Abstract

β-Adrenergic receptor antagonists (β-blockers) have been recognized for their cardioprotective properties, prompting use of these pharmacologic agents to become more mainstream in acute myocardial infarction (AMI) and congestive heart failure (CHF). Despite their popularity as a class, the ability to protect the myocardium varies significantly between different agents. Carvedilol is a non-selective β-blocker with α₁-adrenergic receptor antagonism properties. It is unique among β-blockers because in addition to improving exercise tolerance and its anti-ischemic properties secondary to a reduction in heart rate and myocardial contractility, carvedilol exerts other beneficial effects including: antioxidant effects; reduction in neutrophil infiltration; apoptosis inhibition; reduction of vascular smooth muscle migration; and improvement of myocardial remodeling post-AMI. These properties, documented in animal models and subsequent clinical trials, are consistent with established evidence demonstrating decreased morbidity and mortality in patients with CHF and post-AMI. This article reviews the role of carvedilol compared with other β-blockers in the treatment of CHF and post-AMI management.

1. Background

Carvedilol is a third-generation, non-selective β-blocker (β-adrenergic receptor antagonist) with vasodilatory properties due to α₁-adrenergic receptor antagonism. [1] It has been shown to have potent antioxidant, anti-proliferative, and free radical scavenging action along with anti-ischemic effects in the myocardium. [2–6] Carvedilol exists as a racemic mixture of two enantiomers, S-(-) and R-(+) carvedilol, each of which has different pharmacodynamic profiles. The S-(-)-isomer has both α₁- and β-adrenergic receptor blocking activity, whereas the R-(+)-isomer has only weak α-blocking properties. [1,7]

The cardioprotective effect of β-blockers in reducing mortality after acute myocardial infarction (AMI) has been well documented in multiple clinical trials utilizing various β-blockers. [8] Although not completely understood, cardioprotection by β-blockers appears to be the result of several mechanisms including: salvage of the myocardium in the acute phase of myocardial infarction (MI); anti-fibrillatory effects and antioxidative properties; prevention of reinfarction and potential effects on hemostasis; and delay in the development of atherosclerosis. [9] In this article, we review the clinical and laboratory data available on carvedilol and its properties, as well as its effects in the context of ischemia, AMI, post-MI ventricular remodeling, and arrhythmias.

2. Carvedilol and Ischemia

Carvedilol has been proposed to ameliorate the adverse effects of ischemia and reperfusion by its properties involving antioxidation, inhibition of adhesion and activation of neutrophils, quenching of oxygen free radicals, protection of endothelial function, and direct vasodilation. [4] An overview of its pharmacodynamic properties is illustrated in figure 1.
Pharmacodynamic properties of carvedilol. AMI = acute myocardial infarction.

2.1 Antioxidant Effect of Carvedilol

The known antioxidant activity of carvedilol may also contribute to its beneficial role during ischemic events. As a likely result of its carbazole moiety, carvedilol has been shown to scavenge oxygen free radicals. In addition, carvedilol preserves endogenous antioxidant systems (i.e. vitamin E, glutathione) that are typically consumed during tissue exposure to oxidative stress, with an antioxidant profile approximately 10 times greater than that of vitamin E. Several metabolites of carvedilol are 50–100 times more potent than the parent drug itself (and up to 1000 times more potent than vitamin E), which may further contribute to its overall antioxidant properties.

Brunvand et al. studied one of these main metabolites, SB211475, in a rabbit model for myocardium ischemia and reperfusion injury. Comprised of a hydroxyl group introduced at the third position of the carbazole moiety in carvedilol, the SB211475 metabolite has α1-adrenergic receptor antagonistic effects similar to that of carvedilol, but lacks significant β-blocking properties. Nevertheless, SB211475 has been found to be a very potent antioxidant in vitro. Lastly, the antioxidant activity of carvedilol inhibits the process of apoptosis and subsequent cardiac remodeling that occurs in response to programmed cell death. In other words, apoptosis induced by ischemia, reperfusion, and pressure overload-induced hypertrophy has been shown to be responsive to carvedilol.

2.2 Effect of Carvedilol on Neutrophil Activation

An important component of ischemic-induced myocardial damage is leukocyte accumulation in the ischemic zone. Neutrophils
are a source of oxygen radicals as they release chemokines and proteolytic enzymes that increase the extent of ischemic damage. In pigs and rabbits subjected to myocardial ischemia and reperfusion, carvedilol significantly decreased neutrophil infiltration (as assessed by myeloperoxidase [MPO] activity), \[15,16\] via inhibition of neutrophil attachment and activation of endothelial cells, which occurs by suppression of genes regulating intra-cellular adhesion molecule-1 (ICAM-1) expression. ICAM-1 is a key adhesion molecule responsible for neutrophil attachment to endothelial and smooth muscle cells. \[4,11\]

In human polymorphonuclear leukocytes, Drábiková et al. \[17\] found that carvedilol interfered with both in vitro and ex vivo reactive oxygen metabolite generation, in addition to previously generated reactive oxygen species, suggesting a preventative and potentially therapeutic mechanism against oxidative stress-related injury. \[17\] Similarly, in a study comparing the effects of carvedilol versus propranolol on oxidative stress in leukocytes in hypertensive patients, carvedilol was found to inhibit oxidative stress in polymorphonuclear and mononuclear cells, as well as decrease C-reactive protein levels, to a greater extent. \[18\]

### 2.3 Effect of Carvedilol Through Free Radical-Scavenging Properties

By scavenging free radicals and attenuating endothelial dysfunction, \[4,19–22\] carvedilol may (i) improve the recovery of myocardial blood flow after reperfusion; (ii) prevent platelet aggregation; and (iii) ameliorate neutrophil-induced myocardial injury. \[4\]

Two lines of evidence strongly suggest that carvedilol may exert myocardial protective effects through its free radical-scavenging properties. First, it is well documented that ischemia followed by reperfusion is associated with a burst of oxygenderived free radical generation. These highly reactive molecules play a pivotal role in the pathogenesis of post-ischemic reperfusion injury in the heart. \[23\] Second, by utilizing electron paramagnetic resonance techniques, it has been demonstrated that carvedilol scavenges both superoxide anions \[24\] and hydroxyl radicals in aqueous and lipid environments. Taken together, these results suggest that carvedilol may also scavenge superoxide and hydroxyl radicals generated after reperfusion following myocardial ischemia, and thus protect the myocardium from reperfusion injury. \[12\]

### 2.4 Effect of Carvedilol on Preserving the Nitric Oxide System

Common disorders that promote atherosclerosis, such as hypertension, hyperlipidemia, smoking, and diabetes mellitus, are all associated with endothelial dysfunction. In 1980, Furchgott and Zawadzki \[25\] reported a product of endothelial cells that causes relaxation of blood vessels. This endothelium-derived relaxing factor (EDRF) was discovered to be nitric oxide (NO). NO is a potent endogenous inhibitor of polymorphonuclear neutrophil (PMN) chemotaxis, adherence, and activation. \[26\] Decreased NO release may promote PMN adherence to the endothelium \[27\] and increase PMN-induced myocardial damage during the reperfusion period. Reduction in NO release also promotes vasoconstriction, which contributes to the 'lack of reflow phenomenon' following myocardial ischemia and reperfusion. Loss of NO release may also facilitate platelet aggregation and the release of platelet mediators (e.g. thromboxane A2 and platelet-activating factor-PAF), potentially exacerbating myocardial injury. \[27\]

Treatment with carvedilol significantly attenuates endothelial dysfunction induced by various conditions considered to be cardiovascular risk factors. This action occurs through properties that inhibit low-density lipoprotein oxidation, a process that is thought to stimulate foam cell formation and accelerate the development of atherosclerotic plaques. This ability to prevent formation of oxidized low-density lipoprotein, in addition to carvedilol's overall antioxidant properties that may provide vascular protection by improving NO bioavailability, results in a beneficial effect on the endothelium. \[2\] Recent studies have indicated that carvedilol is able to improve endothelial function. Bank et al. \[28\] compared the effects of metoprolol and carvedilol on endothelial function and oxidative stress in a randomized clinical trial of 34 patients with hypertension and type 2 diabetes. Despite no differences between the two groups in terms of markers of oxidative stress and glycemic control, carvedilol significantly improved brachial-artery flow-mediated dilation (FMD), compared with the metoprolol group (p < 0.001). \[28\] Furthermore, this effect was reinforced in a study involving the forearm microcirculation of patients with dilated cardiomyopathy. \[29\]

### 2.5 Effect of Carvedilol Through \(\alpha_{1}\)-Adrenergic Receptor Blocking Vasodilation

One of the mechanisms that may contribute to the dramatic protection offered by carvedilol is the vasodilating effects through \(\alpha_{1}\)-adrenergic receptor blockade. \[16\] Arteriole vasodilation may increase collateral blood flow to the ischemic region, and thus ameliorate ischemic myocardial injury. \[16,30\] Furthermore, \(\alpha_{1}\)-adrenergic receptor blockade could contribute to further reduction in infarct size by reducing myocardial work, and therefore oxygen demand, through reductions in both afterload and myocardial wall tension. \[30\]

In a review by Galderisi and D'Errico, \[31\] the vasodilating capacity of carvedilol is quoted as well as its ability to improve hyperemic coronary blood flow, a phenomenon attributable to reduction in minimal resistance as a result of adrenergic blockade...
and NO-mediated effects. This improvement may be of benefit to patients with coronary artery disease as it signifies improved coronary microvascular function. Coronary flow reserve (CFR) is defined as the 'maximal increase in coronary blood flow above resting level for a given perfusion pressure when coronary vasculature is maximally dilated'. It is also suggested that increases in CFR due to vasodilating β-blockers, such as carvedilol, may have beneficial effects in microvascular angina pectoris or silent ischemia in patients without epicardial artery stenosis. [31]

Considering all together the ability of carvedilol to inhibit neutrophil adhesion and activation, scavenge free radical species, facilitate the endogenous NO system, and cause direct vasodilation, it may be a preferential β-blocker in patients at risk for cardiac ischemic events.

3. Pre-treatment With Carvedilol in Acute Myocardial Infarction (AMI)

The stress-induced sympathetic response during AMI may have a negative impact on clinical outcome. In a study by Hansen et al. in 1994, [9] pretreatment with carvedilol prevented or attenuated many of the potentially deleterious effects of increased plasma epinephrine as studied by the infusion of epinephrine in healthy male volunteers on two separate occasions to achieve serum concentrations similar to that reached in AMI. The study is reviewed below to highlight the effects of carvedilol that may be of benefit in AMI.

Hypomagnesemia has been associated with arrhythmias in patients with no evidence of clinical heart disease. [4] Although no clear association has been established in patients with AMI, [5,9] evidence favoring the infusion of magnesium to decrease arrhythmias and mortality in AMI has been reported. [9,32] Animal experiments have also shown that hypokalemia in myocardial ischemia lowers the threshold for stimulated ventricular fibrillation, and potassium depletion may increase the risk of spontaneous ventricular fibrillation in experimental myocardial ischemia. [9,10,33] In clinical AMI, hypokalemia has been associated with an increased risk of malignant ventricular arrhythmias. [9]

In terms of study design, [9] healthy male volunteers were pretreated for 2 weeks with carvedilol or placebo in randomized order before receiving epinephrine infusions. The results were as follows:

1. **Serum electrolytes**: Epinephrine caused significant decreases in serum levels of potassium, magnesium, calcium, and phosphate (all p < 0.001). Whereas pretreatment with carvedilol did not significantly abrogate the reduction in serum calcium (p = 0.06), the decline in serum phosphate (p < 0.01) was lessened, serum magnesium level remained constant during epinephrine infusion (p < 0.01), and the epinephrine-induced reduction in serum potassium was completely inhibited (p < 0.001).

2. **Glucose and insulin**: Epinephrine infusion resulted in significant reductions in serum insulin and C-peptide, while serum glucose was increased. Pretreatment with carvedilol augmented the decline in serum insulin (p < 0.05) and C-peptide (p < 0.05) while significantly attenuating the epinephrine-induced increase in serum glucose (p < 0.001).

3. **Lipids**: While epinephrine caused significant decreases in total cholesterol (p < 0.001), high-density lipoprotein cholesterol (p < 0.001), low-density lipoprotein cholesterol (p < 0.05), and apolipoprotein [Apo](A) [p < 0.001], and no significant effect on serum triglyceride, Apo(B), or lipoprotein (a) levels, there was a rapid increase in serum free fatty acids (FFA) [p < 0.001] and similar increase in serum glycerol (p < 0.05). High levels of serum FFA may be toxic to the ischemic myocardium and potentially contribute to the development of arrhythmias. The epinephrine-induced spike in both serum FFA and glycerol levels was significantly attenuated by carvedilol (p < 0.001).

4. **Hemodynamic profile**: In the control group, epinephrine infusion caused a significant increase in systolic blood pressure (SBP) [p < 0.01], a significant decrease in diastolic blood pressure (DBP) [p < 0.001], a non-significant increase in heart rate (p = NS), and overall, a significant increase in cardiac work (p < 0.01). Although carvedilol had no significant effect on SBP prior to epinephrine infusion, pretreatment with carvedilol diminished the epinephrine-induced increase in SBP (p < 0.001) and inhibited the epinephrine-induced decrease inDBP(p < 0.001). Carvedilol infusion prior to epinephrine resulted in a significant decrease in cardiac workload (p < 0.05) and completely abolished the epinephrine-induced increase in cardiac workload (p < 0.001).

5. **Electrophysiologic findings**: Epinephrine infusion caused a significant increase in QT (p < 0.001) and QTc duration (p < 0.01) on ECG. Although the increase in QTc duration after epinephrine infusion was not significantly altered by carvedilol, the epinephrine-induced QTc prolongation noted was completely prevented (p < 0.001) by carvedilol. QTc prolongation is a recognized risk factor for arrhythmias and may also predict unfavorable prognosis after AMI. [4,9]

4. Carvedilol Treatment in AMI
4.1 Immediately Following AMI

A study by Basu et al. [34] investigated the effects of acute (intravenous) and long-term (oral medications for 6 months) treatment with carvedilol versus placebo in 151 patients with AMI. Aside from monitoring patients for cardiovascular events, exercise ECG, ambulatory monitoring, and 2-dimensional echocardiography were performed before hospital discharge, as well as at 3- and 6-month follow-up. The Cox proportional hazards model was used to compare time from randomization to the occurrence of a cardiovascular event, allowing for calculation of Kaplan-Meier survival curves. Carvedilol was found to significantly reduce cardiac events compared with placebo (p < 0.02). Moreover, patients subjected to carvedilol treatment demonstrated significant reductions in heart rate (p < 0.0001), blood pressure at rest (p < 0.005), and rate-pressure product (RPP) at peak exercise (p < 0.003), while exercise capacity remained unchanged. Even though left ventricular ejection fraction (LVEF) was not altered significantly by carvedilol, stroke volume was found to be higher on pre-hospital discharge examination (63 vs 53 mL; p < 0.01). Diastolic filling of the left ventricle (E/A ratio) was also improved in the treatment group (1.2 vs 0.9; p < 0.001). Interestingly, treatment with carvedilol showed attenuation of remodeling in a subgroup with LVEF <45%. [34]

Based on multiple clinical trials of ACE inhibitors underscoring the pathophysiologic importance of neuroendocrine activation in the development and progression of heart failure, and the importance of cardiac remodeling in the development of left ventricular (LV) systolic dysfunction, this background served as the rationale for the study of carvedilol in post-infarct patients. [35] The CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) study was a double-blind, randomized, placebo-controlled, multicenter, multinational, trial that investigated the effects of carvedilol treatment in patients with an AMI and LVEF dysfunction. The trial results indicated that carvedilol reduced all-cause mortality by 23% (p = 0.031) over a mean follow-up of 1.3 years. [35–37] In 2007, Fonarow et al. [38] assessed the impact of carvedilol within the first 30 days of randomization in the CAPRICORN trial. The carvedilol group experienced reductions in: 30-day mortality (19 vs 33; hazard ratio [HR] 0.58; 95% CI 0.33, 1.02); fatal or nonfatal MI (13 vs 23; HR 0.57; 95% CI 0.29, 1.12); the composite endpoint of death, nonfatal MI, or cardiac arrest (31 vs 53; HR 0.58; 95% CI 0.38, 0.91); and the composite of all-cause mortality or nonfatal MI (29 vs 51; HR 0.57; 95% CI 0.36, 0.90), concluding that carvedilol treatment provides an early benefit which is similar to that of long-term therapy. [38]

4.2 Following Thrombolysis

Carvedilol significantly reduces the increased risk of cardiac events in post-AMI patients managed with thrombolytic therapy and evidence of exercise-induced myocardial ischemia (p = 0.03). It is well tolerated, safe to use in patients immediately after AMI, and has been documented to significantly improve outcome. [39]

A randomized, double-blind, placebo-controlled, parallel-group study was designed by Basu et al. [39] to assess the extent of myocardial ischemia in clinically stable patients 6 weeks after AMI and thrombolysis. This study also aimed to determine the influence of carvedilol on ischemic events during the subsequent 6 months. Of the 101 patients who remained event-free at 6 weeks post-MI, reversible ischemia was detected in 70 patients after undergoing rest and exercise thallium-201 (TI-201) imaging. In patients identified to have ischemia, 13 events were recorded, compared with 1 event in the remaining 31 patients without ischemia. Furthermore, only 4 of 56 patients on carvedilol were noted to have adverse cardiac events, which is a significantly lower rate (p = 0.04) than those on placebo (10/45). In patients with reversible ischemia, carvedilol was shown to be more effective than the placebo in reducing these events as well (p = 0.03). This study demonstrated that reversible myocardial ischemia is present in clinically stable patients following thrombolysis, and that there is an increased rate of cardiac events that may be reduced by carvedilol therapy. [39]

4.3 Following Percutaneous Transluminal Coronary Angioplasty and Coronary Artery Bypass Grafting

Vascular smooth muscle cell migration and proliferation is believed to be of fundamental importance in neointima formation following both acute and chronic vascular injury. Acute vascular insults may be iatrogenically produced by percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), while atherosclerotic plaque formation is considered a chronic process. Carvedilol has been shown to attenuate free radical-associated lipid peroxidation and inhibit vascular smooth muscle mitogenesis induced by various growth factors, the findings which are of interest because smooth muscle proliferation and abnormal lipid metabolism are suggested to play key roles in the pathogenesis of atherosclerotic plaque formation and the development of stenotic lesions following vascular injury incurred during PTCA and CABG. [40]

The precise mechanism underlying the inhibition of vascular smooth muscle cell migration and proliferation by carvedilol has not been elucidated. However, these effects are well documented in both in vitro and in vivo studies.

In vitro: Sung et al. [41] demonstrated that carvedilol is able to block mitogen-stimulated proliferation of cultured vascular smooth muscle cells in rats. Surprisingly, they report that carvedilol inhibits cell proliferation that is mediated by several pharmacologically unrelated mitogens such as thrombin, platelet-derived growth factor (PDGF), epidermal growth factor,
The underlying mechanism of remodeling attenuation by carvedilol in the setting of AMI is likely multifactorial. Conventional inhibition of progressive LV remodeling by carvedilol favorably alters left ventricle geometry. Infarction was noted along with a reduction in LV wall thickness in the non-infarcted segment, a decrease in total LV mass, and by decreasing LV size and wall motion abnormalities at the infarct site. Additionally, a decrease in wall thickening at the site of infarcted and non-infarcted segments of the myocardium. In particular, the ventricular remodeling response is affected by mechanical injury to the blood vessel wall initiates a series of events leading to vascular smooth muscle cell migration and proliferation, ultimately resulting in profound vascular stenosis secondary to neointima formation. Carvedilol administration reduced the neointimal growth following angioplasty by 84% without altering either medial or adventitial cross-sectional areas.

In a subgroup of patients with LVEF <45% after AMI, it was shown that carvedilol treatment attenuated the remodeling process between the placebo and carvedilol groups at 7 months. In the EUROCARE (European Carvedilol Atherectomy Restenosis) trial, a prospective, randomized, double-blind, placebo-controlled trial, carvedilol was evaluated for prevention of coronary restenosis. These findings were reiterated in a study by Sung et al. [42] investigated the biochemical mechanism of carvedilol's anti-proliferative effect on vascular smooth muscle cells. Their results showed significant concentration-dependent inhibition of mitogen-induced mitogen-activated protein kinase (MAPK) activity in rat smooth muscle cells. Carvedilol also demonstrated direct enzyme inhibition of purified MAPK from mitogen-stimulated cells and 50% inhibition of MAPK activity in cell-free assays. Cell flow cytometry studies revealed that quiescent rat smooth muscle cells had 96% of the population in the G0/G1 phase of the cell cycle. With the addition of serum, the number of cells in S and G2/M phases increased, a phenomenon that was noted to be significantly blunted by carvedilol. Lastly, serum-induced stimulation of the S phase-specific marker thymidine kinase was significantly inhibited in the presence of carvedilol. Based on these data, it was suggested that anti-mitogenic actions of carvedilol on vascular smooth muscle may be partly explained by inhibition of MAPK activity and regulation of cell cycle progression.

Although a mechanism of action is not yet firmly established, carvedilol may find utility in the treatment of disorders associated with pathologic vascular smooth muscle growth. Namely, it may be effective in preventing atherosclerosis and vascular changes that lead to stenosis following PTCA or CABG. Nonetheless, recent trials have not documented significant effects of carvedilol on stent restenosis in the clinical setting.

In a clinical trial comparing the effect of carvedilol sustained-release formulation with atenolol on coronary stent restenosis, there was no significant difference between the two groups in restenosis rate (17.1% vs 19.4%, p=0.732). In a recent clinical trial comparing the safety and effects of carvedilol-loaded BiodivYsio® (Biocompatibles Ltd., Farnham, UK) stents implanted into 20 patients with those of baremetal BiodivYsio® stents implanted into 21 patients for de novo coronary lesions, the degree of neointimal hyperplasia, as measured by intravascular ultrasound (IVUS) 6 months after the procedure, documented that although there was no significant difference (p > 0.05) between the carvedilol and bare-metal stent groups in terms of larger liminal area, smaller neointimal area, and reduced net decrease in luminal area, carvedilol-loaded stents tended to inhibit neointimal hyperplasia without the occurrence of cardiac death, myocardial infarction, or stent thrombosis at 2-year follow-up.

In the EUROCare (European Carvedilol Atherectomy Restenosis) trial, a prospective, randomized, double-blind, placebo-controlled trial, carvedilol was evaluated for prevention of coronary restenosis. In patients undergoing successful atherectomy, there were no differences in minimal luminal diameter (1.99 – 0.73mm vs 2.00 – 0.74 mm), angiographic restenosis rate (23.4% vs 23.9%), target lesion revascularization (16.2% vs 14.5%), or event-free survival (79.2% vs 79.7%) between the placebo and carvedilol groups at 7 months.

5. Ventricular Remodeling Post-AMI

Remodeling that occurs after AMI is characterized by deleterious alterations of LV size, shape, and thickness involving both infarcted and non-infarcted segments of the myocardium. In particular, the ventricular remodeling response is affected by infarct size, infarct healing, and loading characteristics such as LV distention pressure, inotropic state, heart rate, and neuroendocrine activation. Progressive changes of this nature are associated with worsening of LV function, which is the main determinant of poor prognosis after an MI. In a subgroup of patients with LVEF <45% after AMI, it was shown that carvedilol treatment attenuated the remodeling process by decreasing LV size and wall motion abnormalities at the infarct site. Additionally, a decrease in wall thickening at the site of infarction was noted along with a reduction in LV wall thickness in the non-infarcted segment, a decrease in total LV mass, and favorable alteration of left ventricle geometry. An echocardiographic sub-study of the CAPRICORN trial also demonstrated inhibition of progressive LV remodeling by carvedilol in patients with LV dysfunction after AMI.

The underlying mechanism of remodeling attenuation by carvedilol in the setting of AMI is likely multifactorial. Conventional β-
6. Carvedilol Treatment in Chronic Stable Angina

Carvedilol increases exercise capacity, reduces myocardial oxygen consumption, increases total exercise time and onset time of ST-segment depression in patients with chronic stable angina. [55] Wendt et al. [56,57] studied patients with angina pectoris and compared single oral doses of 50 mg of carvedilol with 40 mg of propranolol. Carvedilol was associated with a fall in vascular resistance at rest and little effect during exercise. With administration of propranolol, resistance increased at rest and remained elevated compared with control group measurements during exercise. Additionally, a fall in cardiac output at rest and with exercise was noted with propranolol, whereas carvedilol had minimal impact on cardiac output, both at rest and with exercise. [56] In a further study of patients with angina, carvedilol was found to improve ejection fraction at rest, but not during exercise, and to reduce systolic and diastolic volume. Exercise-induced ST-segment depression was also noted to improve significantly with carvedilol compared with placebo. These beneficial effects on LV function lead the authors to suggest possible advantages of carvedilol in long-term treatment of patients with chronic stable angina. [58]

6.1 Carvedilol and Exercise Tolerance

Kaski et al. [59] performed a single-blind study of carvedilol compared with placebo in 15 patients with chronic stable angina. They found that carvedilol increased the time to 1mm ST depression and increased total exercise time. The ST-segment changes at peak exercise were reduced and the rate pressure product also declined. In a double-blind study by Jamal et al., [60] a placebo, 25 mg, or 50 mg dose of carvedilol was administered in randomized fashion to 12 patients with stable effort angina. Two hours post-treatment, exercise time was found to increase by 24% and 35%, in active treatment recipients, respectively, and ST depression at both maximal and submaximal work levels was reduced. [60] Following a modified treatment regimen, Rodrigues et al. [61] administered oral carvedilol 25 mg twice daily for 2 weeks followed by 50 mg doses twice daily for another 2 weeks in a single-blind study of 20 patients with chronic stable angina. They found that exercise time was significantly increased from 7.4 – 0.5 minutes on placebo to 9.0 – 0.5 minutes after 25 mg twice daily and to 9.2 – 0.4 minutes after 50mg twice daily.

6.2 Ambulatory Monitoring of Silent Ischemia

Rodrigues et al. [61] also performed 24-hour monitoring of ST-segment changes. The total number of ST-segment depressions

Previous evidence has shown that several pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin (IL)-10, and IL-6 may be involved with the remodeling process. Conversely, the anti-inflammatory cytokine IL-10 has a neutralizing effect on pro-inflammatory cytokines. [47,48] Li et al. [49] evaluated the effects of carvedilol on myocardial cytokine expression and extracellular matrix remodeling in rats subjected to AMI. First, they found that carvedilol treatment was associated with a reduction in myocardial levels of proinflammatory cytokines and the fibrogenic cytokine transforming growth factor-β-1. Elevated LV diastolic pressure was also ameliorated with carvedilol. Second, they noted increased expression of anti-inflammatory cytokine IL-10. Last, a reduction in matrix metalloproteinase (MMP)-2 and MMP-9 activity as well as myocardial collagens was observed with treatment groups receiving carvedilol.

As far as comparing the efficacy of different β-blockers in preventing LV remodeling after AMI, Tang [54] reported an effective attenuation of LV remodeling by carvedilol and improvement of hemodynamics and LV function after AMI in rats. Metoprolol exhibited similar benefits regarding hemodynamics, LV dilatation and function, but not LV hypertrophy. Therefore, in instances where the use of β-blockers is indicated such as during the peri- and post-MI period, carvedilol may be superior to other medications in the same class.
was reduced by 57% on 25 mg twice daily of carvedilol and by 47% on 50 mg twice daily. Similarly, Kishida et al. studied the effect of 20 mg carvedilol daily in 13 Japanese patients. Their results showed a reduction in frequency of ST depression by over 50%, as well as a reduction in the total magnitude and duration of ST depression episodes.

7. Anti-arrhythmic Properties of Carvedilol

β-Blockers exert their anti-arrhythmic activity by a variety of pharmacologic and electrophysiologic properties. Diastolic depolarization of sinus and ectopic pacemaker activity is suppressed by β-blockade. Atio-ventricular and nodal conduction are also depressed by prolongation of the refractory period and slowing of conduction velocity. Certain β-blockers, such as carvedilol, also have membrane-stabilizing abilities. β-Blockers are generally effective in the treatment of sinus tachycardia, supraventricular premature depolarizations, paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation. Drugs in this class are also utilized to treat ventricular premature complexes and for prophylaxis of recurrent ventricular tachycardia secondary to sympathetic stimulation. Several experimental studies have shown that β-blockers possess both anti-arrhythmic and anti-fibrillatory properties in normal and ischemic myocardium. Carvedilol exerts a weak blockade of the slow-type calcium channel. As a class, calcium channel-blockers inhibit the inwardly directed Ca²⁺ current, delaying conduction through the atrial and atrioventricular nodes. The ability to depress this particular calcium-ion current is the basis for use of carvedilol in the management of supraventricular arrhythmias, ischemia and reperfusion-induced arrhythmias, the latter including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardias.

Arrhythmias precipitate unstable hemodynamics in addition to myocardial ischemia and decreased cardiac output. Atrial fibrillation is the most worrisome of all the supraventricular arrhythmias as it decreases cardiac output by 15–20%. Diastole is abridged due to the increase in heart rate, which subsequently leads to decreased coronary blood flow and myocardial ischemia secondary to myocardial oxygen consumption. The incidence of paroxysmal atrial fibrillation after CABG is reported to be 10–40%. Tsuboi et al. conducted a cohort study that compared a control group (n = 80) with a treatment group (n = 80) of patients given carvedilol to determine its effect on prevention of paroxysmal atrial fibrillation after CABG. The incidence of paroxysmal atrial fibrillation was 15% in the treatment group and significantly lower than that of the control group (34%, p = 0.0094). Further regression analysis revealed that only postoperative carvedilol administration was significantly associated with the development of atrial fibrillation (95% CI 0.169, 0.832; p = 0.0159). Therefore, they concluded that postoperative carvedilol treatment has a beneficial effect in prevention of paroxysmal atrial fibrillation after CABG. Although the prevention of postoperative atrial fibrillation is a class effect of β-blockers, carvedilol has been reported to be superior.

In a retrospective study of 115 patients who underwent cardiac surgery, the group that received carvedilol immediately after surgery demonstrated a marked reduction in postoperative atrial fibrillation (8% vs 32%, p < 0.05) compared with the metoprolol or atenolol groups.

In a randomized clinical trial of 110 patients investigating the efficacy of carvedilol compared with metoprolol succinate in preventing postoperative AF in the first 3 days after CABG, 20 patients (36%) in the metoprolol group and 9 patients (16%) in the carvedilol group developed AF (p = 0.029). Multiple stepwise logistic regression analysis showed that metoprolol use, older age, and impaired LVEF were independent risk factors for developing AF, whereas carvedilol use was found to be independently related to maintenance of sinus rhythm after CABG (p = 0.02). In another randomized clinical trial of 120 patients undergoing CABG, carvedilol was compared with metoprolol in the occurrence of the new-onset AF during the first 5 days after on-pump CABG. Postoperative AF occurred in 24% of the study group (29 of 120 patients), with a significantly lower incidence of postoperative AF in the carvedilol group (15.0%, 9 of 60) versus the metoprolol group (33%, 20 of 60) [p = 0.022].

Atrial and ventricular arrhythmias are also commonly seen post-AMI. In the aforementioned CAPRICORN trial, the antiarrhythmic potential of carvedilol was observed. Specifically, post hoc analyses of arrhythmic events from trial data showed that carvedilol had a beneficial effect on arrhythmias when taken with an ACE inhibitor. First, the results demonstrated that carvedilol significantly reduced supraventricular arrhythmias (52%; p = 0.0015) and atrial flutter or fibrillation (59%; p = 0.0003). Second, carvedilol significantly reduced ‘any ventricular arrhythmia’ by 63% (p < 0.0001) and ‘malignant ventricular arrhythmias’ by 70% (p < 0.0001). Last, treatment with carvedilol lead to a decrease in time to first occurrence of atrial flutter or fibrillation (59%; p = 0.0003) and first malignant ventricular arrhythmia (76%; p < 0.0001).

In a 6-month, randomized, placebo-controlled study of 168 patients with heart failure due to ischemic etiology or idiopathic dilated cardiomyopathy, carvedilol administered at 12.5–50.0 mg twice daily led to reduced ventricular arrhythmia activity and improved ventricular function. Carvedilol was noted to increase LVEF as well as to reduce total premature ventricular contractions (PVCs)/hour, repetitive PVCs/hour, and non-sustained ventricular tachycardia (p < 0.05). Interestingly, the anti-arrhythmic efficacy of carvedilol was significantly greater in patients with ischemic heart failure by the end of the first month. The effect of carvedilol on arrhythmias was also studied in 71 patients with a variety of cardiac disease syndromes, where 24-
hour Holter monitoring was performed before and after 4–8 weeks of active carvedilol therapy. Median PVCs per 24 hours decreased from 25.5 to 6.0 (p < 0.001), 77% of patients showed a reduction in PVCs. Non-sustained ventricular tachycardia, which was present in four patients prior to treatment, was abolished in all patients. An improvement based on Lown's classification occurred in 50% of patients, an observation that was increased to 73% of patients in the congestive heart failure (CHF) group. [71]

8. Conclusion

Although many β-blockers are recognized to have cardioprotective properties and their use in AMI and CHF has become mainstream, the ability of β-blockers to protect the myocardium varies significantly. Carvedilol is unique among other drugs in the same class for several reasons. Aside from its anti-ischemic properties of decreasing heart rate and myocardial contractility, thus improving exercise tolerance, carvedilol also possesses the following additional beneficial properties: antioxidant effects; neutrophil infiltration inhibition; apoptosis inhibition; reduction in vascular smooth muscle migration; improvement in myocardial remodeling post-AMI; and well established vasodilatory α1-adrenergic receptor blockade effects. These properties have been demonstrated in both animal models and clinical trials, with subsequent decreased morbidity and mortality in CHF as well as post-AMI patients. Combined, these findings warrant further consideration of carvedilol as the preferred β-blocker in this patient population.

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