data from treadmill exercise tests of 33 male patients with CHF and 34 healthy men. At ventilatory threshold, V_E/V_{O_2} and V_E/V_{CO_2} were about 25% higher among patients with HF compared to normal subjects. Sullivan et al. [151] compared normal subjects and HF patients at matched submaximal workloads using bicycle exercise and expired gas analysis. The V_E/V_{CO_2} ratio was found to be significantly higher in the patient group at rest and submaximal exercise compared to the normal group. The V_E vs. V_{CO_2} slope is also useful to predict HF mortality. In a group of patients with HF, an increased V_E vs. V_{CO_2} slope (mean = 43.1 L/min) was associated with a 69% 18-month survival rate. This is compared to a 95% 18-month survival rate in those subjects demonstrating a V_E vs. V_{CO_2} slope within the normal range (mean= 32.3 L/min) [145]. Ponikowski et al. [146] demonstrated HF patients with a high V_E vs. V_{CO_2} slope (mean 41.1) had survival rates of 80% at 6 months and 57% at 3 years compared to 98% at 6 months and 93% at 3 years in HF patients with normal V_E vs. V_{CO_2} slopes (mean 26.5). Furthermore, the group of patients with high V_E vs. V_{CO_2} slopes had a mean peak V_{O_2} of 22mL·min^{-}

$^{1}\cdot kg^{-1}$, which would normally imply a low risk of mortality while those patients with lower V_E vs. V_{CO_2} slopes had a mean peak V_{O_2} of 24mL·min^{-1}·kg^{-1}.

3.1.3 Exercise training

There are many studies showing the benefits of chronic dynamic exercise training on hemodynamic and functional variables in HF. Exercise training has been shown to improve NYHA functional class [152-154]. Resting HR decreases significantly after training compared to controls [153-155]. Cardiac output at rest has been shown to improve after training in some studies [154, 155], but not in others [156,157]. LVEF has not been shown to change in most studies after training [152, 155, 157-159]. At steady state submaximal exercise, exercise duration increases [152, 159], and HR decreases for a given workload after exercise training [152, 156, 158]. Patients with HF on an exercise training program have shown increases in peak HR, peak V_{O_2}, peak ventilation, maximum work, and exercise time compared to control patients with HF and not on an exercise program [152-157, 159]. Peak leg blood flow and O_2 consumption have also been found to increase after training compared to baseline and controls [154]. Thus exercise training is an integral component of rehabilitation in HF patients.

3.1.4 Mechanism for impaired exercise performance

The major symptoms of HF are breathlessness and fatigue during exercise [160] but the cause of breathlessness remains unclear. Dyspnea, the unpleasant awareness of breathing inappropriate for the level of physical activity, may be mediated by a number of mechanisms. HF limits exercise Qc, which becomes the weakest link of the O_2 transport system. Re-writing the Fick equation thus provides the potential to examine the deleterious effects of a limited Qc on the central and peripheral factors related to O_2 transport. (Fick equation: Cardiac output (Qc) = V_{O_2} (mL·min^{-1}) / a-vO_2 difference (mL per mL blood) x 100)

3.1.4.1 Circulatory factors

Central factors

At rest, patients with HF have a reduced Qc principally through a decline in stroke volume (SV) (Qc = SV * HR) [134]. During exercise, Qc increases, but to a lesser extent than controls as a result of a reduction in stroke volume despite a greater elevation in HR in patients [130, 134]. Sullivan et al. [130] measured the central hemodynamic responses of patients with HF compared to normal controls (Figure 5). In patients with severe systolic dysfunction, HR is increased compared to controls during submaximal exercise at any given work load (Figure 8 A), with a 20% reduction in peak HR in patients when compared to normal controls. Qc and SV are reduced in patients at rest and during exercise (Figure 8 B and C), and there is a tendency for SV not to be maintained with increasing exercise loads. This may be related to both a limitation in systolic function as well as a potential limitation in diastolic function limiting the potential contribution of the Starling effect to ventricular ejection. Thus, most of the cardiac output increase during exercise occurs from exaggerated increases in HR to compensate for limited changes in stroke volume but there is a limit as to how much the failing heart can adapt.

Sullivan et al. [130] found central arteriovenous O_2 difference is increased at rest and during submaximal exercise compared to controls (Figure 8 D). These results suggest reduced muscle mass, reduced muscle perfusion capacity or an intrinsic abnormality of muscle metabolism play an important role in limiting exercise tolerance.

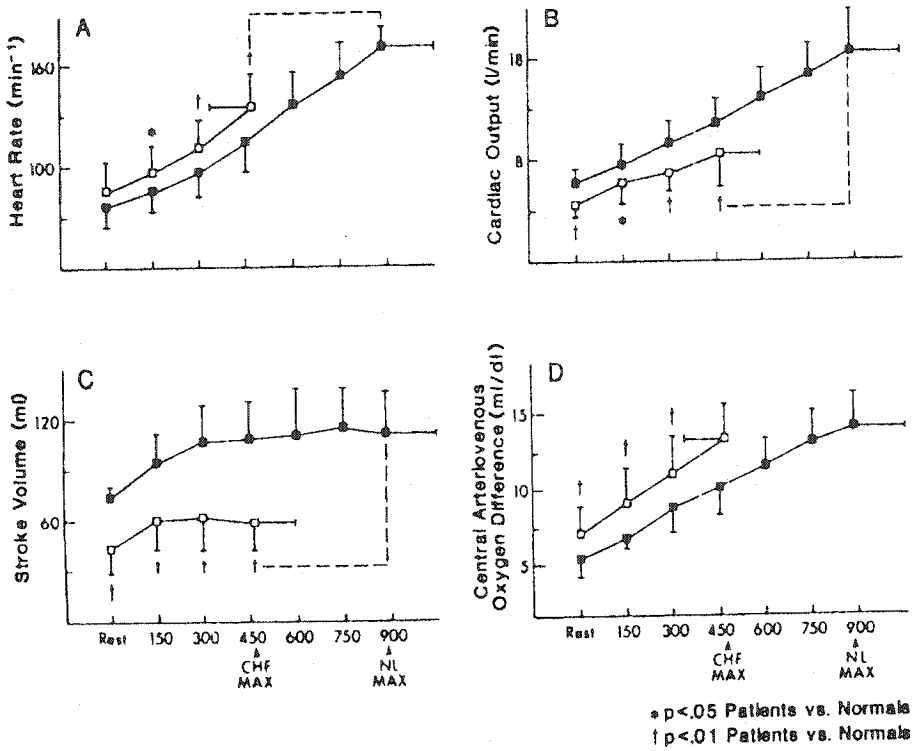

Figure 5. Central hemodynamic responses of patients with HF compared to normal controls From Sullivan et al. [130]

Peripheral Vascular Changes

As previously described, the response at rest to endothelium-mediated vasodilation is blunted in patients with HF [21, 42], but we do not know how this contributes to regulating blood flow during exercise. When healthy people exercise, arteriolar vasodilation increases blood flow to working muscle because of raised arterial BP secondary to increased cardiac output as well as neurohumoral regulatory effects on vascular smooth muscles to selectively increase flow in exercising vascular beds [9]. In patients with HF, skeletal muscle blood flow is reduced during exercise [44, 130,161] perhaps because of an exaggerated resting arterial vasoconstrictor tone simply to maintain BP and perfusion to important non-exercising vital organs during exercise [162]. Sullivan et al. [130] and Isnard et al. [150] observed leg vascular resistance is increased and leg blood flow is reduced at rest and during exercise in HF patients compared to equivalent workloads in normal controls despite the maintenance of arterial

blood pressure and flow to nonexercising tissues. Thus reduced muscle blood flow may be one of the causes for the limitations to exercise seen in HF but there are probably other contributing factors.

3.1.4.2 Ventilatory factors

Reduced exercise ventilatory efficiency in patients with HF remains to be completely elucidated. The relative ventilatory inefficiency is a reflection of gas exchange disturbance combined with an exaggerated breathing stimulus.

Heart failure is associated with peripheral disease that may be related to inadequate perfusion and/or to muscle anomalies inherent to the disease [130,163-167]. The result of this might be an excessive afferent stimulation leading to excess ventilatory drive. Chemoreflex activation causes increased sympathetic activity, HR, BP, and minute ventilation and these responses have been found to be higher in HF patients compared to normal controls [168-170]. Overactivity of peripheral and central chemoreceptors may contribute to the increased ventilatory response to exercise and the perception of muscle fatigue and dyspnea. Chemoreceptors in skeletal muscle may ultimately result in hyperpnea and possibly breathlessness, thus providing a link between peripheral metabolism and dyspnea during exercise. A significant correlation between V_E/V_{CO_2} slope and hypoxic and hypercapnic chemosensitivity in HF patients has been found [146]. Compared to normal controls, patients with HF have earlier acidosis and increased adenosine diphosphate (ADP) concentration for each minute of exercise [163] as well as acceleration in the development of acidosis in relation to workload [164] during exercise in skeletal muscle that may contribute to changes in receptor activation [171]. These skeletal muscle metabolites may activate receptors and, along with the chronic hyperstimulation of sympathetic outflow, lead to respiratory centre activation and exaggerated vasoconstriction in distant nonexercising vascular beds [169].

Results from studies on HF patients have demonstrated conflicting results on chemosensitivity in the HF population. Ponikowski et al. [146,170] found augmented hypoxic and hypercapnic chemosensitivity at rest in HF patients with a high V_E/V_{CO_2} slope compared to normal controls. This group of investigators tested transient peripheral chemosensitivity using pure nitrogen as a hypoxic stimulus and 100% O_2 as a hyperoxic stimulus and central hypercapnic chemosensitivity with CO_2 rebreathing. Narkiewicz et al. [168] found hypercapnia, but not hypoxia, to increase minute ventilation and HR in patients with HF and not in controls suggesting increased central chemoreflex sensitivity in HF patients. Van de Borne et al. [172] demonstrated muscle sympathetic nerve activity, which is elevated in HF patients, does not decrease while breathing 100% O_2, suggesting hyperoxia does not deactivate peripheral chemoreflexes. One reason for the discrepancy in results could be the fact that not all patients with HF have increased peripheral chemosensitivity. It is interesting that Ponikowski et al. [173] found only 42% of HF patients had abnormal chemosensitivity. Therefore, it remains to be determined whether there is a hypersensitivity to hypoxic stimulation in HF and if a hypoxic stimulus exists, does it contribute to the exaggerated V_E/V_{CO_2} response.

Independent of its underlying mechanism, increasing ventilation should lead to an increase in Pa_{O_2} and a decrease in Pa_{CO_2}. While hypoxia may occur with acute pulmonary edema, numerous studies have shown that arterial hypoxia does not occur during exercise in stable patients with HF. Blood gases during incremental exercise have found Pa_{O_2} to rise at peak exercise, as is seen in normal subjects [127,174] and most studies have found no change or a lower Pa_{CO_2} compared to controls during exercise [127,151,175,176]. Thus, if high ventilatory drive from peripheral chemoreceptors or skeletal muscle ergoreceptors were to increase the V_E/V_{CO_2} slope, it is not by driving down Pa_{CO_2} and these receptors, while perhaps playing a role in dyspnea, do not cause hypocapnic hyperventilation. Furthermore, investigators have found that Pa_{CO_2} and the ratio of alveolar ventilation to V_{CO_2} are maintained during

exercise in patients with CHF, similar to healthy controls, suggesting that neural and chemoreceptor control mechanisms are intact in patients with HF [151].

It is also unlikely that earlier than normal metabolic acidosis [163, 164] causes the excess ventilation as relative hyperventilation in patients with HF starts at the beginning of exercise and is observed both below and above the ventilatory threshold [129]. Wasserman et al. [177] found that pH and $PaCO_2$ were not affected by the degree of impairment in subjects with HF. Arterial pH was well controlled at the low metabolic rates of the more exercise-limited HF patients but decreased as VO_2 increased in a similar pattern to that for normal subjects, indicating it does not reflect on the ventilatory efficiency in patients with HF.

As per the standard alveolar gas equation, the increased VE/VCO_2 reflects high dead space ventilation (V_D) since blood gases remain stable. In normal subjects, V_D/V_T decreases during exercise as ventilation and perfusion matching improves. Similarly, in patients with HF, V_D/V_T decreases during exercise even though V_D/V_T is elevated at rest and at peak exercise [129,151,174,176,178], (See Figure 6). The change in V_D/V_T can occur from low tidal volume with respect to anatomical dead space or high physiologic dead space [179]. Reindl et al. [35], found impairment in ventilatory efficiency in patients with HF was mainly caused by increased ventilation of physiologic dead space while anatomic dead space contributed little to the impairment. A low V_T could explain only 33% of the increased V_D. This occurs despite the fact that HF patients usually do not exhibit abnormal resting pulmonary function in the absence of coexisting lung disease. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) have indeed been reported to be only mildly impaired in patients with HF [134,144,145,178,180,181]. Kleber et al. [144] found no correlation between FEV_1

Standard alveolar gas equation

$VE = VCO_2 \times 863/PaCO_2 \times (1 - VD/VT)$

-VD/VT describes dead space ventilation as a proportion of tidal volume
-$PaCO_2$ is the arterial partial pressure of carbon dioxide
-863 is a constant to standardize gas measurement to body temperature, pressure and saturation

and the V_E vs. V_{CO_2} slope suggesting abnormal pulmonary function was not a major determinant of the elevated V_E/V_{CO_2} slope.

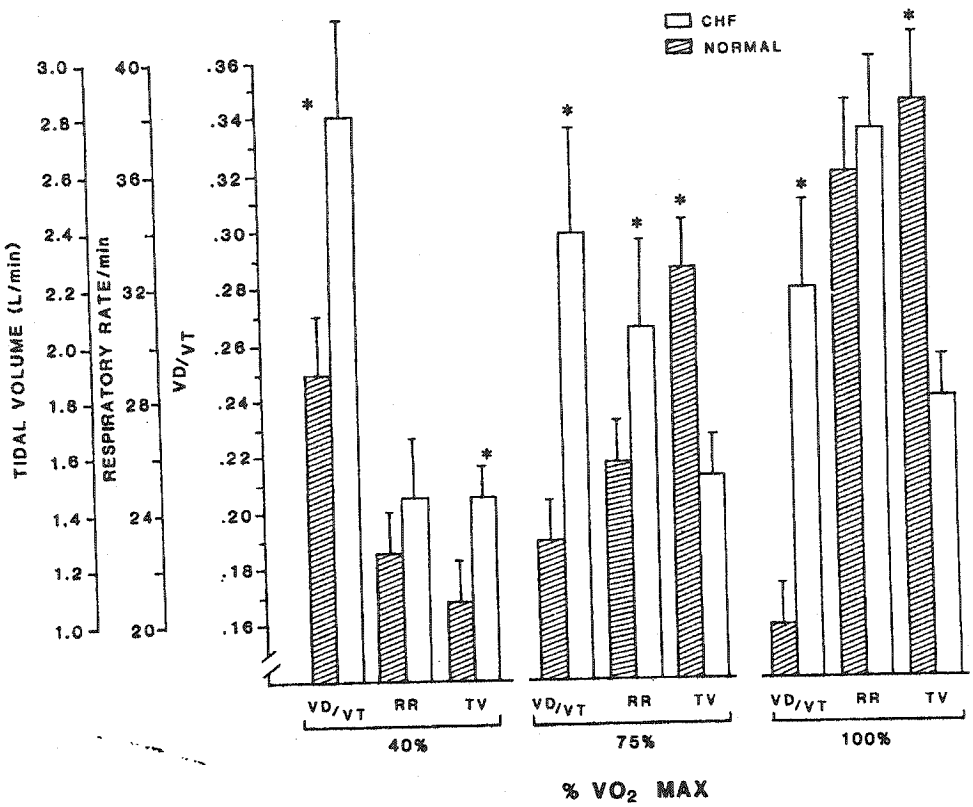

Figure 6. Mean values for VD/VT, respiratory rate, and tidal volume at matched percentages of maximal oxygen uptake among patients with HF and normal subjects, from Myers et al. [129]

Sullivan et al. [151] noted peak exercise V_E/V_{CO_2} did not correlate with pulmonary vascular pressures but was inversely related to peak exercise cardiac output ($p<0.001$) suggesting that pulmonary hypoperfusion and not increased LV filling pressures may contribute to excess ventilation by worsening V_D/V_T abnormalities. The abnormally high V_E/V_{CO_2} slope during exercise testing in patients with heart failure may be associated with a reduced pulmonary perfusion and hemodynamic abnormalities causing ventilation/perfusion (VQ) mismatch [151,174,176,182,183]. The resulting alveolar hypoperfusion causing increased physiologic dead space may be a contributor to impairment of ventilatory efficiency[35]. Uren et al [182] found the global VQ mismatch index was reduced from rest to peak exercise in HF patients and the ability to reduce the

mismatch correlated with $V_{O_{2max}}$ and $V_{E_{max}}$. It is therefore conceivable that during exercise when pulmonary artery pressure (PAP) is increased [140, 151], an additional constraint to alveolar diffusion is added resulting in VQ mismatch. In fact, results from several studies examining PAP and pulmonary capillary wedge pressure (PCWP) in patients during exercise indicate values higher than those of normal controls [140, 151]. However, in the study by Fink et al. [140], acute reduction in PCWP during exercise with prazosin or dobutamine did not reduce V_E/V_{CO_2}. Furthermore, the increased V_E/V_{CO_2} did not correlate with peak exercise PCWP and correlated only weakly with resting PCWP (r=0.48). These observations may be taken to indicate that the excess ventilation found in HF patients is not a result of acute changes in intrapulmonary pressure during exercise.

A significant correlation has been found between diffusion capacity for carbon monoxide and V_E vs. V_{CO_2} slope in patients with HF [144]. In an attempt to understand the relationship of pulmonary perfusion and metabolic gas exchange, Smith et al. [134] measured carbon monoxide transfer factor (TLCO) and pulmonary blood flow (Qc) at rest and at steady-state cycling in patients with HF and healthy controls. There was no evidence of airflow obstruction (FEV_1/FVC was normal) but TLCO and Qc were reduced at rest in the HF patients compared to controls. At steady state exercise, TLCO and Qc increased in both the healthy controls and in patients with HF, the V_E/V_{CO_2} correlated significantly with TLCO. The magnitude of the increase in TLCO with respect to Qc was normal in the HF group, but the diffusion was reduced at any given blood flow. The ratio of pulmonary diffusion to effective pulmonary blood flow (TLCO/Qc) was used as an index of efficiency of gas exchange across the alveolar-capillary membrane and was impaired in patients with HF compared to controls at both rest and exercise. Thus, there may be impairment in pulmonary diffusion for a given blood flow.

Guazzi et al. [178,180,181] also examined pulmonary diffusion in patients with CHF and found evidence of reduced pulmonary diffusing capacity for carbon monoxide (DLCO) in patients compared to controls at rest. The reduction in DLCO was caused by a decrease in alveolar-capillary membrane diffusing capacity. In an attempt to understand the mechanism of this response, the same group of investigators [184] measured right atrial pressure (RAP), pulmonary artery pressure and wedge pressure at rest since high pressure could lead to interstitial edema and impaired gas transfer. Using ultrafiltration to decrease RAP by 50% in HF patients, they did not find an increase in DLCO or alveolar-membrane diffusing capacity after ultrafiltration despite significant reduction in PAP and PCWP. Thus fluid excess in the alveolar capillary membrane is not the major cause of the reduction in lung diffusing capacity. This suggests that some of the membrane impairment might be due to increased cellularity and fibrosis. On the other hand, enalapril has been shown to increase DLCO [181,185] and reduce V_D/V_T and V_E/VCO_2 [185] thus part of the impairment in pulmonary diffusion and/or ventilatory impairment may be due to angiotensin II and inactivation of bradykinin.

In recent years, a special attention has been given to the heart-lung mechanical interactions during exercise in both chronic obstructive pulmonary disease (COPD) patients and those with congestive heart failure. Results from a recent study [142] indicate many patients with HF to be expiratory flow limited upon minimal dynamic exercise. The breathing at reduced lung volumes may be related to activation of expiratory muscles or to an inspiratory muscle weakness. Nanas et al. [186], investigated pulmonary mechanics in patients with HF. Peak inspiratory (Pi_{max}) and expiratory pressures (Pe_{max}), at rest and after exercise, were greater in controls than patients with HF. The reduction of Pi_{max} at peak exercise or immediately after exercise in HF patients likely represents fatigue of the respiratory muscles as Pi_{max} was not decreased 10 minutes after exercise in the majority of HF patients and the pattern of recovery was similar to that observed in controls, with a significant decline in the first 2 minutes after

exercise and a gradual return to baseline after. In a subset of patients with significantly lower exercise capacity and delayed recovery of resting V_{O_2}, there was a greater than 10% decrease of $P_{i_{max}}$ at 10 minutes of recovery than in controls. Thus, the reduction of $P_{i_{max}}$ after exercise may be associated with prolonged early recovery of oxygen kinetics in HF patients. They also found a weak but significant correlation at rest and after exercise between $P_{i_{max}}$ and peak V_{O_2}. Whatever the cause, breathing at lower lung volumes may lead to dynamic compression of airways, which may be compatible with an exaggerated physiologic dead space and contribute to their ventilatory inefficiency.

3.1.4.3 Skeletal muscle changes

Wasting of skeletal muscle has been found using magnetic resonance imaging (MRI) to detect water and/or fat infiltration of calf muscles. This muscle atrophy is not accompanied by generalized loss of total body weight and fat stores[187]. There is a strong correlation between peak V_{O_2} and skeletal muscle mass in HF patients, most likely as a result of reduced tissue available to utilize O_2 or reduced oxidative capacity of the muscle during exercise [188]. There is a reduction in the percentage of slow twitch type I fibres, a higher percentage of type IIb fast twitch fibres which are smaller than those seen in controls, and a decreased number of capillaries per fibre for type I and type IIa fibres found in patients with HF compared to normal controls [167,189]. Belardinelli et al. [190] found a significant increase in size of both type I and II fibers after exercise training has been observed, however, in the same study, no significant change in fiber type (80% type II), capillary density, or capillary to fiber ratio was seen.

Skeletal muscle biopsies have demonstrated significant ultra structural abnormalities of skeletal muscle in patients with HF. Sullivan et al. [167] performed biochemical analysis of rest mixed-fibre muscle samples and reported no difference in phosphorylase and glycolytic enzyme activities in patients with HF compared to controls. They did find significant differences

between HF patients and controls in mitochondrial enzymes involved in terminal oxidation. Succinate dehydrogenase, citrate synthetase, and 3-Hydroxyacyl-CoA-dehydrogenase (an enzyme mediating B-oxidation of fatty acids) were reduced in patients compared to controls.

Total mitochondrial volume density and surface density of cristae mitochondria are significantly reduced in patients with severe HF. In a study by Drexler et al. [189], the percentage of cytochrome oxidase-positive mitochondria was reduced in patients with moderate and severe HF irrespective of age, indicating a reduced oxidative capacity of working muscle. They reported a significant relation (independent of peak Vo_2) between the duration of HF and mitochondrial volume density. Furthermore, a close relation was observed between the change in mitochondrial volume density and the change in peak Vo_2, indicating both a limitation in O_2 transport and oxidative capacity of mitochondria. This suggests alterations in aerobic enzymes in skeletal muscle play an important role in determining submaximal and maximal exercise performance in HF. Furthermore, total volume density of mitochondria is significantly improved after exercise training compared to sedentary controls [154,190] and the percent of cytochrome oxidative-positive mitochondria increases significantly after training and is related to improvements in Vo_2 at peak exercise [154].

Compared to normal controls, patients with HF have early acidosis and increased adenosine diphosphate (ADP) concentrations during exercise in skeletal muscle [163, 164, 171]. Investigators have monitored skeletal muscle metabolism with ^{31}P-MRI using forearm [163,164] and leg exercise [165, 166]. Massie et al. [163] compared skeletal muscle metabolism in patients with HF and healthy controls during forearm exercise. The initial resting values of intracellular pH and ADP in patients with HF and healthy controls were almost identical. During submaximal aerobic and ischemic exercise, the HF group produced more lactate and consumed more ATP for each minute of exercise than the controls. There were early reductions

in pH and increases in ADP in patients with HF compared to controls. Weiner et al. [164] demonstrated acceleration in the development of acidosis in relation to workload with ^{31}P-NMR that was not accompanied by a reduction in arm blood flow or a difference in forearm blood flow between patients with HF and controls. Furthermore, femoral venous lactate production has been shown to be accelerated at submaximal exercise in patients compared to controls [130,167]. These findings suggest abnormal skeletal muscle metabolism in the form of reduced oxidative metabolism and an earlier shift to glycolytic metabolism. These changes cannot be explained by impaired blood flow or oxygen delivery alone and are consistent with a primary abnormality of muscle metabolism.

Similar findings were reported by Okita et al. [165] and Hanada et al. [166] in evaluation of supine unilateral plantar flexion. When local exercise was compared to a maximal upright cycle ergometer test [165], muscle pH was significantly greater in patients with HF compared to controls during the maximal systemic exercise. Muscle phosphocreatine (PCr) was nearly depleted in both patients with HF and normal controls, however, PCr depletion occurred at a significantly lower peak V_{O_2} in patients. Systemic muscle metabolic capacity (slope of PCr decrease in relation to increasing workload) was correlated with peak V_{O_2} during maximal exercise. Thus, a primary abnormality of muscle metabolism may be one reason for impaired exercise performance rather than muscle atrophy or alterations in skeletal muscle blood flow [163,165,166,191]. The mechanism by which these metabolic changes impair exercise performance has not been found but it has been suggested that the early increase in inorganic phosphate and decrease in pH may be responsible for producing the early fatigue in patients with HF.

Oxygenation of the vastus lateralis muscle during exercise and recovery in patients with HF and controls has been monitored using near infrared spectroscopy (NIRS) [133,166]. Recovery V_{O_2} [133] and muscle oxygenation [133, 166] mean response times for a constant work rate exercise test have been found to

be significantly longer in patients with HF than controls. These variables were inversely related to peak V_{O_2}, suggesting the recovery of muscle and total body oxygenation from submaximal exercise is more delayed the greater the cardiac dysfunction, as assessed by peak V_{O_2} [133]. When comparing PCr recovery to oxyhemoglobin recovery from submaximal plantar flexion exercise, they were similar in normal subjects, but PCr recovery was significantly greater than oxyhemoglobin recovery in patients with HF. This suggests that muscle metabolic recovery may depend more on oxygen utilization than on hemoglobin resaturation or oxygen delivery in patients with HF [166].

3.2 Effect of β-blockers on the exercise response

Measures that directly inquire about symptoms and disability, such as the NYHA classification, are a normal part of office management of HF. However, these measures are subjective and may be insensitive to modest changes produced by an intervention. On the other hand, measures that quantify the impact of a specific activity, such as maximal exercise testing or the 6-minute walk test, do not necessarily quantify the severity of symptoms but evaluate the patient's ability to carry out a specific activity [192]. The majority of studies report an improvement in NYHA functional class after β-blocker therapy [85,89,93,95-97,102-106, 109,110,112], which should theoretically translate to an improvement in measured exercise capacity, but the effect of β-blockers on the exercise response remains unclear.

3.2.1 Peak exercise

Improvement in peak exercise workload has been observed after treatment with metoprolol [92,93, 96, 99, 102, 103] but not generally with carvedilol [106-109](Table 5). Metoprolol and carvedilol have been found to significantly improve peak exercise cardiovascular parameters in clinical trials (Table 6). At peak exercise, both drugs have been found to reduce HR [92, 96,97, 104, 106, 107, 109], and increase stroke volume and stroke work index [96, 99, 109]. However, metoprolol has been found to increase peak V_{O_2} in some studies [92, 96, 100] but not in one other [104] while

increased peak VO_2 after carvedilol treatment has not been generally observed [96, 104, 106,109] except in one study [100].

Table 5. Peak exercise study outcomes

Trial	Drug	Maximal exercise test	Results
Engelmeier (1985)	metoprolol	max treadmill	inc exercise performance
Nemanich (1990)	metoprolol	graded max cycle	inc max work rate
Andersson (1991)	metoprolol	graded max cycle	25% inc in max watts
Fisher (1994)	metoprolol	graded max cycle	inc duration
Metra (1994)	carvedilol	graded max cycle	n/c in duration or peak VO_2
ANZ Carvedilol I (1995)	carvedilol	max treadmill	n/c in duration
Olsen (1995)	carvedilol	graded max cycle	n/c duration or peak VO_2
Guazzi (1999)	carvedilol	graded max cycle	n/c peak VO_2
Gilbert (1996)	carv vs met	max treadmill	n/c peak VO_2 or time in both groups
Kukin (1999)	carv vs met	graded max cycle	inc peak VO_2 in both groups
Metra (2000)	carv vs met	graded max cycle	inc peak VO_2 in metoprolol

max = maximal, inc = increase, n/c = no change, carv = carvedilol, met = metoprolol

Table 6. Effect of β-blockers on peak exercise cardiovascular parameters

Parameter	Metoprolol	Carvedilol
Peak HR	Decrease [92,96, 104]	Decrease [61, 96,104,107,109]
Peak SBP	N/C [92, 104]	Decrease [61, 107] or N/C [104]
Peak DBP	N/C [92]	Decrease [107]
Peak VO_2	Increase [92, 96, 100]	Increase [100] or N/C [96,180]
Peak LVEF	Increase [98, 104]	Increase [104, 180]
Peak cardiac index	Increase [99] or N/C [96]	Increase [96,109]
Peak stroke volume index	Increase [96,99, 104]	Increase [96, 104,109]
Peak stroke work index	Increase [96,99, 104]	Increase [61, 96, 104,109]
Peak PCWP	Decrease [96,99]	Decrease [61, 96, 104,109]
Peak PVR	N/C [96]	Decrease [109] or N/C [96]
Peak RAP	N/C [96,99]	Decrease or N/C [96,109]

HR: heart rate
SBP: systolic blood pressure,
DBP: diastolic blood pressure,
PCWP:pulmonary capillary wedge pressure
PVR: pulmonary vascular resistance
RAP: right atrial pressure
NE: norepinephrine
N/C: no change

Metra et al. [96] examined the effects of 13 to 15 months of carvedilol or metoprolol on cardiovascular and exercise performance in 150 patients with HF. Peak exercise HR decreased in both groups but to a greater extent in the carvedilol group. Stroke volume and stroke work index at peak exercise increased in both

groups after therapy but to a greater extent in the carvedilol group. In addition, peak exercise pulmonary artery and wedge pressure decreased to a greater extent in the carvedilol group compared to metoprolol. Peak exercise right atrial pressure and pulmonary vascular resistance did not change in either group. However, peak exercise V_{O_2} increased in the metoprolol group only ($p=0.035$). Thus, carvedilol seemed to improve cardiac performance to a greater extent than metoprolol although metoprolol increased maximal exercise V_{O_2} more than carvedilol.

Gilbert et al. [104] also compared hemodynamics and maximal exercise capacity with metoprolol vs. placebo or carvedilol vs. placebo over 4-6 months. PCWP was decreased in the carvedilol group only, whereas maximal HR decreased and SVI, SWI and LVEF increased in both groups. Both metoprolol and carvedilol were associated with a trend towards reduction in LVEDD but it did not reach significance. Guazzi et al. [180] compared the effects of a 6-month treatment of carvedilol or placebo on pulmonary function, cardiac function and exercise capacity in a small group of patients with HF. They did not observe any effect of carvedilol over time or compared to placebo on peak V_{O_2}, peak V_E, peak V_D/V_T despite significant improvement in LVEF and stroke volume.

3.2.2 Submaximal exercise

At constant workload submaximal exercise, HR decreases [93,98, 113] and LVEF increases [98] after a 3-month course of metoprolol. However, inconsistent results are also seen for submaximal exercise performance with metoprolol or carvedilol therapy, which is less dependent on maximal heart rate (Table 7). While some studies of submaximal exercise capacity do show improvement in distance walked over a 9 minute treadmill walk or 6-minute walking test following long-term carvedilol administration [95- 97, 109], improvements in 6-minute walk distance or distance traveled in a 9-minute treadmill walk have not been reported in other trials [84, 85, 88, 89, 100, 106,107] despite significant improvements in symptoms. The MOCHA [84] and PRECISE [89] trials did not demonstrate an

improvement in their submaximal primary endpoints with carvedilol treatment despite reductions in death and hospitalizations. The Australia-New Zealand trial had 2 phases, an initial 6-month submaximal exercise trial [107] and a longer morbidity and mortality trial [108]. There was no improvement in submaximal exercise time despite a reduction in mortality and cardiovascular hospitalizations. When both metoprolol and carvedilol groups are compared in trials, 6 minute walk time improves significantly after therapy in both groups without a difference seen between groups [96,97] or does not improve at all in either group [100].

Table 7. Submaximal exercise study outcomes

Trial	Drug	Submaximal exercise test	Results
Andersson (1991)	metoprolol	cycle at 50% max watts	inc work, n/c duration
ANZ Carvedilol I (1995)	carvedilol	6min walk distance	n/c distance
Olsen (1995)	carvedilol	66-85% of VO2 max	n/c distance
MOCHA (1996)	carvedilol	6min walk distance	n/c distance
		9min self propelled TXT	n/c distance
Metra (1994)	carvedilol	cycle at 80% max watts	inc duration
PRECISE (1996)	carvedilol	6min walk distance	n/c distance
		9min self propelled TXT	n/c distance
Guazzi (1999)	carvedilol	constant 50-Watt cycle	n/c VO_2 or VE/VCO_2
Metra (2000)	carv vs met	6min walk distance	inc distance both carv and met
Sanderson (1999)	carv vs met	6min walk distance	inc distance both carv and met
Arumanayagam (2001)	carv vs met	6min walk distance	inc distance in carv, not met
Kukin (1999)	carv vs met	6min walk distance	n/c in both groups

inc = increase, n/c = no change, carv = carvedilol, met = metoprolol, TXT = treadmill test

Guazzi et al. [180] compared the effects of a 6-month treatment of carvedilol or placebo on pulmonary function, cardiac function and exercise capacity in a small group of patients with HF. Although nor the slope of the increase in V_E with respect to V_{CO_2} at submaximal exercise nor peak V_E/V_{CO_2} were reported, authors reported on a V_E/V_{CO_2} at 1L which was not affected by carvedilol. Similarly, the same group of authors [113] examined the effects of 6 months of carvedilol treatment in HF patients on steady state 50 W exercise. They did not observe any changes with carvedilol over the length of the study or compared to placebo in submaximal constant workload V_{O_2}, V_E/V_{CO_2}, and V_{CO_2}/V_{O_2}, despite

significantly reduced resting LVEDD and LVESD after 6 months of carvedilol therapy. Thus improvement in resting cardiac function does not necessarily translate into significant changes in V_{O_2} kinetics and ventilatory efficiency at submaximal constant workloads.

3.2.3 Mechanisms

There is still little evidence to know exactly the effects of either selective or non-selective beta-blocker on the maximal and/or submaximal exercise response. Improvement in peak exercise capacity has been observed after treatment with metoprolol [92,93, 96, 102, 103] but not generally with carvedilol [106-109]. In a practical sense, it is difficult to demonstrate improvement in exercise in response to β-blocking agents in HF as inhibition of the maximal HR occurs in subjects who are dependant on an increase in HR to increase cardiac output (Figure 8). No improvement in maximal exercise time or peak V_{O_2} have been seen despite improvements in LV function with carvedilol treatment [109]. This may be due to the reduction in peak HR. In fact, a direct correlation has been observed between the change in peak HR and the change in peak exercise duration with bucindolol therapy [193]. On the other hand, as β-blockers lower exercise HR, this theoretically should increase the period of diastolic filling and myocardial perfusion and thus may improve stroke volume and overall myocardial performance. Clements et al. [98] found decreased exercise HR and increased LVEF at constant workload submaximal exercise after metoprolol therapy. The decreased HR was associated with a longer time to peak filling rate and a decreased peak-filling rate indicating a less restrictive filling pattern.

There is also little evidence on the physiological mechanism for improved exercise performance in the literature. It has been postulated that the improvement in peak exercise capacity with metoprolol [92, 93,96, 100, 102, 103] is related to the restoration of downregulated β-receptors in the heart that may facilitate the inotropic and chronotropic response to sympathetic stimulation during exercise and lead to improved exercise tolerance. Improvement in

maximal exercise capacity is observed in some studies [96, 100] but not all [106-109] with carvedilol. It does not upregulate β_1 receptors and, as a non-selective agent, it also blocks β_2 receptors in the heart, significantly reducing the maximal HR attained during exercise compared to metoprolol [96] and perhaps reducing peak myocardial performance [192]. White et al. [194] found β-receptor density in resting human hearts was correlated with maximal exercise VO_2. The data in Figure 7 indicate a good relation between decrease in total β-receptor density and impaired maximal exercise response in patients with idiopathic dilated cardiomyopathy. In contrast, LVEF and cardiac index exhibited only weak correlations with peak VO_2. It is interesting that this same group of investigators [104] did not find an improvement in maximal exercise times when patients were randomized to equipotent β-blocking doses of metoprolol or carvedilol (assessed by equal reduction in maximal exercise HR). Thus conclusions about the effect of β-blockers on receptors and exercise tolerance cannot be drawn.

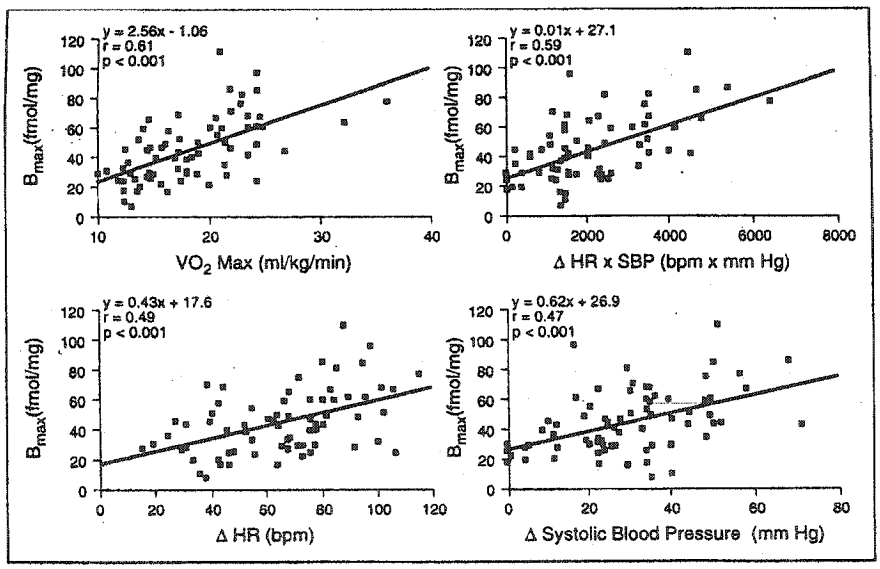

Figure 7. Decreased inotropic and chronotropic responsiveness to β-agonist stimulation. Bmax=right ventricular biopsy β-receptor density. From White et al. [194]

There are limited numbers of studies that have attempted to examine systolic and/or diastolic function during exercise in patients with heart failure [96, 99, 106, 109]. Using radionuclide ventriculography during maximal supine bicycle exercise, Olsen et al. [106] found an increase in LVEF after 4 months of carvedilol. Metra et

al. [172] measured hemodynamic responses to maximal upright cycle exercise with cardiac catheterization. After 4 months of carvedilol therapy, peak exercise duration and Vo_2 did not change. Peak exercise HR decreased while CI, SVI and SWI increased significantly after long-term administration of carvedilol. RAP and PCWP decreased significantly while MAP did not change after treatment. The same group of investigators [96] compared the effects of 12 months of treatment with metoprolol or carvedilol on peak exercise. Exercise duration increased in both the metoprolol and carvedilol groups, but only the metoprolol group increased peak VO2 after therapy. Both groups significantly increased SVI and SWI, and decreased pulmonary artery pressure and PCWP, but the magnitude of the changes were significantly greater in the carvedilol group. It is impossible to draw conclusions about the mechanism of action of carvedilol or metoprolol from these studies, but it is possible that myocardial function improved as EF increased without a significant change in LVEDV and systemic vascular resistance.

Andersson et al. [99,195] measured hemodynamic data during supine bicycle exercise at 50% of maximal workload using right heart catheterization and an arterial line. Cardiac index (CI), stroke volume index (SVI), and stroke work index (SWI) all increased significantly [99,195] after metoprolol treatment. Coronary sinus blood flow increased during exercise from baseline, but treatment with metoprolol did not provide a further increase in flow. Similarly, myocardial O_2 consumption, while higher during exercise, did not change with metoprolol therapy. Thus, stroke volume increased with metoprolol but not the metabolic cost of work [99].

Furthermore, it is very difficult to dissociate any improvement in exercise tolerance from a training effect. If patients are experiencing improvements in quality of life [95-97,105, 109] and NYHA class [85, 89, 93,95-97, 102-106, 110, 112] with β-blockers, one can postulate they are increasing activities in their daily life and, in effect, training. In addition, β-blockers may exhibit an anxiolytic effect, contributing to

improvement in sense of well being and thus producing improvements in measured test parameters.

4.0 Position of the Problem

While there is increasing evidence that β-blockers are useful for patients with heart failure to decrease mortality [83-88] and hospitalizations [83, 86, 88, 89,108] and improve NYHA classification [85, 89, 93,95-97, 102-106, 109, 110, 112], there is less conclusive evidence about the usefulness of β-blockers to improve exercise capacity. Slight improvements in peak V_{O_2} are indeed reported with second generation agents such as metoprolol which are selective and up-regulate β_1-receptors [92,96,100] but improvement in peak V_{O_2} is not generally reported in studies using the non-selective agent, carvedilol [96, 104, 106, 109]. Inconsistent results are also seen for submaximal exercise performance in HF patients despite significant improvements in symptoms.

Recently, much attention has been devoted to exercise ventilatory efficiency as a prognostic factor for CHF [144, 146, 147]. Ventilatory requirements for O_2 uptake or CO_2 removal have been used as indices of ventilatory efficiency. V_E/V_{CO_2} may be a better marker of ventilatory efficiency than V_E/V_{O_2}. In patients with heart failure, the ventilatory response to exercise is augmented compared to healthy controls [129, 143, 144, 151]. A decrease in submaximal V_E/V_{CO_2} ratio has been previously reported following long–term captopril administration [69] but to our knowledge there is only limited information on the effects of β-blockers on exercise ventilatory efficiency. Thus, the effect of treatment with carvedilol or metoprolol on maximal exercise parameters as well as ventilatory efficiency during submaximal and maximal exercise needs to be further investigated.

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Part two: experimental study

Abstract

Purpose: to examine the outcome of a 6-month treatment with carvedilol or metoprolol on peak and submaximal exercise performance and ventilatory efficiency in patients with heart failure (HF).

Methods: 27 patients with HF were randomized to receive either metoprolol or carvedilol for 6 months and compared with 12 healthy controls. Maximal exercise capacity was assessed at baseline and after 6 months with a symptom limited incremental treadmill protocol (RAMP). Submaximal exercise was determined to be the portion of exercise below a respiratory exchange ratio of 1.0. Peak heart rate (HR), oxygen uptake (V_{O_2}), and ventilatory equivalent for O_2 and CO_2 were recorded. The slopes of the V_E vs. V_{CO_2}, V_E vs. V_{O_2} and V_E/V_{CO_2} vs. V_{O_2} relationships were calculated for each subject from submaximal values.

Results: Resting HR decreased to similar extent in both treatment groups. There were no other significant changes in resting hemodynamics or ventricular function. Peak V_{O_2} and HR decreased significantly in both treatment groups. Peak V_E/V_{CO_2} and submaximal V_{CO_2} vs. V_E slope were not changed significantly after therapy

Conclusion: β-blocker treatment with either metoprolol or carvedilol does not decrease the slope of the V_{CO_2} vs. V_E relationship. The present observations may suggest that the exaggerated ventilatory response of patients with moderate HF is not mediated by β-adrenergic receptors.

Introduction

Heart failure, the inability of the heart to perfuse metabolizing tissue adequately, affects over 400 000 Canadians, with more than 50 000 new cases occurring annually [1]. In Montreal, the annual rate of admissions to hospital between 1990 and 1997 increased by 35% and the readmission rate within 6 months rose from 46.7% to 49.4% over the same period [2]. There is increasing evidence that β-blockers are useful for patients with heart failure with several large scale studies

showing β-blockers to decrease mortality [3-9] and hospitalizations [4,8-11] and improve NYHA classification [5,11-13].

Metoprolol is a second-generation β_1 selective antagonist with no intrinsic sympathomimetic activity (ISA) [14]. Carvedilol is a third generation B-blocker, mildly selective for β_1 with no ISA, which combines alpha$_1$-blockade and antioxidant activity [15]. Long term administration of both of these agents have been shown to decrease resting HR [4,10,13,16-21], increase left ventricular ejection fraction (LVEF) [3,5,8,10,11,13,16,18-22], reduce left ventricular (LV) volumes [10,16,19,22,23] and decrease resting pulmonary artery (PA) pressure and pulmonary capillary wedge pressure (PCWP) [16-18].

Observations on the effects of β-blocker therapy on functional capacity suggest that improvements in maximal functional capacity may only be observed if β-adrenergic receptors are up-regulated to allow for a sufficient increase in cardiac output during exercise. Slight improvements in peak oxygen consumption (peak VO_2) are indeed reported with second generation agents such as metoprolol which are selective and up-regulate β_1-receptors [20,24,25]. An improvement in peak VO_2 has been reported in some [25] but not all studies using carvedilol [16-18,26] or bucindolol [27], which are only slightly selective and do not affect β_1-receptor density [24]. Inconsistent results are also seen for submaximal exercise performance, which are less dependent on maximal heart rate. While some studies of submaximal exercise capacity do show improvement in distance walked over a 9 minute treadmill walk or 6-minute walking test following long-term carvedilol administration [16,18,19, 21], improvements in 6-minute walk distance or distance traveled in a 9-minute treadmill walk have not been reported in multicenter trials [3,5,9,22] despite significant improvements in symptoms.

Recently, much attention has been devoted to exercise ventilatory efficiency as a prognostic factor for CHF [28-30]. Ventilatory requirements for oxygen (O_2) uptake or carbon dioxide (CO_2) removal have been used as indices of ventilatory

efficiency. Minute ventilation (V_E), expressed as a ratio of V_{O_2} (V_E/V_{O_2}), may not be the best marker because ventilation is the start of the oxygen transport line, a ventilatory defect could be counteracted by an increase in O_2 delivery through a higher cardiac output and vice-versa. However, ventilation is at the end of the CO_2 transport line, and an adaptation of other mechanisms can have only a limited effect in maintaining CO_2 excretion. Thus, V_E/V_{CO_2} may be a better marker of ventilatory efficiency than V_E/V_{O_2}. In healthy humans, CO_2 expired during exercise (V_{CO_2}) increases linearly with V_E when work is done below the ventilatory threshold [31] and the slope of the regression line relating V_E and CO_2 output (V_E-V_{CO_2} slope) can be used to describe the ventilatory efficiency. In patients with heart failure, the ventilatory response to exercise is augmented compared to healthy controls [28,31-33,35] despite normal O_2 saturation [28,33] and a normal or low end-tidal P_{CO_2} [31,32,34,36].

A steep slope of the increase in V_E with respect to V_{CO_2} at submaximal exercise or a high V_E/V_{CO_2} ratio at peak exercise is characteristic of patients with HF [35,28,32,37], even in patients whose exercise tolerance is well preserved and is an independent, highly reproducible prognostic marker of mortality[28-30,34,38]. The augmented ventilatory response of HF may result from a combination of impaired cardiorespiratory reflex control of ventilation and ventilation/perfusion mismatch [29]. A decrease in submaximal V_E/V_{CO_2} ratio has been previously reported following long–term captopril administration [39], which could be related to potential improvements in peripheral muscle blood flow on account of the after-load reducing properties of ACE-inhibitors. To our knowledge there is only limited information on the effects of β-blockers on exercise ventilatory efficiency. Guazzi et al. [40] compared the effects of a 6-month treatment of carvedilol or placebo on pulmonary function, cardiac function and exercise capacity in a small group of patients with HF. Their results showed no effect of carvedilol on pulmonary function or maximal exercise capacity despite significant improvement in LV function. Although nor the slope of the increase in V_E with respect to V_{CO_2} at submaximal exercise nor peak V_E/V_{CO_2} were reported, authors reported on a

V_E/V_{CO_2} at 1L which was not affected by carvedilol. Similarly, these authors examined the effects of the carvedilol treatment on steady state 50 W exercise and found no changes with carvedilol [23]. The purpose of the present study was to compare the outcome of a 6-month treatment with carvedilol or metoprolol on maximal exercise parameters as well as ventilatory efficiency during submaximal and maximal exercise.

Methods

Patient population

Twenty-seven patients with congestive heart failure in NYHA functional class II or III with a resting left ventricular ejection fraction (LVEF) of less than 35% completed the 6-months clinical trial. For comparison purposes on the exercise parameters, data from twelve healthy age and gender matched volunteers demonstrating no evidence of cardiovascular or other chronic disease were used to constitute the control group. Informed consent was obtained from each subject.

Patients were randomized in a double-blind fashion to receive either metoprolol or carvedilol while normal medications were maintained. Metoprolol was started at 12.5 mg bid and titrated weekly as tolerated to a maximum dose of 50 mg twice daily. Carvedilol was started at 3.125 mg daily and titrated weekly as tolerated to a maximum dose of 50 mg. Clinical characteristics of the subjects are presented in Table I. As can be seen, there was no significant difference in age or gender distribution between groups. Patients were predominantly of NYHA functional class II with a primary etiology of ischemic cardiomyopathy. All patients in the metoprolol group completed the 6-month trial. One patient in the carvedilol group was discontinued from the study due to severe depression. The maximum dose of metoprolol was achieved in 9 of the 16 subjects with an average daily dose of 75 mg. The maximum daily dose of carvedilol was achieved in 6 of the 11 subjects with an average daily dose of 37.8 mg.

Table I. Baseline characteristics

	Metoprolol	Carvedilol	Controls
	N=16	N=11	N=12
Age (yrs)	60.4	55.9	53.8
Sex			
male	14	10	9
female	2	1	3
Etiology			
IDC	5	5	
ICM	10	6	
Val	1	0	
Treatment			
Furosemide	11	7	0
ACEi	10	8	0
Nitrates	1	2	0
Digoxin	11	8	0

IDC= idiopathic dilated cardiomyopathy
ICM = ischaemic cardiomyopathy
Val = valvular

Resting Evaluation

Prior to the initiation of β-blocker therapy and after 6 months of therapy, echocardiographic assessment of patients' left ventricular function was done. No echocardiographic assessment was done on controls. Measurements included: LV volume and EF quantified by biplane Simpson's rule, LV geometry assessed by a ratio of the major-to-minor axis at end-diastole, LV filling pattern by pulsed Doppler technique, mitral inflow pattern analyzed for maximal E and A velocities, E/A ratio (E-wave to A-wave ratio on mitral inflow) and deceleration time (t decel), and mitral regurgitation was assessed by Doppler flow mapping. The same cardiologist who was blinded to the patients' medication, clinical status and exercise test results did all echographic assessments.

Exercise protocol and peak gas exchange determination

At the beginning of the study and prior to initiation of β-blocker therapy, patients and controls performed a maximal exercise test on a motor-driven treadmill with a symptom limited incremental protocol (RAMP), which included a 2min warm-up to remove effects of anxiety related hyperventilation and 3 min walking recovery.

The treadmill speed and RAMP rate were individualized to the patients self-described activity level in order to yield a test duration of approximately 10min. Patients who had difficulty with 1 flight of stairs were exercised on a RAMP 4 (average increase of 0.21 METS per min), patients who had no difficulty with 1 flight of stairs but were exhausted after 2 flights were exercised on a ramp 6 (average increase of 0.41 METS per min) and patients who had mild difficulty with 2 flights of stairs were exercised on ramp 8 (average increase of 0.75 METS per min).

Continuous ECG tracing and respiratory gas exchange were monitored throughout the warm up, exertional protocol and recovery with the Quinton Qplex®. Blood pressure was measured by sphygmomanometry at the end of each stage of exercise. The gas exchange variables that were analyzed were the oxygen uptake (V_{O_2} ml/min, STPD); CO_2 production (V_{CO_2} L/min, STPD); minute ventilation (V_E [L/min], BTPS); respiratory exchange ratio (V_{CO_2}/V_{O_2}); and ventilatory equivalents for O_2 and CO_2 (V_E/V_{O_2} and V_E/V_{CO_2}). All tests were continued until volitional fatigue or dyspnea was experienced. Patients underwent repeat maximal exercise testing using the same ramp protocol as the baseline test at 6 months post treatment, controls did not repeat testing at 6 months.

Biochemical Analysis

A venous canula was inserted at least 20min before patients and controls underwent exercise testing. Blood was drawn in a standing position just before initiation of the test and at the time of exhaustion. All samples were immediately stored at –80°C venous lactate concentration was measured within 3 months of sampling at the Montreal Heart Institute.

Data Treatment

Because carbon dioxide expired during exercise (V_{CO_2}) increases linearly with minute ventilation (V_E) when work is done below the ventilatory threshold [31], the

slopes of the relationships between V_E and V_{O_2}, V_{CO_2} and the ratio of V_E/V_{CO_2} vs V_{O_2} were constructed for each individual subject using data points after the 2 minute warm up until a respiratory exchange ratio (RER) less than 1.0 during the maximal exercise test. The average slope for each group was then calculated by averaging each individual slope of members within each group.

Peak values for V_E, V_{O_2} and V_{CO_2} were taken as the average of the final 20 sec of exercise for each individual. V_E/V_{O_2}, V_E/V_{CO_2} and the ratio of V_E/V_{CO_2} vs. V_{O_2} were calculated for each subject. The group average was calculated from the individual ratios.

Statistical Analysis

Values are reported as mean ± standard deviation (SD). One-way (3X 1) ANOVA were used to compare the baseline characteristics and baseline exercise data of the metoprolol, carvedilol and control groups. For dependent variables related to submaximal and maximal exercise tests before and after medication, a two-way repeated measures ANOVA with group (metoprolol, carvedilol) and time (pre and post β-blocker treatment) as main effects was also performed. In case of significant group x time interactions, post hock tests were done to examine the difference between pre and post treatment in each group. Comparisons in the relationship between V_E and V_{CO_2}, V_E and V_{O_2} were examined using a 2-way ANOVA on average slopes for each group before and after training.

Association between baseline clinical status and or cardiac function and peak exercise capacity and/or ventilatory efficiency were assessed using Pearson's correlation coefficients. All tests were done considering a p-value of less than 0.05 as significant. Analyses were conducted with SAS, release 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Resting cardiac function status

The results for the resting data are presented in Table 2. There were no significant differences between groups at the beginning of the study for resting heart rate, systolic and diastolic blood pressure, left ventricular ejection fraction, t decel, E/A ratio, left ventricular end diastolic and end systolic diameters. As expected in response to 6 months of β-blocker therapy, resting HR was significantly lower in both groups (p=0.01). The decrease in HR was not accompanied by any significant change in LVEDD. LVESD decreased after 6-months of treatment when the results for both groups were pooled (p=0.0517) but there was no significant group effect. The LVEF was significantly higher at the end of the 6 months compared to the baseline condition in both groups (p=0.0006); no significance difference between groups was observed. There was no significant change in either systolic or diastolic resting blood pressure. Following the 6-month period, the E/A ratio, an index of diastolic function, was not affected by β-blocker therapy. T decel appeared longer after β-blocker treatment but it did not reach significance.

Table 2. Resting Data

		Metoprolol		Carvedilol	
		Pre	post	pre	post
NYHA class (%)	I	0	0	0	18.2
	II	81.25	100	81.8	81.8
	III	18.75	0	18.2	0
HR (beats/min)		76.3 ± 13.8	64.8 ± 10.7*	74.6 ± 12	58.9 ± 4.9*
SPB (mmHg)		113.6 ± 15	118.9 ± 19.1	121 ± 16.7	125.1 ± 15.6
DBP (mmHg)		65.9 ± 9.2	72.1 ± 10.5	75.5 ± 10.7	70.0 ± 11.8
LVEF (%)		27.0 ± 5.5	28.9 ± 5.1*	25.5 ± 3.7	29.8 ± 6.2*
LVEDD(mm)		66.3 ± 7.0	65.7 ± 7.2	66.5 ± 5.4	64.5 ± 5.6
LVESD (mm)		55.7 ± 8.2	54.9 ± 8.2	56.5 ± 5.9	51.6 ± 7.5*
T decel (msec)		178.8 ± 45.9	203.3 ± 77.5	162.1 ± 40.4	173.7 ± 61.7
E/A		1.43 ± 1.01	1.26 ± 0.90	1.68 ± 0.71	1.73 ± 1.48

Values are group means ± SD, * p<0.05 pre to post treatment
NYHA: new York Heart Association, HR: heart rate, SBP: systolic blood pressure
DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter
T decel: deceleration time, E/A: E-wave to A-wave ratio on mitral inflow

Peak Exercise Response

Peak exercise data is presented in Table 3. As expected, peak workload in METS and peak VO_2 were significantly less in HF patients compared to age matched asymptomatic controls. No significant difference was observed between carvedilol and metoprolol groups in peak lactate, peak exercise tolerance (expressed in METs), VO_2 (L/min) or VO_2 (ml/kg/min) either at baseline or at 6 months post treatment. Peak exercise VO_2 decreased significantly ($p=0.027$) in both groups at the end of the 6 months of treatment but there was no significant difference between groups.

At baseline, patients in the metoprolol group showed a peak HR that was significantly lower than both the carvedilol and the control groups. Peak exercise HR in the carvedilol group was similar to controls. At the end of 6 months of β-blocker treatment, peak HR was significantly lower from baseline in both patient groups ($p<0.0001$). The average absolute change in peak HR was –22 beats per minute in both groups, which corresponds to relative changes of –14% for the carvedilol group, and –17% for the metoprolol group. This relative change was not statistically significant between patient groups. Nonetheless, there was a significant difference between patient groups at baseline and at the end of 6 months in peak HR.

Peak V_E was significantly lower in both patient groups compared to controls but not different between heart failure patient groups, however, there was a tendency for the metoprolol group to be lower. Peak V_E showed a slight decrease in both patient groups at the end of the 6 months ($p=0.0639$) but there was no difference between groups.

Peak V_E/VO_2 ratio was significantly higher in both patient groups at baseline compared to controls. There was no significant difference in peak V_E/VO_2 from baseline to 6 months in either group. Similarly, peak V_E/VO_2 at 6 months was not different between groups.

Peak exercise V_E/V_{CO_2} ratio was significantly higher in patients than in controls at baseline. No difference was found between heart failure patient groups at baseline or at 6 months. After 6 months of β-blocker treatment, a significant decrease in peak V_E/V_{CO_2} ratio was seen in the metoprolol group ($p=0.002$), but not in the carvedilol group, however this decrease is probably due to arithmetic as peak V_{CO_2} did not change after treatment and peak V_E decreased non-significantly. The peak V_E/V_{CO_2} ratio was found to be significantly correlated to peak V_{O_2} at both baseline ($r= -0.70$, $p<0.0001$) and at 6-months of treatment ($r= -0.55$, $p= 0.003$). There was no correlation between the peak V_E/V_{CO_2} ratio and resting ejection fraction ($r= -0.31$, $p= 0.11$) or E/A ($r= 0.10$, $p= 0.70$) (data not shown).

Table 3. Peak Exercise Data

	Metoprolol		Carvedilol		Controls
	pre	post	pre	post	
Peak MET	5.38 ± 1.45	5.11 ± 1.41	5.76 ± 1.85	5.24 ± 1.90	9.85 ± 1.65*
Peak VO_2 (L/min)	1.42 ± 0.48	1.31 ± 0.44‡	1.68 ± 0.60	1.54 ± 0.69‡	2.56 ± 0.53*
Peak VO_2 (ml/min/kg)	18.8 ± 5.1	17.9 ± 5.0‡	20.2 ± 6.5	18.3 ± 6.7‡	34.5 ± 5.8*
Peak VCO_2 (L/min)	1.47 ± 0.62	1.47 ± 0.55	1.78 ± 0.65	1.68 ± 0.79	2.79 ± 0.71*
Peak HR (bpm)	133 ± 17#	110 ± 18‡§	151 ± 22	129 ± 20‡	159 ± 19
Peak VE (L/min BTPS)	48.9 ± 18.5	44.0 ± 13.5	57.9 ± 16.2	54.1 ± 19.7	76.7 ± 17.7*
Peak VE/VO_2	36.3 ± 7.2	34.5 ± 6.3	37.2 ± 6.1	37.4 ± 7.9	30.3 ± 3.9*
Peak VE/VCO_2	35.0 ± 5.1	31.8 ± 5.2‡	33.8 ± 4.0	33.6 ± 5.4	27.9 ± 3.0*
Peak lactate (mmol/L)	2.76 ± 1.50	2.27 ± 1.40	3.02 ± 1.22	2.54 ± 0.88	5.17 ± 2.84*

Values are means ± SD. *$p<0.05$ controls vs patients at baseline, ‡$p<0.05$ after 6 months of treatment, #$p<0.05$ metoprolol vs carvedilol and control groups, §$p<0.05$ metoprolol vs carvedilol

Exercise Ventilatory Efficiency

Table 4 shows the group means of the slope of the V_{CO_2} vs. V_E relationship and the V_{O_2} vs. V_E relationship calculated from the exercise data (all points after the warm-up up to an RER of 1.0). Table 4 also shows the slope of the relationship between the submaximal V_E/V_{CO_2} ratio and V_{O_2}.

As seen for peak ratios of V_E/V_{CO_2} and V_E/V_{O_2} , the slope of the submaximal relationships between V_{CO_2} and V_E or V_{O_2} and V_E were significantly lower in the control group compared to both patient groups. There were no significant

changes in the slopes of the V_E vs. V_{O_2} or V_E vs. V_{CO_2} relationships for either patient group after β-blocker treatment (Figures 3 and 4). Similarly, when results from both metoprolol and carvedilol treatment groups were pooled, the pre-post β-blocker difference on the submaximal V_E vs. V_{CO_2} slope exhibited a decrease in slope with a p value= 0.10. In addition, five patients of 26 exhibited a baseline V_E vs. V_{CO_2} slope greater than 1 SD above the group average. In these patients, a pre-post statistical analysis revealed a significant decrease in slope following β-blocker therapy. Finally, V_E/V_{CO_2} vs. V_{O_2} was significantly different between groups, such that the metoprolol group was greater than the carvedilol group prior to treatment, but not different after treatment in either group (Table 4).

Table 4- Effect of treatment on the slope of the relationship between VE and VCO_2 and VO_2 respectively during submaximal exercise (RER<1.0).

	Metoprolol		Carvedilol		Controls
	pre	post	pre	Post	
Slope VCO_2 (L/min) vs VE (L/min)	30.96 ± 5.51	27.62 ± 5.13	30.61 ± 3.98	29.31 ± 4.70	23.69 ± 4.56*
Slope VO_2 (L/min) vs VE (L/min)	31.97 ± 7.86	30.12 ± 5.80	31.80 ± 5.03	30.36 ± 5.73	24.45 ± 5.40*
Slope VE/VCO_2 vs VO_2	-9.35 ± 5.83§	-10.63 ± 6.57§	-5.63 ± 4.94	-6.11 ± 3.34	-6.70 ± 2.75

*p<0.05 controls vs patients at baseline, §p<0.05 metoprolol vs carvedilol

Discussion

In this 6-month study comparing metoprolol to carvedilol in patients with chronic heart failure, both agents significantly increased resting LVEF, decreased resting and peak exercise HR and decreased peak V_{O_2}. The main finding from the study was that ventilatory efficiency was not significantly affected by β-blocker therapy suggesting that the abnormal exercise ventilatory response of HF patients is not mediated by β-adrenergic receptors.

Effect of treatment on resting characteristics

Resting HR decreased significantly in both groups after 6 months of β-blocker treatment. Similarly, increases in resting LVEF of 7% and 17% were found in the metoprolol and carvedilol groups respectively after 6 months of β-blocker treatment. A significant improvement in LV function is a common observation after long-term β-blocker therapy with greater improvements being reported

following treatment with third generation blockers [40]. While a clear mechanism is yet to be provided, it seems that β-blockers could act to halt or reverse cardiac remodelling resulting from the increased mechanical stress and the excessive neurohormonal stimulation on the heart [24]. This potential explanation is further supported by a dose-dependent effect on LVEF seen after 6 months of therapy using carvedilol [3].

Changes in diastolic function have also been reported following long-term β-blockers; Sanderson et al. [19] found a significant decrease in E/A with 12 weeks of metoprolol and carvedilol treatment, however, in agreement with results from Arumanayagam et al. [21], we found no change in the E/A index of diastolic function in either group after 6 months of therapy. In addition, significant decreases in LVEDV and LVESV have been seen with both metoprolol [16] and carvedilol [10,16,22,23]. In the present study, resting LVEDD remained unchanged in both patient groups after 6 months of β-blocker treatment despite the longer diastolic filling time resulting from the reduction in heart rate. Failure of LVEDD to increase in presence of a longer diastolic filling time may be related to the increase in LVEF resulting in greater emptying. This is compatible with the significant reduction in LVESD seen after 6 months in the carvedilol group but cannot be an explanation in the metoprolol group. No changes in diastolic or systolic arterial pressure were observed after treatment suggesting that changes in ventricular afterload were not a factor in the observed improvement in resting ventricular systolic function.

Effect of treatment on exercise performance

As expected, the peak V_{O_2} of healthy controls was significantly higher than that of patients. The peak V_{O_2} at baseline was similar [26] or higher than that of previously published studies [16,18,20,25]. Six-months of β-blocker treatment resulted in a significant decrease in peak V_{O_2} of approximately 8% in both treatment groups, which could be explained by a significant decrease in peak HR. Increasing HR during exercise is related to increasing stimulation on the β_1-

receptors on the sino-atrial node. Post-synaptic desensitization of β-adrenergic receptors in sino-atrial tissue has been proposed to explain an attenuated HR response to exercise in patients with heart failure [24]. In the present study, the lower peak HR following β-blocker treatment was obtained with no change in the levels of circulating catecholamines.

In studies comparing the effects of metoprolol and carvedilol on peak exercise parameters, peak V_{O_2} has been shown to be increased in the metoprolol only group [16], both the metoprolol and carvedilol groups [25], or not changed in either group [26]. Olsen et al. [17] found a marked improvement in rest and peak exercise LVEF although peak V_{O_2} did not change in patients treated with carvedilol on account of a significantly lower maximal exercise HR.

In the present study, peak HR was significantly different between patient groups at baseline despite true randomization occurring at the initiation of the study. Multiple regression analysis was performed to determine if there was any significant predictor between the dependent variable of peak HR and the etiology of the HF, LVEF and medications, but no significant association was found. A statistically significant difference was not found between groups for mean age, and the correlation coefficient between peak HR and age was –0.35. Thus it is difficult to explain the difference in baseline peak HR.

Ventilatory Efficiency

In this study, as in other previously published studies [32, 33,35, 37], peak V_E/V_{CO_2} [30] and the slope of V_{CO_2} relative to V_E [28,31,34,36,38] were found to be significantly higher than controls in both groups at baseline.

The reduction in exercise ventilatory efficiency seen in HF results from a combination of enhanced cardiorespiratory reflex control of ventilation and ventilation/perfusion mismatch [29]. Recent experimental evidence suggest that the exaggerated ventilatory response to exercise in HF could be related to an

increased chemosensitivity and/or an altered control of ventilation from peripheral chemoreceptors or skeletal muscle ergoreceptors [42,43]. However, since the exaggerated ventilation of HF is not generally associated with an abnormal fall in $PaCO_2$, ventilation/perfusion mismatch must be a contributing factor to the elevated exercise V_E/VCO_2 [31,33,36]. Irrespective of the precise mechanism for the exaggerated exercise ventilatory response of HF, results from the present study suggest that the phenomenon may not be mediated by β-adrenergic receptors since changes in the slopes of the submaximal exercise V_E vs VCO_2 or V_E/VCO_2 vs VO_2 relationships were not observed after 6-months of either β-blocker therapy and, as discussed previously, the decrease in peak V_E/VCO_2 seen after metoprolol treatment may likely be ascribed to an artefact of computation. This conclusion is further supported by recent observations from Guazzi et al. [23,41] showing no effect of 3 or 6 months of 50 mg/daily of carvedilol on peak or submaximal exercise V_E/VCO_2. In addition, these authors found no effect of carvedilol on exercise ventilatory parameters including the ratio of dead space volume to tidal volume suggesting unchanged pulmonary ventilation and perfusion characteristics following carvedilol. They did however find persistent lung function disturbances in HF, which could contribute to the exercise intolerance and ventilatory inefficiency of patient with HF. More recently, preliminary findings by the same authors [44] report a significant decrease in the slope of the V_E vs. VCO_2 relationship in HF patients exhibiting higher baseline V_E vs. VCO_2 slopes than in the present study suggesting that there may be a β-blocker treatment effect mainly in patients with more marked exercise ventilatory impairment. Our present observations that there was a significant decrease in V_E vs. VCO_2 slope in 5 patients showing a baseline slope 1 SD above the average group value would be in accordance with this proposition.

An interesting observation of the present study is the similarity in the slope of the V_E/VCO_2 vs. VO_2 relationship found in HF patients from the carvedilol group and controls. The relationship was established in all subjects using the ventilatory and metabolic parameters during the incremental peak exercise test between the

end of the warm-up period and the achievement of a respiratory exchange ratio of 1.0. This inverse relationship between ventilatory efficiency and metabolism confirms that dead space ventilation decreases similarly with increasing submaximal exercise intensity in patients and controls despite an upward shift of the V_E/VCO_2 line. This observation may be taken to suggest that factors contributing to the ventilatory inefficiency of HF are not triggered by exercise but are already present at very low exercise intensity.

In conclusion, the present results indicate that neither second generation β_1-selective blockers nor third generation β-blockers only mildly selective for β_1 receptors with combined $alpha_1$-blockade properties had any effect on maximal and submaximal exercise ventilatory efficiency. The fact that there was only a relatively small number of patients in each group and that for ethical reasons, a placebo group could not be included in the study must however be recognized as limitations of this study. Although this study was not designed to specifically examine the underlying mechanism for the exercise ventilatory inefficiency of heart failure, the present observations may be taken to suggest the response is not mediated by β-adrenergic receptors.

Figure 1. Peak exercise V_E and V_E/VCO_2 for groups Carvedilol (A) and Metoprolol (B) before (pre) and after (post) 6 months of treatment

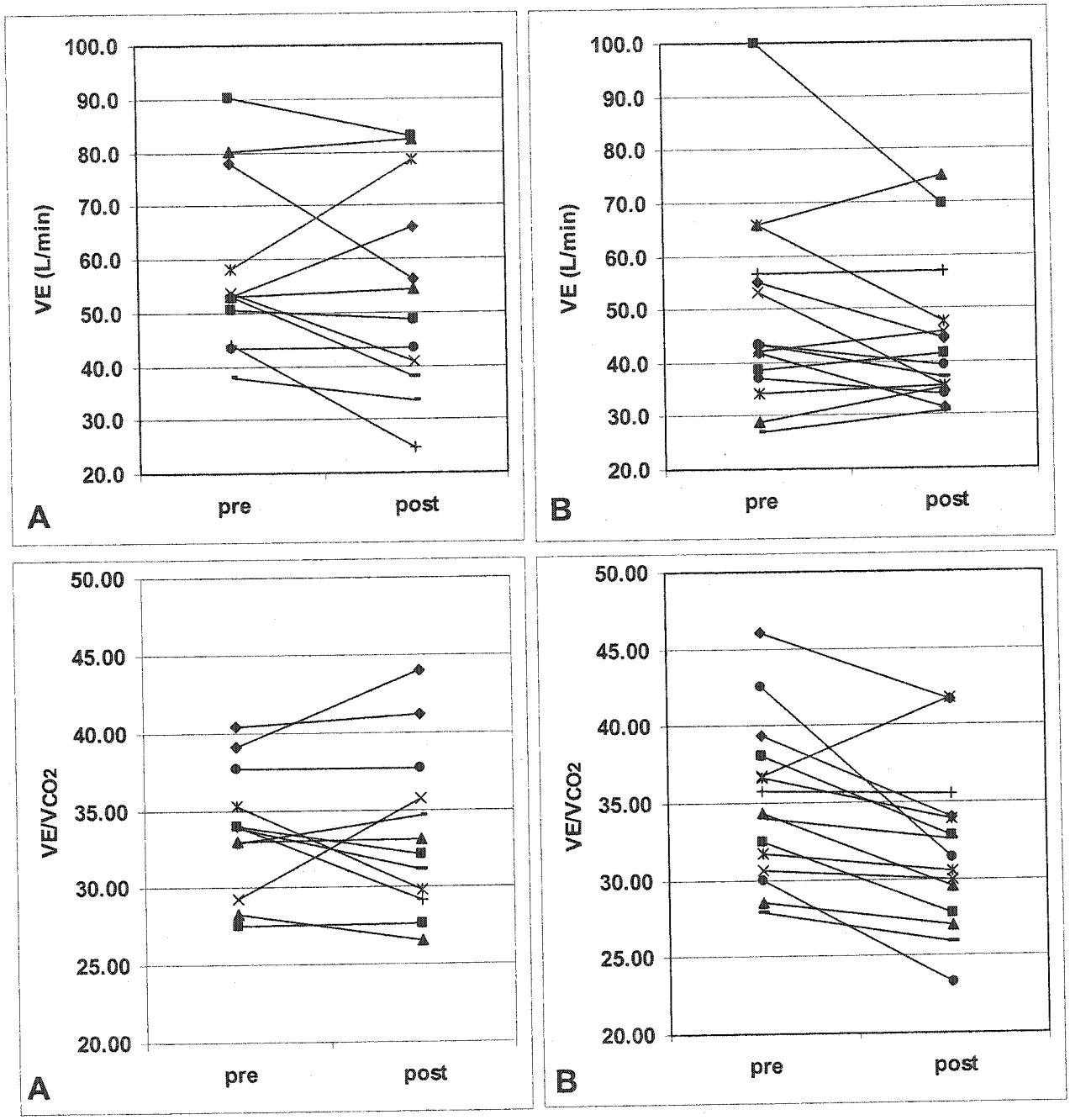


Figure 2. Peak exercise V_{O_2} and V_{CO_2} for groups Carvedilol (A) and Metoprolol (B) before (pre) and after (post) 6 months of treatment.

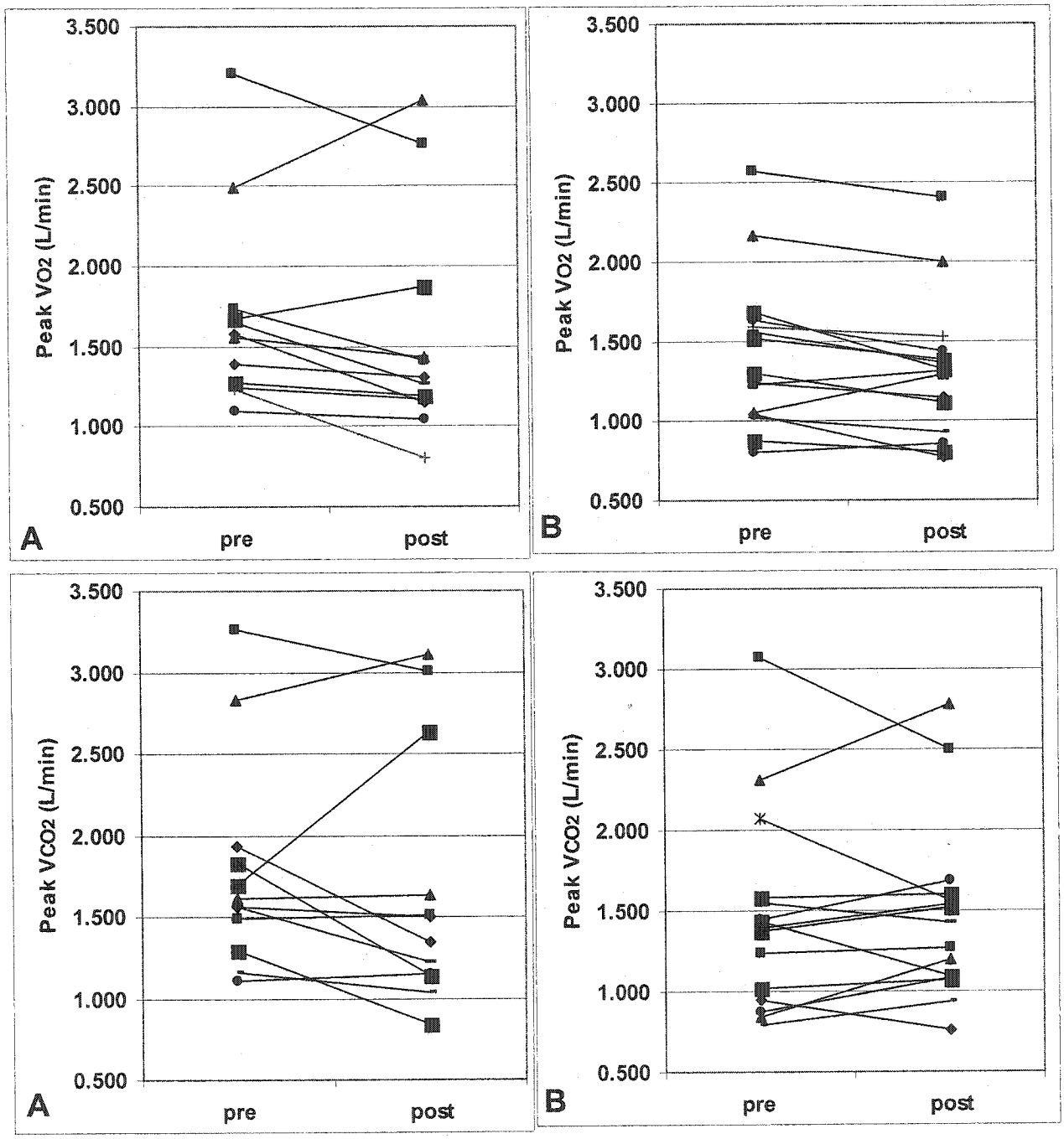


Figure 3. Submaximal Exercise V_E vs V_{O_2} relationship in Groups Carvedilol pre (A) and post (C) 6 months of treatment, and Metoprolol pre (B) and post (D) 6 months of treatment

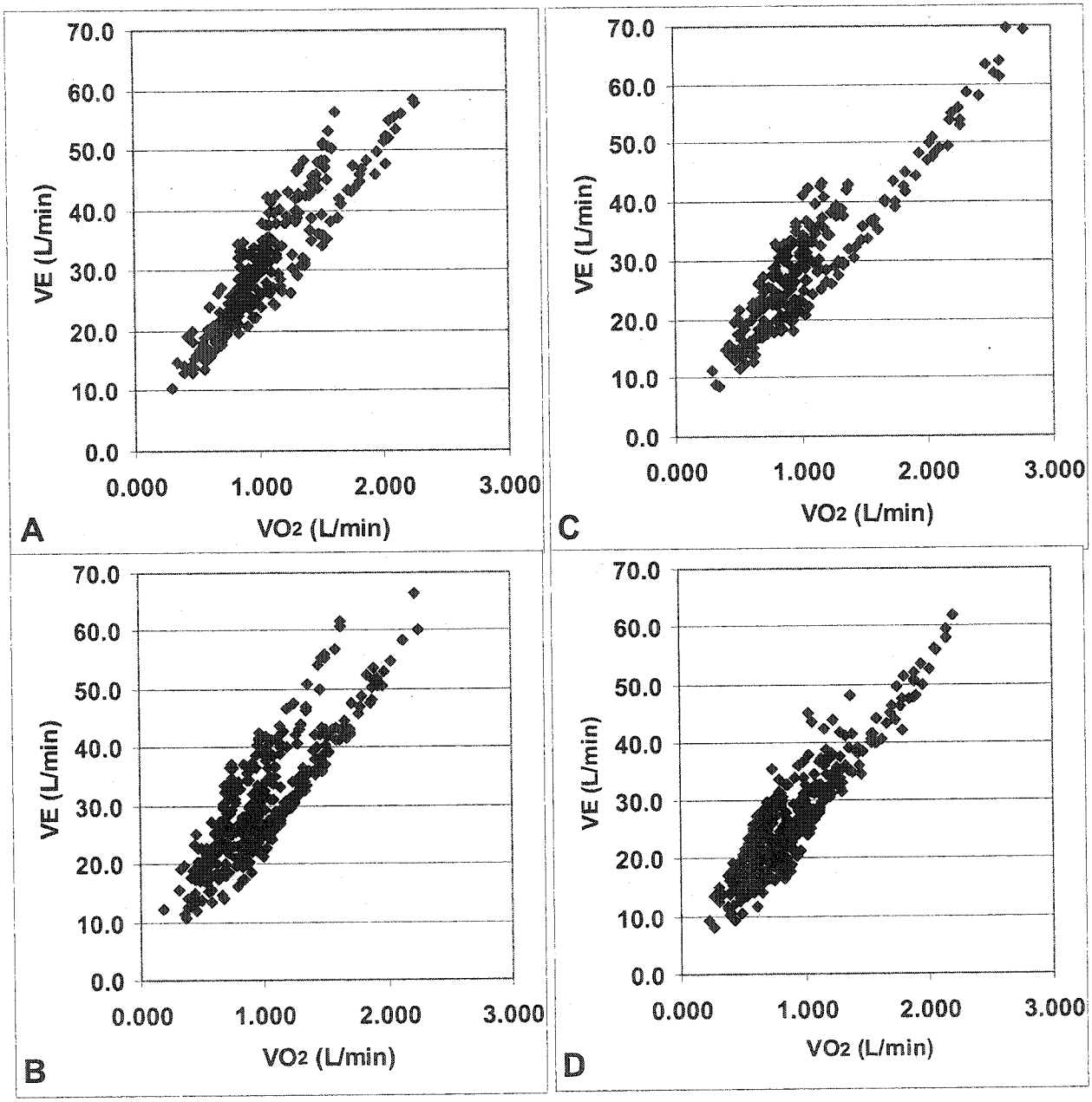
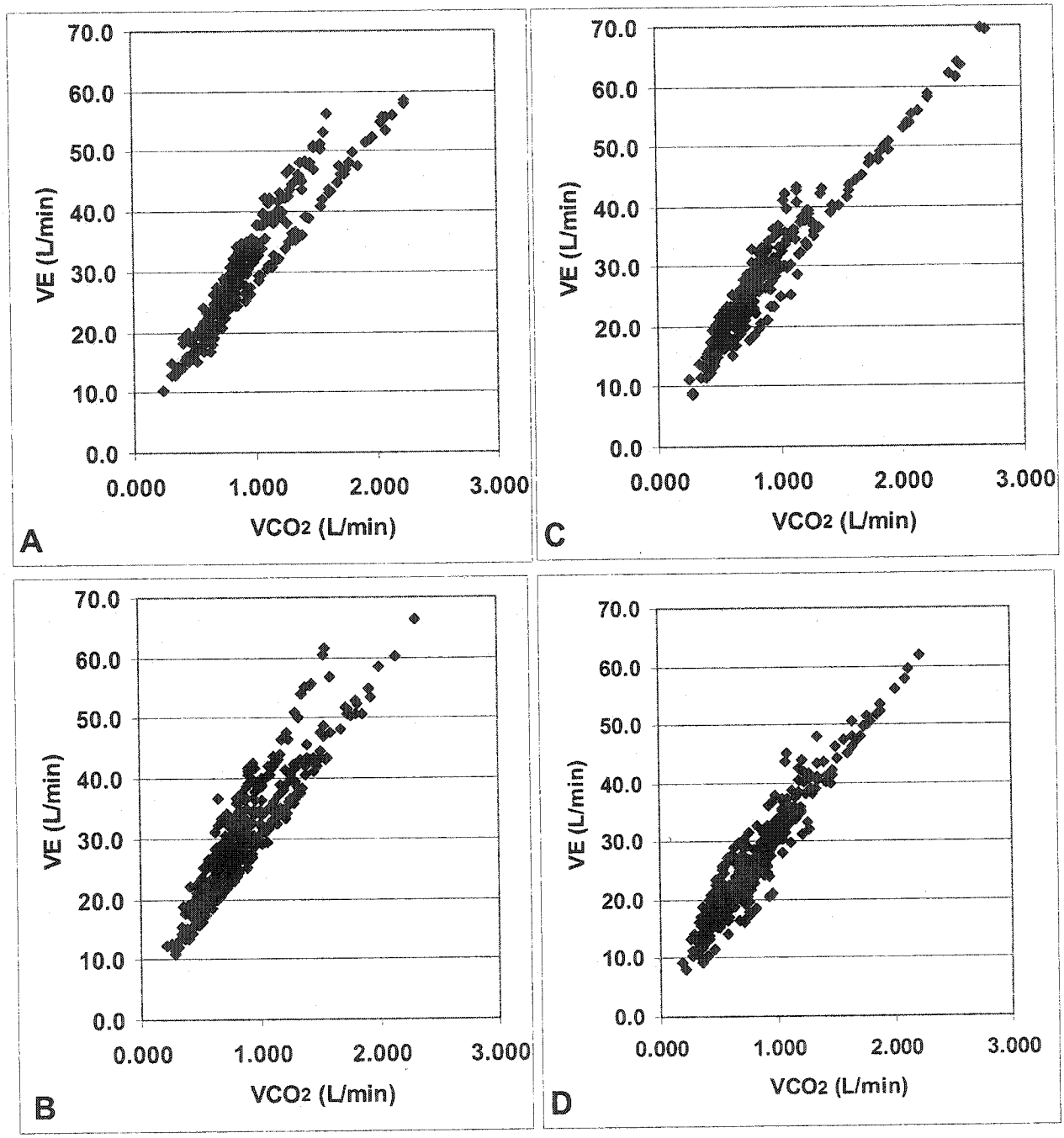


Figure 4. Submaximal Exercise VE vs. VCO_2 relationship in Groups Carvedilol pre (A) and post (C) 6 months of treatment, and Metoprolol pre (B) and post (D) 6 months of treatment



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