Acute Heart Failure – Basic Pathomechanism and New Drug Targets

Heinz Rupp, Thomas P. Rupp, Peter Alter, Bernhard Maisch[1]

[1]Department of Internal Medicine and Cardiology, Philipps University of Marburg, Germany.

Abstract

In view of the high incidence of heart failure and sudden cardiac death, efforts in the development of compounds which target-specific mechanisms such as a reduced expression of SERCA2, the Ca^{2+} pump of sarcoplasmic reticulum, of hypertrophied cardiomyocytes of pressure-overloaded or infarcted hearts should be strengthened. Lead compounds for correcting a dysregulated gene expression are the carnitine palmitoyltransferase-1 (CPT-1) inhibitors etomoxir and oxfenicine. Since bypassing the CPT-1 inhibition by a medium-chain fatty acid diet had a lesser effect on myosin V1 proportion than on lipid droplet number, one has to infer also other mechanisms such as PPARα activation (FOXIB/PPARα). In view of the intricate interrelationship between depressed pump function and malignant arrhythmias, stimulation of endogenous antiarrhythmogenic mechanisms linked to an enhanced production of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) could potentially provide alternatives to the administration of 1 g EPA and DHA ethyl esters (minimum 84% EPA + DHA) for secondary prevention of myocardial infarction. The apparently greater efficacy of ω-3 fatty acids in post-myocardial infarction patients (GISSI-Prevention study) compared with ICD patients (SOFA study) can be attributed to the greater ischemia-induced release of membrane-bound EPA and DHA and a better compliance (one vs. four capsules daily).

Akute Herzinsuffizienz – Pathomechanismen und neue therapeutische Ansätze

Zusammenfassung

Im Hinblick auf die zunehmende Inzidenz der akuten und chronischen Herzinsuffizienz verdienen Ansätze zur Behandlung pathogenetisch und pathophysiologisch relevanter Defekte von Kardiozyten bei hypertensiver Herzkrankheit und Myokardinfarkt, wie eine nicht ausreichende Expression der Ca^{2+}-Pumpe des sarkoplasmatischen Retikulums (SERCA2a), besondere Aufmerksamkeit. Leitsubstanzen zur Korrektur einer dysregulierten Genexpression des Kardio-zyten sind die Carnitinpalmitoyltransferase-1-(CPT-1-)Hemmer Etomoxir und Oxfenicin. Da eine Umgehung des CPT-1-Blocks durch diätetische Verabreichung mittelkettiger Fettsäuren eine geringere Wirkung auf das erhöhte Myosin V1 als auf die Zahl der Lipidtröpfchen hatte, müssen noch andere Mechanismen, wie eine PPARα-Aktivierung (FOXIB/PPARα), beteiligt sein. In Anbetracht der engen Beziehungen zwischen Pumpversagen und malignen Arrhythmien könnte auch die Stimulierung endogener antiarrhythmogener Mechanismen von Eicosapentaensäure (EPA) und Docosahexaensäure (DHA) möglicherweise eine Alternative zur Verabreichung von 1 g EPA + DHA-Ethylestern (mindestens 84% EPA + DHA) zur Sekundärprävention des Myokardinfarkts sein. Die beobachtete größere Wirksamkeit von EPA und DHA bei Postinfarktpatienten (GISSI-Prevention-Studie) im Vergleich zu ICD-Patienten (SOFA-Studie) kann auf eine ischämiebedingte verstärkte EPA- und DHA-Freisetzung und eine bessere Patientencompliance (eine vs. vier Kapseln täglich) zurückgeführt werden.

Introduction

An epidemic increase in heart failure mortality, hospitalization, and prevalence rates has been observed among older persons in recent years [4]. Despite progress in the treatment of various cardiovascular risks such as hypertension, insulin resistance and dyslipidemia, therapy of the failing heart has not been advanced greatly. This is exemplified by COMET (Carvedilol Or Metoprolol European Trial) in patients with functional class II–IV heart failure and an ejection fraction < 35%, where the 5-year mortality rates were 34–40% [34]. Although acute heart failure is a syndrome, which can represent the acute and the terminal stage of various unrelated etiologies, there is increasing evidence that it is associated with specific defects which are potential drug targets. Mechanisms are, therefore, examined which render the heart prone to acute failure and fibrillation. The focus in this contribution is placed on the failing hypertrophied heart and promising drug interventions are explored.

Increased Afterload

A major cause for the steadily increasing incidence of heart failure is the inadequately treated hypertension. It not only increases the afterload of the heart, but in its advanced stage, i.e., systolic hypertension, also markedly impairs coronary perfusion. While during hypertension an adverse vascular remodeling affects arterioles and conduit arteries, functional consequences are observed first in an increased peripheral resistance of the arterioles. A greater stiffness of the aorta and large arteries leading to a reduced diastolic blood pressure and further increased systolic blood pressure becomes manifest only at a later stage. A low diastolic blood pressure further reduces the already impaired coronary perfusion in hypertensive heart disease. A total of 39% of all patients and 67% of patients aged ≥ 60 years attending primary care practices in Germany were diagnosed hypertensive [44]. Treatment and control rate (blood pressure < 140/90 mmHg) were 64% and 19%, respectively. In 60- to 74-year-old patients, the target systolic blood pressure < 140 mmHg was achieved in only 23%. Diastolic pressure < 90 mmHg was achieved in 47%, which should, however, not be interpreted as a better blood pressure control but rather indicates the occurrence of systolic hypertension in elderly. The incidence of isolated systolic hypertension (> 160 mmHg systolic, < 90 mmHg diastolic) was 17% in patients aged ≥ 65 years [48]. Pulse pressure (target < 50 mmHg) is, therefore, more appropriate for monitoring the cardiac risk during antihypertensive treatment. One should also take into account that overweight subjects have an increased risk of hypertension and exhibit a raised sympathetic outflow of the brain [19]. Since the sympathetic nervous system activity is the major determinant of renin release, an overweight-associated rise in sympathetic activity also affects the activity of the renin-angiotensin II-aldosterone system (RAAS). During progression of heart failure, depression of pump function further enhances sympathetic activity.

Dysregulated Gene Expression of Hypertrophied Cardiomyocytes

In approximately 90% of patients with heart failure, hypertension and cardiac hypertrophy are present [29]. Hypertrophy of cardiomyocytes also occurs in the surviving myocardium after myocardial infarction. Although hypertrophy is required for coping with an increased afterload, various defects in gene expression occur which result in a depressed pump function [36]. DNA chip studies on rats after myocardial infarction showed that the previously identified changes in myosin isoenzymes and the Ca^{2+} pump (SERCA2) of the sarcoplasmic reticulum (SR) are markers of a large group of genes expressed in an apparently coordinated manner. Also the so-called fetal gene expression, which was initially characterized on the basis of a reduced α-myosin heavy chain expression, was observed [45]. Modifications in gene expression were, however, more extensive and the concept of a fetal phenotype covers, therefore, only one aspect. More than 200 out of approximately 4,000 genes studied were altered in the hypertrophied ischemic ventricle after myocardial infarction [45]. A repression of genes which are responsible for the oxidation of fatty acids was particularly pronounced. This coordinated repression of enzymes involved in β-oxidation indicates a reduced fatty acid oxidation. As a consequence, glucose utilization is expected to be increased [5, 9, 15, 47]. The expression of genes involved in fatty acid oxidation is modulated by the transcription factor PPARα (peroxisome proliferator-activated receptor-alpha). Since PPARα was found to be reduced as a consequence of pressure overload [42], the switch in fuel metabolism has been attributed to a reduced influence of PPARα [3]. One of the consequences of the fetal phenotype including an inadequately increased SERCA2 expression in hypertrophied cardiomyocytes is that they rely more on the sarcolemmal Na^+-Ca^{2+} exchanger resulting in a long-term loss of intracellular Ca^{2+} which would be associated with a depressed force development.

Extracellular Matrix Remodeling and Dilatation

Hypertensive heart disease is characterized by a markedly increased collagen volume fraction or fibrosis which cannot be prevented by current antihypertensive therapy [6]. Well-characterized factors stimulating collagen synthesis are angiotensin II, aldosterone, and endothelin. Angiotensin II is increased not only by the angiotensin-converting enzyme but also by local proteases such as chymase and cathepsins. The angiotensin II production was increased in the atherosclerotic aorta and correlated with plasma cholesterol [21]. Fibrosis not only impairs relaxation of the myocardium but has also an adverse influence on the conduction system and coronary perfusion. Although during progression of heart failure, the neuroendocrine influence is enhanced favoring collagen deposition, chamber dilatation often occurs.

A major factor predisposing the heart to acute failure is dilatation of hypertrophied ventricles leading to an increased wall stress. Dilatation requires degradation of the collagen network involving activation of matrix metalloproteinases (MMPs). Cardiac mast cells have been implicated in the activation of MMPs which results in fibrillar collagen degradation
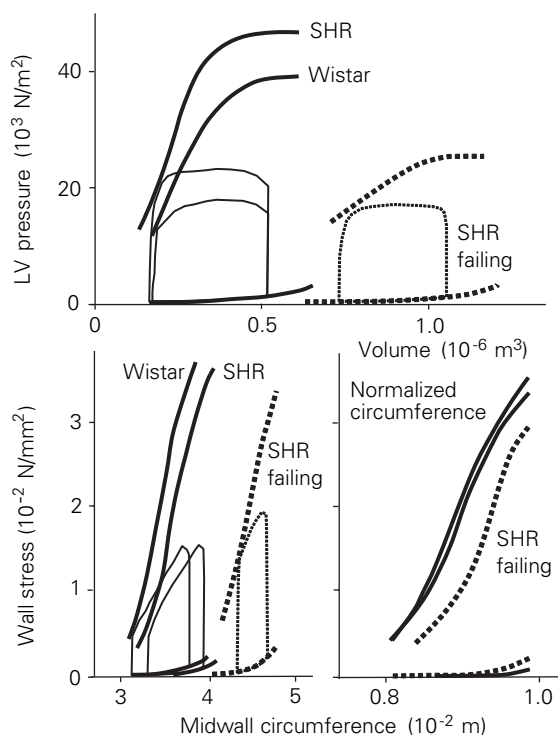
Figure 1. Transition from "compensated" concentric to dilated left ventricular hypertrophy in spontaneously hypertensive rats (SHR). Data adapted from Vogt et al. [53].

Abbildung 1. Übergang von „kompensierter" konzentrischer zu dilatativer linksventrikulärer Hypertrophie bei spontan hypertensiven Ratten (SHR). Daten aus Vogt et al. [53].

Figure 2. Hemodynamic performance of normal and dilated (idiopathic cardiomyopathy) human left ventricle. Data adapted from Jacob et al. [22].

Abbildung 2. Hämodynamik des normalen und dilatierten (idiopathische Kardiomyopathie) menschlichen linken Ventrikels. Daten aus Jacob et al. [22].

[23]. Mast cells are known to store and release a variety of biologically active mediators including tumor necrosis factor-(TNF-)α and proteases such as tryptase and chymase which can activate MMPs. Dilatation appears to occur subsequent to a dysregulated gene expression of cardiomyocytes. This sequence can be deduced from the transition from concentric to dilated hypertrophy of overloaded hearts (Figure 1). However, even in the phase of concentric hypertrophy which has often been referred to as "compensated" hypertrophy, functional deficits are present. Thus, although the working capacity of the whole hypertrophied left ventricle is increased, the actively developed wall stress, which takes the increased ventricular mass into account, is significantly depressed when determined in the isovolumetrically beating left ventricle [49]. This phenomenon is observed in rats with pressure- and volume-overloaded hearts where dilatation occurs subsequent to a prolonged sustained overload. In dilated ventricles, the actively developed wall stress is increased, which arises, however, not from an increased myocardial performance but from the dilatation. When ventricular circumference is normalized to unit circumference, the developed wall
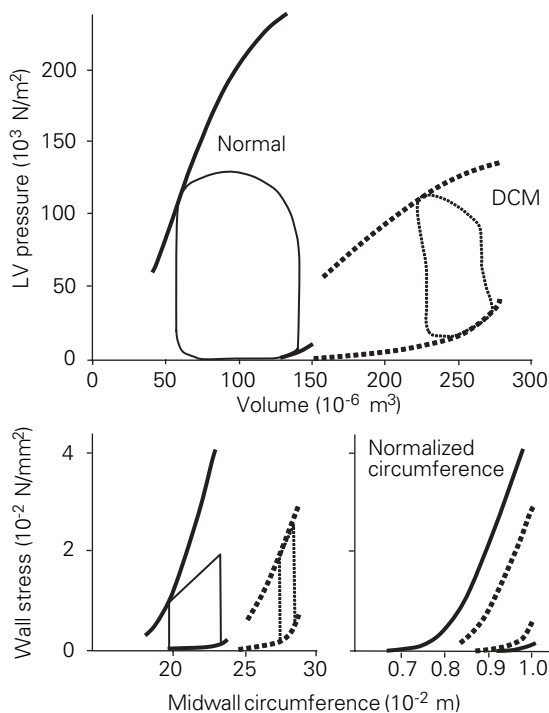
stress becomes reduced, again demonstrating functional defects. It is examined by magnetic resonance imaging to what extent this type of analysis (Figure 2) can provide new diagnostic criteria for assessing the progression of heart failure in patients [1].

Electrical Conduction and Arrhythmias

In NYHA functional class II and III failure, sudden cardiac death remains the major cause of death. Only in functional class IV, pump failure predominates. While sudden cardiac death has often been attributed to ischemic events, there is increasing evidence that cardiac hypertrophy itself has various adverse effects. In the UK-HEART study in patients with mild to moderate chronic heart failure, a predictor of sudden death was a greater cardiothoracic ratio in addition to greater QRS dispersion, greater QT dispersion and the presence of nonsustained ventricular tachycardia [24]. While ischemia can contribute to the risk in patients with left ventricular hypertrophy and depressed pump function, specific alterations can be identified which provide potential drug targets. During progression of heart failure, an increased wall stress is associ-

ated with stretch of cardiomyocytes, which results in opening of nonselective cation channels and influx of Ca^{2+}. While this mechanism is well documented for an ischemic border zone after myocardial infarction, it is also a likely factor in cardiac hypertrophy contributing to the high risk of sudden cardiac death. Also the re-expression of genes of the fetal phenotype in the overloaded heart could represent a factor predisposing the heart to arrhythmias. Of particular interest is that the occurrence, density and conductance of the atrial pacemaker current I_f are increased in the hypertrophied ventricle. Also the expression of hyperpolarization-activated, cyclic nucleotide-gated cation channels (HCN2 and HCN4) was increased [16]. This proarrhythmogenic influence could be enhanced by focal or diffuse fibrosis characteristic of hypertensive heart disease. On this basis, sustained malignant arrhythmias could be triggered by an increased wall stress or transient ischemia. Progress in the identification of such specific mechanisms is related to the accurate determination of wall stress in a clinical setting and the prospective evaluation of its role in malignant arrhythmias. In particular, the factors contributing to a reduced ejection fraction which represents an important predictor of sudden cardiac death [20], remain to be examined.

Drug Approaches for Improving the Function of Hypertrophied Cardiomyocytes

Lead compounds for interfering with the fetal gene expression of overloaded cardiomyocytes are inhibitors of mitochondrial carnitine palmitoyltransferase-1 (CPT-1) which also exhibit PPARα activation (*f*atty acid *ox*idation *inhib*itors, FOXIB/PPARα) [37]. Currently best studied is etomoxir which reduced the expression of the fetal phenotype [41, 52], increased pump function of hypertrophied hearts [49] and attenuated left ventricular dilatation [50]. It is important that the CPT-1 inhibitor oxfenicine improved pump function also in pacing-induced heart failure in dogs [30]. In this model of ischemic heart failure, it might be assumed that CPT-1 inhibition promotes a latent energy starvation due to the reduced fatty acid oxidation which was, however, not observed. It appears that normalization of various genes including MMP-2 and MMP-9 activity was responsible for the improved function [30]. The question remains whether the functional improvements are solely due to CPT-1 inhibition or additional influences most probably related to PPARα activation [54]. Oxirane compounds such as methylpalmoxirate can bind and activate PPARα and would contribute to the action of raised cytoplasmic fatty acids which are endogenous PPARα agonists.

To examine putative influences beyond CPT-1 inhibition, etomoxir-treated rats were fed a diet containing the medium-chain fatty acids nonanoate and decanoate. Medium-chain fatty acids do not require CPT-1 for their entry into mitochondria. Thus, a medium-chain fatty acid diet is expected to result in an unaltered fatty acid oxidation although CPT-1 is inhibited by etomoxir. In rats treated with etomoxir and fed a regular long-chain fatty acid diet, the lipid droplet number was moderately increased which was greatly prevented by exchanging the dietary long-chain fatty acids for medium-chain fatty acids [38] (Figure 3). Lipid droplet number was not significantly increased in the medium-chain fatty acid-fed rats corresponding to 28.6% of the increase observed in etomoxir-treated rats fed a regular diet. The etomoxir treatment resulted in a harmonious ventricular growth (+21% left ventricle, +17% right ventricle) which, based on the observed phenotype, resembles that of exercised hearts. It has, therefore, been referred to also as "physiological" hypertrophy. The increase in left ventricular weight was reduced by the medium-chain fatty acid diet similarly to the lipid droplet number. Also the etomoxir-induced decrease in serum triglycerides was prevented by the medium-chain fatty acid diet. By contrast, the etomoxir-induced increase in myosin V1 was prevented to a lesser extent than lipid droplet number and growth parameters suggesting that on top of CPT-1 inhibition additional influences occur. The myosin V1 proportion was 64% of the increase seen in etomoxir-treated rats fed the regular diet. Etomoxir increased the number of active E~P Ca^{2+} pumps of SR which was prevented to a similar extent as the lipid droplet number. The SR phospholamban content was not affected by etomoxir. SR Ca^{2+} uptake of ventricular homogenates was increased in etomoxir-treated rats irrespective of the presence of the SR Ca^{2+} release inhibitor ruthenium red or the catalytic subunit of protein kinase A which phosphorylates phospholamban. The medium-chain fatty acid diet resulted in SR Ca^{2+} uptake rates that were in between those of etomoxir-treated and untreated rats. Since etomoxir increased SR Ca^{2+} pumps but not phospholamban, Ca^{2+} pumps can be inferred which are not inhibited by dephosphorylated phospholamban thereby leading to a higher overall SR Ca^{2+} uptake rate. It remains nonetheless noteworthy that a medium-chain fatty acid diet had a smaller effect on the SR Ca^{2+} uptake rate when compared with the SR active E~P Ca^{2+} pumps.

CPT-1 Inhibition in Patients with Heart Failure

In the first clinical etomoxir trial in patients with functional class II–III failure, patients with impaired heart performance but without diabetes mellitus type

2 exhibited an improved cardiac function [43]. A dose of 80 mg daily was given to ten patients (one with ischemic heart disease and nine with dilated cardiomyopathy) for 12 weeks on top of standard therapy. All patients improved clinically and no patient had to stop taking etomoxir. Maximum cardiac output during exercise increased after treatment. This increase was mainly due to a higher stroke volume. Resting heart rate was slightly reduced. For any given heart rate, stroke volume was significantly enhanced during exercise. The left ventricular ejection fraction also increased significantly. Mean pulmonary pressure and pulmonary capillary wedge pressure were significantly reduced. Based on echocardiographic data, it was concluded that the etomoxir treatment had no influence on left ventricular muscle mass. In acute studies, etomoxir showed neither a positive inotropic effect nor vasodilatory properties [43]. Thus, although the results of this pilot study were not placebo-controlled, all patients seem to have benefited and no significant side effects were observed. The follow-up multicenter trial ERGO-1 including more than 380 patients with NYHA functional class II–III with no metabolic or other severe diseases was, however, terminated prematurely (*http://www.medigene.com/englisch/pressemitteilungen.php?ID=1293*). Side effects had occurred in a small number of patients. It was, however, stated that etomoxir may be efficacious at a lower dosage than that administered so far (40 or 80 mg/day).

In this respect it should be mentioned that in animal experiments, a high dosage of etomoxir can cause lipid accumulation in the liver [46]. 125 mg/kg/day (+)-etomoxir was administered, which, however, is much higher than the dose (15 mg/kg/day racemic etomoxir) used for increasing SR Ca^{2+} transport [38]. Lipid accumulation might be inferred from a marked CPT-1 inhibition alone, which should, however, be counteracted by the hypolipidemic action described for etomoxir which arises from a reduced de novo fatty acid synthesis due to acetyl-CoA carboxylase inhibition.

Our experimental studies provide clear evidence in favor of the principal possibility of dissociating unwanted effects of CPT-1 inhibition such as cardiac growth and desired alterations in cardiac phenotype. A low etomoxir dosage also had a specific effect in pressure-overloaded hearts which was not associated with significant left ventricular hypertrophy [49]. One should nonetheless take into account that etomoxir is also expected to accumulate in slow/poor metabolizers [13]. As in the case of perhexiline which also exhibits CPT-1 inhibition, the dosage should be adjusted according to plasma level in any upcoming trial with FOXIBs which have the inherent risk of lipotoxicity. Using this precau-
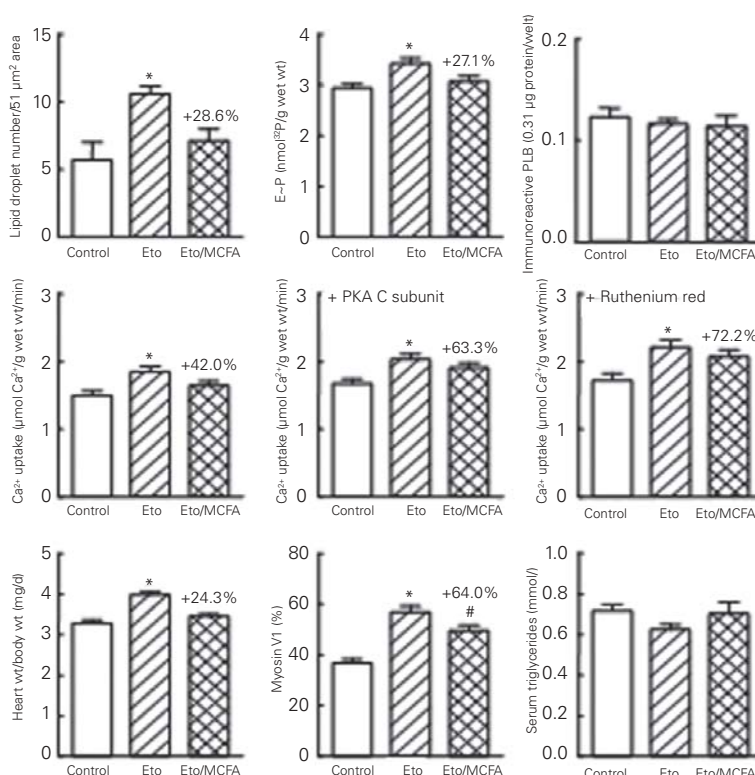

Figure 3. Comparative analysis of the effect of a medium-chain fatty acid diet on etomoxir-induced changes in left ventricular lipid droplet number, phosphorylated intermediate E~P of the SR Ca^{2+}-ATPase, immunoreactive SR phospholamban content, oxalate-supported SR Ca^{2+} uptake rate measured also in the presence of C-subunit of protein kinase A or ruthenium red, the heart-to-body weight ratio, myosin V1 proportion and serum triglycerides. The percentage values given on the bars of the etomoxir-treated WKY rats fed a medium-chain fatty acid diet refer to the increase seen in etomoxir-treated rats fed a long-chain fatty acid regular diet. Eto: etomoxir-treated rats fed a long-chain fatty acid regular diet; Eto/MCFA: etomoxir-treated rats fed a medium-chain fatty acid diet (50–65% C9:0, 30–40% C10:0). Data adapted from Rupp et al. [38].

Abbildung 3. Vergleichende Analyse der Auswirkungen einer mittelkettigen Fettsäurendiät auf etomoxirverursachte Änderungen in der linksventrikulären Lipidtröpfchenzahl, des phosphorylierten E~P der SR-Ca^{2+}-ATPase, des immunreaktiven Phospholambangehalts, des oxalatstimulierten SR-Ca^{2+}-Transports, gemessen in Anwesenheit der C-Untereinheit der Proteinkinase A oder von Rutheniumrot, des Herz/Körpergewicht-Quotienten, des Anteils an Myosin V1 und der Serumtriglyzeride. Die Prozentwerte auf den Säulen der etomoxirbehandelten WKY-Ratten beziehen sich auf die Zunahme bei etomoxirbehandelten Ratten mit einer regulären langkettigen Fettsäurendiät. Eto: etomoxirbehandelte Ratten mit einer langkettigen Fettsäurendiät; Eto/MCFA: etomoxirbehandelte Ratten mit einer mittelkettigen Fettsäurendiät (50–65% C9:0, 30–40% C10:0). Daten aus Rupp et al. [38].

tion, perhexiline that augments glucose metabolism by blocking muscle mitochondrial free fatty acid uptake improved the VO$_{2max}$, ejection fraction, symptoms, resting and peak stress myocardial function, and skeletal muscle energetics in heart failure patients [28].

Endogenous Antiarrhythmogenic Mechanisms

While all drugs which improve pump function are expected to reduce the risk of sudden cardiac death, β-blockers have additional specific effects. Besides a reduced cardiac oxygen consumption and metabolism, the effects of raised intracellular cyclic adenosine monophosphate (cAMP) on various phosphorylation sites and channels are attenuated [14]. Also for aldosterone antagonists which reduce mortality and sudden cardiac death risk in NYHA III and IV patients (RALES study) and in post-myocardial infarction patients with an ejection fraction ≤ 35% (EPHESUS study), specific mechanisms should be considered. Since aldosterone stimulates collagen synthesis comparably to angiotensin II (unpublished), aldosterone antagonists can counteract fibrosis which is a substrate for malignant arrhythmias. Proarrhythmic and negative inotropic effects of class Ia and Ic antiarrhythmics are more pronounced during progression of heart failure. The class III antiarrhythmic D-sotalol, which lacks β-blocking action, even increased mortality in post-myocardial infarction patients with reduced pump function [12]. For amiodarone, no significant mortality reduction was observed in chronic heart failure or after myocardial infarction and hence, on prognostic terms, it represents no alternative to an implantable cardioverter defibrillator (ICD).

We addressed, therefore, the hypothesis that the body has endogenous antiarrhythmogenic mechanisms which could be enhanced by drug interventions. Of particular importance is the role of the long-chain ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They are produced in the body from α-linolenic acid which is present to a variable extent in dietary plant oils and has also been shown to increase prostacyclin production [39]. In humans with a background diet high in saturated fat, the conversion rate of α-linolenic acid was found to be 6% for EPA and 3.8% for DHA [17]. However, with a diet rich in ω-6 polyunsaturated fatty acids, conversion was reduced by 40–50% [17]. Of particular relevance is that in women of reproductive age, an increased conversion of α-linolenic acid into EPA (21%) and DHA (9%) was found [2, 8] In ongoing studies we examine, therefore, mechanisms which can upregulate the endogenous EPA and DHA production. While the proportion of arachidonic acid can be increased in the rat with a PPARα agonist by increasing most probably the expression of δ-5 desaturase and δ-6 desaturase, no parallel increase in EPA and DHA was observed (unpublished). One has to conclude that α-linolenic acid cannot be converted into amounts corresponding to a daily intake of 1 g EPA + DHA used in the GISSI-Prevention study [18, 31, 32] and specified in the guidelines of the European Society of Cardiology for ST elevation myocardial infarction (level of evidence Ib) [51] as well as in a statement of the American Heart Association for patients with documented coronary heart disease [25].

Dietary EPA and DHA Intake

The notion prevails that variations in blood EPA and DHA level and the associated risk of sudden cardiac death arise primarily from fish intake. To assess the amount of EPA and DHA derived from fish, we determined fatty acids in fish dishes prepared at the University Hospital Marburg [40] and samples of frozen fish. The EPA and DHA content of 100 g fish was variable and was low when compared with the daily dosage of 1 g for which a 45% risk reduction in sudden death in post-myocardial infarction patients was observed [18]. Therefore, results of food questionnaire-based studies referring to fish intake should be interpreted in terms of EPA and DHA only if supported by differences in measured blood EPA and DHA levels. It appears unlikely that all confounding variables of a lifestyle with no or high fish consumption can be identified in a multivariate analysis. It is also considered important to include blood EPA and DHA levels in subanalyses particularly in fish oil studies where more than one daily capsule had to be taken.

Release of Membrane-Bound EPA and DHA in Myocardial Infarction Versus ICD Shock

Since the antiarrhythmogenic action of EPA and DHA involves inhibition of Na^+ and Ca^{2+} channels by the respective free fatty acids [27] and inhibition of the Na^+ channel current was not observed when EPA and DHA were covalently bound to the membrane, mechanisms are required which raise the free EPA and DHA concentration to a level which has antiarrhythmogenic effects (Figure 4). Ischemia is known to raise free fatty acids in the serum and the heart. If EPA and DHA are present in membranes, sympathetic activation results in activation of phospholipase A_2 which releases free fatty acids from the inner sn-2 position of membrane phospholipids where polyunsaturated fatty acids are predominantly incorporated. The observed overproportionate increase of free EPA and DHA in the ischemic heart [33] contributes to the critical free EPA and DHA concentration required for antiarrhythmogenic effects. It can thus be predicted that protective effects are smaller in patients with an ICD. In contrast to ischemic events arising from myocardial infarction which raise free EPA and DHA to levels required for their antiar-

rhythmogenic action, the ICD is expected to terminate reentrant ventricular tachycardias or ventricular fibrillation before marked sympathetic activation and adequate release of EPA and DHA occur.

In the trial by Raitt et al. [35], 1.8 g/day EPA and DHA ethyl esters did not reduce the risk of ventricular tachycardia or ventricular fibrillation in 100 patients with ICDs when compared with 100 patients on placebo (olive oil). In the SOFA trial (Study on Omega-3 Fatty Acids and Ventricular Arrhythmia) by Brouwer et al. [7], a total of 546 ICD patients were enrolled for assessing the effect of 2 g of purified fish oil (four capsules/day) versus placebo (olive oil) on life-threatening arrhythmias. Judged by capsule count, 76% of patients took more than 80% of the fish oil capsules. The primary endpoint (appropriate ICD intervention for ventricular tachycardia or fibrillation or all-cause death) occurred in 30% of patients taking fish oil versus 33% patients taking placebo (olive oil). In subgroup analyses, the hazard ratio was 0.91 (not significant [NS]) for fish oil versus placebo in patients who had experienced ventricular tachycardia in the year before the study, and 0.76 (NS) for patients with prior myocardial infarctions. Although the study might be underpowered for the subgroup analysis (167 in fish oil group vs. 175 in placebo group with prior myocardial infarction), the trend would be in accordance with the GISSI-Prevention study [18] which included, however, 2,835 post-myocardial infarction patients in the EPA and DHA ethyl ester (84% EPA + DHA, one capsule/day) group. Since the compliance especially with natural non-transesterified fish oil capsules is expected to be particularly compromised, blood EPA and DHA concentration before and after the trial should be reported for all patients and included in the analysis. In the study by Leaf et al. [26], 402 ICD patients were randomized to 2.6 g EPA and DHA ethyl ester or olive oil for 12 months. Compliance with the double-blind treatment was similar in the two groups; however, the noncompliance rate was high (35% of all enrollees). This might not be surprising since four 1-g capsules had to be taken daily. The primary endpoint, time to first ICD event (ventricular tachycardia or fibrillation) or death from any cause, was borderline significant (risk reduction of 28%; p = 0.057). For patients who stayed on protocol for at least 11 months, the antiarrhythmic benefit of EPA and DHA ethyl esters was improved for those with confirmed events (risk reduction of 38%; p = 0.034). The reason why in this study capsules with only 65% EPA and DHA instead of 84% as in the case of Omacor and the GISSI-Prevention study were used, remains intriguing. The study again strengthens the fact that patient compliance is greatly reduced with daily four 1-g capsules in addition to standard medication. Also
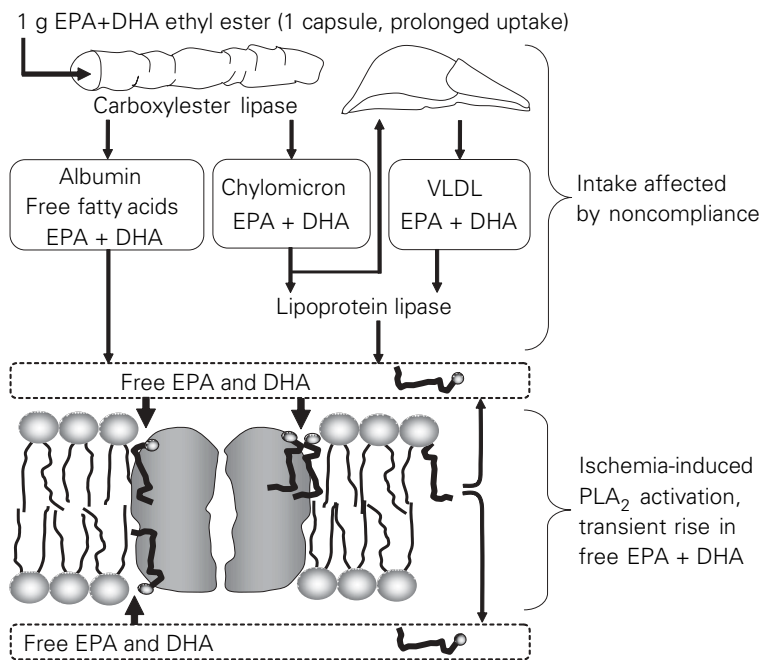

Figure 4. Schematic presentation of mechanisms raising EPA and DHA as free fatty acids to a critical concentration required for antiarrhythmogenic effects. In post-myocardial infarction patients, the ischemia-induced release of EPA and DHA from membranes by phospholipase A_2 (PLA_2) contributes to a greater extent to this free EPA and DHA level than in patients with an ICD. The contribution of EPA and DHA intake versus ischemia-induced release depends on the compliance of capsule intake and the degree of ischemia and remains to be addressed in detail. The impact of noncompliance in taking EPA and DHA supplements is, therefore, expected to be greater in ICD patients.

Abbildung 4. Schematische Darstellung der Mechanismen, die EPA und DHA als freie Fettsäuren bis zum Erreichen einer für antiarrhythmogene Wirkungen erforderlichen Konzentration anheben. Bei Postinfarktpatienten führt die ischämie-induzierte Freisetzung durch die Phospholipase A_2 (PLA_2) zu einem höheren EPA + DHA-Spiegel als bei ICD-Patienten. Der Beitrag der EPA- und DHA-Aufnahme hängt von der Patientencompliance und dem Ausmaß einer Ischämie ab und bedarf weiterer Untersuchungen. Die Auswirkungen einer Non-Compliance sind daher bei ICD-Patienten sehr wahrscheinlich größer als bei Postinfarktpatienten.

in this study, it would be very informative to include the EPA and DHA levels of individual patients in the analysis. Although an intention-to-treat analysis is preferable for eliminating any bias, it is less useful when the noncompliance rate is high. While noncompliance was also present in the GISSI-Prevention study with a PROBE design, only one 1-g capsule had to be taken on top of the recommended four tablets of standard therapy. During any ischemic events in patients with myocardial infarction, EPA and DHA are expected to be released from membranes which contributes to the level required for antiarrhythmogenic effects. Since an increased EPA and DHA serum level is maintained only for a few days in the case of noncompliance and takes approximately 10 days of intake for again reaching the EPA and DHA plateau value (unpublished), any antiarrhythmogenic
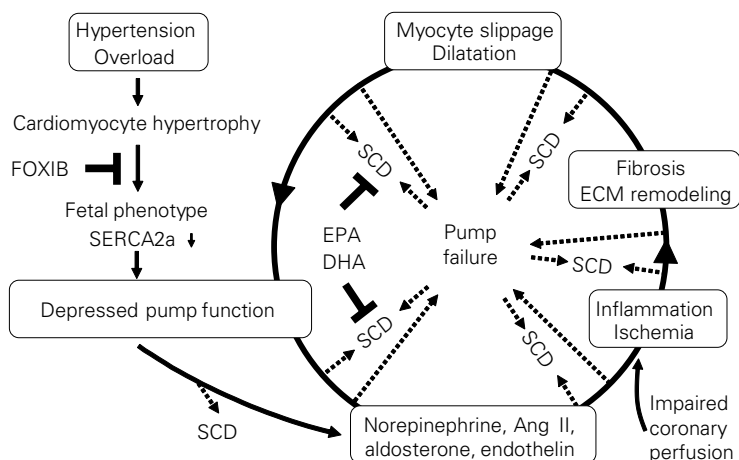
Figure 5. Schematic presentation of pathophysiological events linking hypertension with pump failure and sudden cardiac death (SCD) during progression of heart failure. Ang II: angiotensin II.

Abbildung 5. Schematische Darstellung der pathophysiologischen Vorgänge, die während der Progression der Herzinsuffizienz von Bluthochdruck zu Pumpversagen und plötzlichem Herztod (SCD) führen. Ang II: Angiotensin II.

action had to arise from the release of EPA and DHA from membrane stores. This could explain why noncompliance in a study with myocardial infarction patients would have a lesser impact on the endpoint than in ICD patients. The known low compliance with multiple capsule intake (e.g., 32% permanent noncompliance for β-blocker use in COMET [34]) was also one of the reasons for the production of ethyl esters using transesterification of fish oil triglycerides resulting in a highly concentrated preparation. Compared with fish triglycerides, the ethyl esters also exhibit a prolonged uptake rate [40].

Conclusion

Although major pathophysiological events contributing to pump failure and sudden cardiac death of the overloaded heart are well understood, it remains a challenge to develop novel strategies for targeting specific defects in the hypertrophied heart (Figure 5). With the exception of digoxin, drugs used currently have been developed as antihypertensives and their potential for interfering with progression of heart failure has been examined only later on. It might, therefore, not be unexpected that they can counteract neuroendocrine activation but are less useful in treating pathophysiological events leading to neuroendocrine activation. In view of the high incidence of heart failure and sudden cardiac death, it is considered important to strengthen our efforts in the development of compounds which target specific mechanisms of hypertrophied cardiomyocytes. In view of the intricate interrelationship between impaired

pump function and malignant arrhythmias, also endogenous antiarrhythmogenic mechanisms should be explored to a greater extent. A lead approach in this respect could involve drug-induced stimulation of the endogenous EPA and DHA production.

References

1. Alter P, Rupp H, Czerny F, et al. Relation of ventricular wall stress and autonomic tone in patients with dilated cardiomyopathy assessed by cardiac magnetic resonance imaging. Eur Heart J 2006;27:Abstract Suppl:678.
2. Bakewell L, Burdge GC, Calder PC. Polyunsaturated fatty acid concentrations in young men and women consuming their habitual diets. Br J Nutr 2006;96:93–9.
3. Barger PM, Brandt JM, Leone TC, et al. Deactivation of peroxisome proliferator-activated receptor-alpha during cardiac hypertrophic growth. J Clin Invest 2000;105:1723–30.
4. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970–1974 and 1990–1994. Circulation 2006;113:799–805.
5. Bishop SP, Altschuld RA. Increased glycolytic metabolism in cardiac hypertrophy and congestive failure. Am J Physiol 1970;218:153–9.
6. Brilla CG, Rupp H, Maisch B. Effects of ACE inhibition versus non-ACE inhibitor antihypertensive treatment on myocardial fibrosis in patients with arterial hypertension. Retrospective analysis of 120 patients with left ventricular endomyocardial biopsies. Herz 2003;28:744–53.
7. Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA 2006;295:2613–9.
8. Burdge GC, Wootton SA. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr 2002;88:411–20.
9. Christe ME, Rodgers RL. Altered glucose and fatty acid oxidation in hearts of the spontaneously hypertensive rat. J Mol Cell Cardiol 1994;26:1371–5.
10. De Brouwer KF, Degens H, Aartsen WM, et al. Specific and sustained down-regulation of genes involved in fatty acid metabolism is not a hallmark of progression to cardiac failure in mice. J Mol Cell Cardiol 2006;40:838–45.
11. Degens H, de Brouwer KF, Gilde AJ, et al. Cardiac fatty acid metabolism is preserved in the compensated hypertrophic rat heart. Basic Res Cardiol 2006;101:17–26.
12. Doggrell SA, Brown L. D-sotalol: death by the SWORD or deserving of further consideration for clinical use? Expert Opin Investig Drugs 2000;9:1625–34.
13. Eichelbaum M, Kroemer HK, Mikus G. Genetically determined differences in drug metabolism as a risk factor in drug toxicity. Toxicol Lett 1992;64-65:115–22.
14. El Armouche A, Boknik P, Eschenhagen T, et al. Molecular determinants of altered Ca2+ handling in human chronic atrial fibrillation. Circulation 2006;114:670–80.
15. Feinendegen LE, Henrich MM, Kuikka JT, et al. Myocardial lipid turnover in dilated cardiomyopathy: a dual in vivo tracer approach. J Nucl Cardiol 1995;2:42–52.
16. Fernandez-Velasco M, Goren N, Benito G, et al. Regional distribution of hyperpolarization-activated current (If) and hyperpolarization-activated cyclic nucleotide-gated channel mRNA expression in ventricular cells from control and hypertrophied rat hearts. J Physiol 2003;553:395–405.

17. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int J Vitam Nutr Res 1998; 68:159–73.

18. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447–55.

19. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation in obese normotensive subjects. Hypertension 1995; 25:560–3.

20. Grimm W, Christ M, Bach J, et al. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. Circulation 2003;108:2883–91.

21. Ihara M, Urata H, Kinoshita A, et al. Increased chymase-dependent angiotensin II formation in human atherosclerotic aorta. Hypertension 1999;33:1399–405.

22. Jacob R, Brandle M, Dierberger B, et al. Functional consequences of cardiac hypertrophy and dilatation. Basic Res Cardiol 1991;86:Suppl 1:113–30.

23. Janicki JS, Brower GL, Gardner JD, et al. Cardiac mast cell regulation of matrix metalloproteinase-related ventricular remodeling in chronic pressure or volume overload. Cardiovasc Res 2006;69:657–65.

24. Kearney MT, Fox KA, Lee AJ, et al. Predicting sudden death in patients with mild to moderate chronic heart failure. Heart 2004;90:1137–43.

25. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747–57.

26. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation 2005;112:2762–8.

27. Leaf A, Xiao YF, Kang JX, et al. Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids. Pharmacol Ther 2003;98:355–77.

28. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. Circulation 2005;112:3280–8.

29. Lenfant C, Roccella EJ. A call to action for more aggressive treatment of hypertension. J Hypertens Suppl 1999;17:S3–7.

30. Lionetti V, Linke A, Chandler MP, et al. Carnitine palmitoyl transferase-I inhibition prevents ventricular remodeling and delays decompensation in pacing-induced heart failure. Cardiovasc Res 2005;66:454–61.

31. Marchioli R, Avanzini F, Barzi F, et al. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. Eur Heart J 2001;22:2085–103.

32. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897–903.

33. Nair SS, Leitch J, Falconer J, et al. Cardiac (n-3) non-esterified fatty acids are selectively increased in fish oil-fed pigs following myocardial ischemia. J Nutr 1999;129:1518–23.

34. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.

35. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA 2005;293:2884–91.

36. Rupp H, Benkel M, Maisch B. Control of cardiomyocyte gene expression as drug target. Mol Cell Biochem 2000;212: 135–42.

37. Rupp H, Rupp TP, Maisch B. Fatty acid oxidation inhibition with PPARalpha activation (FOXIB/PPARalpha) for normalizing gene expression in heart failure? Cardiovasc Res 2005;66:423–6.

38. Rupp H, Schulze W, Vetter R. Dietary medium-chain triglycerides can prevent changes in myosin and SR due to CPT-1 inhibition by etomoxir. Am J Physiol 1995;269:R630–40.

39. Rupp H, Turcani M, Ohkubo T, et al. Dietary linolenic acid-mediated increase in vascular prostacyclin formation. Mol Cell Biochem 1996;162:59–64.

40. Rupp H, Wagner D, Rupp T, et al. Risk stratification by the "EPA+DHA level" and the "EPA/AA ratio" focus on anti-inflammatory and antiarrhythmogenic effects of long-chain omega-3 fatty acids. Herz 2004;29:673–85.

41. Rupp H, Wahl R, Hansen M. Influence of diet and carnitine palmitoyltransferase I inhibition on myosin and sarcoplasmic reticulum. J Appl Physiol 1992;72:352–60.

42. Sack MN, Disch DL, Rockman HA, et al. A role for Sp and nuclear receptor transcription factors in a cardiac hypertrophic growth program. Proc Natl Acad Sci U S A 1997;94: 6438–43.

43. Schmidt-Schweda S, Holubarsch C. First clinical trial with etomoxir in patients with chronic congestive heart failure. Clin Sci (Lond) 2000;99:27–35.

44. Sharma AM, Wittchen HU, Kirch W, et al. High prevalence and poor control of hypertension in primary care: cross-sectional study. J Hypertens 2004;22:479–86.

45. Stanton LW, Garrard LJ, Damm D, et al. Altered patterns of gene expression in response to myocardial infarction. Circ Res 2000;86:939–45.

46. Steiner S, Wahl D, Mangold BL, et al. Induction of the adipose differentiation-related protein in liver of etomoxir-treated rats. Biochem Biophys Res Commun 1996;218:777–82.

47. Taegtmeyer H, Overturf ML. Effects of moderate hypertension on cardiac function and metabolism in the rabbit. Hypertension 1988;11:416–26.

48. Trenkwalder P, Ruland D, Stender M, et al. Prevalence, awareness, treatment and control of hypertension in a population over the age of 65 years: results from the Starnberg Study on Epidemiology of Parkinsonism and Hypertension in the Elderly (STEPHY). J Hypertens 1994;12:709–16.

49. Turcani M, Rupp H. Etomoxir improves left ventricular performance of pressure-overloaded rat heart. Circulation 1997;96:3681–6.

50. Turcani M, Rupp H. Modification of left ventricular hypertrophy by chronic etomoxir treatment. Br J Pharmacol 1999;126:501–7.

51. Van de Werf F, Ardissino D, Betriu A, et al. W. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003;24:28–66.

52. Vetter R, Rupp H. CPT-1 inhibition by etomoxir has a chamber-related action on cardiac sarcoplasmic reticulum and isomyosins. Am J Physiol 1994;267:H2091–9.

53. Vogt M, Jacob R, Kissling G, et al. Chronic cardiac reactions. II. Mechanical and energetic consequences of myocardial transformation versus ventricular dilatation in the chronically pressure-loaded heart. Basic Res Cardiol 1987;82:Suppl 2:147–59.

54. Zarain-Herzberg A, Rupp H. Transcriptional modulators targeted at fuel metabolism of hypertrophied heart. Am J Cardiol 1999;83:31H–7H.

Address for Correspondence

Prof. Dr. Heinz Rupp
Molecular Cardiology Laboratory
Department of Internal Medicine and Cardiology
Philipps University of Marburg
35043 Marburg
Germany
Phone (+49/6421) 286-5032, Fax -8964
e-mail: Rupp@staff.uni-marburg.de