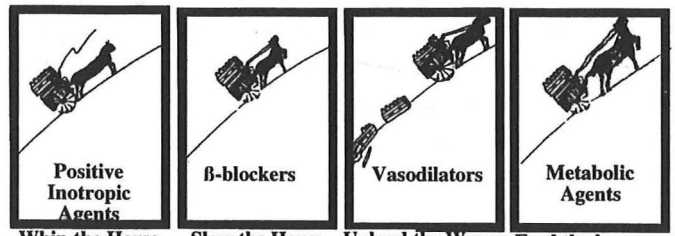
Energetic Alterations in Heart Failure:
Metabolic Effects on Biological Function



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Interests: I am a clinical cardiologist and an interventional cardiologist with a special interest in chronic heart failure. I have spent the last 14 years examining the effects of ß-adrenergic blockade on myocardial function, energetics, pathological remodeling, morbidity, and mortality in patients with heart failure. I was the Principal Investigator and Co-Chairman for the NHLBI-VA Cooperative Study, the ß-Blocker Evaluation of Survival Trial (BEST). This study investiged the effects of ß-blockade in patients with advanced heart failure in 90 hospitals in the US and Canada. I am currently the Principal Investigator for two worldwide studies (EXTEND, ENOXIE) examining the use of low dose enoximone as adjunct therapy to beta-blockade in patients with end-stage heart failure who otherwise would not tolerate a negative inotrope. Other current research efforts and collaborators include: 1) the relationship of myocardial viability and response to ß-blockade and the relationship of reverse remodeling to morbidity and mortality 2) the effects of anti-cytokine therapy on ventricular function and remodeling 3) the effects of endothelin antagonism on ventricular function and morbidity in heart failure and 4) the use of metabolic agents to improve myocardial energetics and to reverse the phenotypical changes induced by neurohormonal activation. This is the topic I will present today.

Introduction

Myocardial failure begins with an insult to pump function, such as a myocardial infarction, inflammation, severe hemodynamic overload from hypertensive or valvular disease, genetic causes, or idiopathic myocardial dysfunction. In response to as yet undefined signals that probably include arterial underfilling, tissue hypoperfusion and central venous congestion, compensatory mechanisms are activated to support the failing heart.[1-3] There are four physiologic adjustments the heart can use to stabilize or increase myocardial performance in the failing heart: 1) increase in heart rate [4] 2) increase in contractility 3) increase in preload [5,6] and 4) increase in the number of contractile elements. [1,7,8] These four adjustments are largely accomplished by an increase in activity of two interrelated neurohormonal/autocrine-paracrine systems, the adrenergic and renin-angiotensin systems.[1-3]

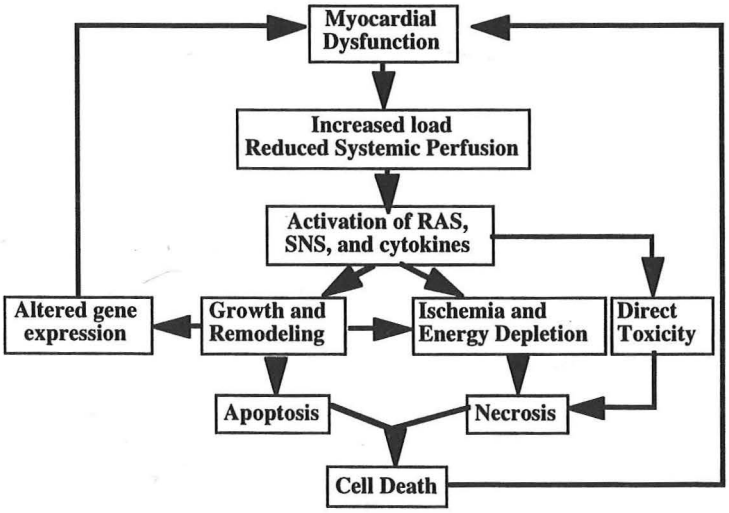


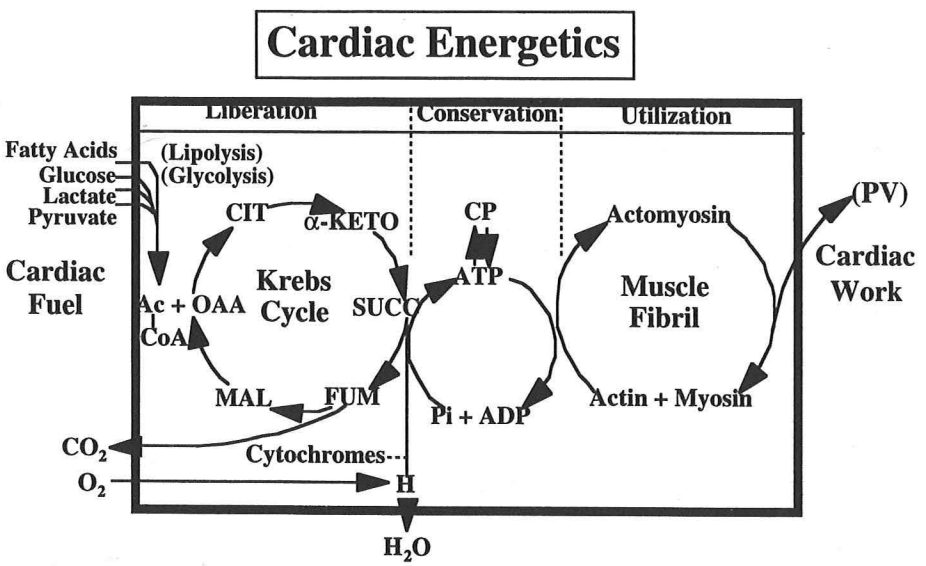
Figure 1

Activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) results in pathological ventricular remodeling in the failing heart.[1] This process produces abnormal myocyte growth and acceleration of cell death leading to further ventricular dysfunction, and a vicious cycle is established.[1] The deleterious effects of these neurohormones include ß-receptor downregulation [9,10], altered chamber geometry [7,11-13] and energetics [14,15], production of a more fetal phenotype [1,16,17], and reduced cell viability.[1,18-21] ACE inhibitors [22,23] and beta-blocking agents [11] slow this pathological remodeling down and in many cases can reverse the process. Thus, interfering with the

neurohormonal growth signals may lead to reverse remodeling and long term improvement in function and energetics.[14,15] These biological effects of ACE inhibitors [24-27] and ß-blockers [28-34] may produce long term improvement in outcome including prolonged survival and a reduction in hospitalizations.

Energy Depletion in the Failing Heart-

A concomitant problem in heart failure is a reduction in myocardial efficiency and energy depletion.[14,15,35-45] The reduction in high energy phosphates is caused by several inter-related problems: 1) inefficient geometry/architecture of the ventricle 2) reduced oxygen delivery 3) mitochondrial changes 4) decreased levels of creatine phosphokinase 5) reduced allosteric effects of ATP 6) a shift in substrate utilization and 7) change in phenotype of contractile proteins and calcium regulatory proteins. These changes in high energy phosphate production and utilization are a direct effect of neurohormonal activation, pathological remodeling, and altered gene expression. Reduction in ATP formation and conservation ultimately will result in reduced cardiac work (Figure 2).



Olson RE et al. Ann NY Acad Sci 1959; 72: 466-79

Figure 2

Altered architecture/geometry of the ventricle

The normal heart is elliptical in shape.[7,11] Ventricular overload and neurohormonal activation results in a pattern of volume enlargement, eccentric hypertrophy, and a change to a more globular shape.[7,11,12] The increase in volume of the ventricle is directly related to an increase in the length of the myocyte which occurs with volume overload.[46] These changes result in several problems. First, the increase in volumes without a concomitant increase in hypertrophy produces an increase in wall stress or load for the ventricle. Load is both a stimulus for more neurohormonal activation [47-51] as well as impedance for ventricular ejection.[52] The remodeled ventricle produces functional mitral insufficiency which results in non-productive work by the heart as some of the contractile force is used to eject blood into the atrium.[12] The increase in neurohormonal activation leads to more myocyte death, interstitial fibrosis, and a loss of contractile units as well as progressive remodeling and failure of the ventricle. The remodeled ventricle with higher load will consume more oxygen to achieve the same degree of stroke work. Myocardial mechanical efficiency can be represented by the equation:

Efficiency = (HR) x (SW) / (MOC) x k

where HR = heart rate, SW = stroke work, MOC = myocardial oxygen consumption, and k = constant.[14,15,53,54] Based on this equation, if myocardial oxygen consumption increases to maintain the same or a lesser amount of forward stroke work, then efficiency is falling.

Reduced oxygen delivery

Oxygen delivery in the dilated failing heart is reduced for several reasons. The nutrient arterioles that penetrate the ventricular wall from their origins in the large epicardial coronary arteries are increased in length due to hypertrophy. There is increased intercapillary distance which impairs diffusion of oxygen.[55,56] In addition, interstitial fibrosis is increased in patients with eccentric myocyte hypertrophy, including subjects with ischemic and nonischemic dilated cardiomyopathies. Both the production and degradation of the collagen network are controlled by fibroblasts, which in the presence of remodeling and eccentric hypertrophy must produce additional extracellular matrix to maintain structural integrity of the ventricular wall.[57,58] However, the presence of increased interstitial collagen may account for reduced capillary density and increased oxygen diffusion distance [59-61], which may contribute to metabolic stress or even overt ischemia. [59,60]

Finally, the elevated filling pressures and lowered diastolic blood pressure in heart failure reduces transmyocardial perfusion pressures which drive coronary blood from

epicardium to endocardium. While absolute blood flow is increased in the failing heart, the amount of blood flow per gram of tissue is reduced [62] as is coronary flow reserve.[63] One study has demonstrated that the reduction in myocardial blood flow reserve is inversely proportional to left ventricular wall stress in patients with dilated cardiomyopathy.[63] In addition, these investigators used PET scanning to demonstrate a mismatch of blood flow to glucose uptake in multiple regions, and the extent of mismatch also correlated with left ventricular wall stress.[63] When glucose uptake to oxygen consumption was compared in regions of mismatch, there was an inverse correlation. These data suggest that in regions of mismatch, as oxygen consumption increases (in patients with large ventricles and high wall stress), glucose metabolism is reduced. This suggests a shift from aerobic to anaerobic metabolism in these mismatched regions. Thus, patients with dilated cardiomyopathy have ventricles which are ischemic and energy depleted.

Mitochondrial changes

There is considerable evidence that mitochondrial energy production is impaired in the failing heart.[64-68] Evidence of mutations in mitochondrial DNA have been found in patients with inherited and idiopathic dilated cardiomyopathy.[69] Current theory suggests two mechanisms of mitochondrial injury: 1) Repair of free-radical induced damage to mitochondrial DNA is poorly developed and copies of damaged mitochondrial DNA can accumulate in failing ventricles and/or 2) Antibody mediated mitochondrial damage can disturb the inner mitochondrial membrane and inhibit the transmembrane nucleotide transport.[66] In general, mitochondria from failing hearts appear morphologically to be smaller and more numerous than in non-failing hearts.[35,64]

Decreased levels of creatine phosphokinase

Creatine phosphokinase levels are reduced in heart failure resulting in slowing of ADP rephosphorylation by the phosphocreatine shuttle.[70,71] This may reduce cytosolic levels of ATP and produce energy starvation. Some compensation for this reduction in enzyme activity is produced by a switch in phenotype for creatine phosphokinase from the M isoform to the more fetal B isoform.[72,73] As the affinity of the B isoform of this enzyme for ADP is higher than the M isoform, there is some increase in the production of ATP by the phsophocreatine shuttle to compensate for lower enzyme levels.

Reduced allosteric effects of ATP

High ATP concentrations may exert allosteric effects on calcium ion exchangers and ion pumps in the myocyte enhancing both contraction force and relaxation.[74,75] These

effects of ATP may facilitate calcium entry into the cell [74] as well as calcium flux in and out of the sarcoplasmic reticulum.[75-77] A reduction in ATP would thus result in a reduction in calcium flux producing a diminished contractile force and slower relaxation.

ATP also has an allosteric effect on actin and myosin dissociation.[78] Thus, the reduction in ATP may prolong relaxation times significantly and increase diastolic stiffness.

Changes in Substrate Utilization

The amount of energy available to the cell is regulated by the phosphorylation potential:

ΔG	=	ΔG_0	+	RT ln [ATP] / [ADP][Pi]
Free energy		Constant		Phosphorylation Potential

This equation states that the amount of energy available to the cell is ultimately proportional to the [ATP] and inversely proportional to [ADP] and [Pi].

Free fatty acids and glucose produce differing amounts of ATP, but utilize different amounts of oxygen to produce that ATP. Figures 3 and 4 show the energy released per carbon molecule of hexanoic acid vs glucose and the oxygen utilization per ATP formed.

Fatty Acid Oxidation versus Glucose Oxidation

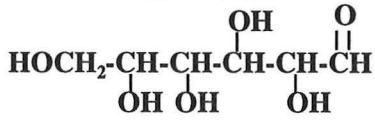
Carbon for carbon, fatty acid oxidation yields more energy than glucose oxidation...

Hexanoic Acid

$HC_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COOH$

$(C_6H_{12}O_2)$

Glucose



$(C_6H_{12}O_6)$

Complete Metabolism

$C_6H_{12}O_2 + 8O_2 \rightarrow 6CO_2 + 6H_2O$

Yield = 44 ATP

$\frac{44\ ATP}{6CO_2} = \frac{7.3\ ATP\ sythesized}{CO_2\ generated}$

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$

Yield = 38 ATP

$\frac{38\ ATP}{6CO_2} = \frac{6.3\ ATP\ sythesized}{CO_2\ generated}$

Figure 3

...but fatty acid oxidation is less oxygen-efficient than glucose oxidation.

Hexanoic Acid ($C_6H_{12}O_2$)	Glucose ($C_6H_{12}O_6$)
Complete Metabolism	
$C_6H_{12}O_2 + 8O_2 \rightarrow 6CO_2 + 6H_2O$	$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$
Yield = 44 ATP	Yield = 38 ATP
Fuel Efficiency	
$\frac{44\ ATP}{8O_2} = \frac{5.5\ ATP\ sythesized}{O_2\ consumed}$	$\frac{38\ ATP}{6O_2} = \frac{6.3\ ATP\ sythesized}{O_2\ consumed}$

Figure 4

Figure 5 shows the energy produced by palmitic acid vs glucose in terms of ATP yield per molecule, ATP yield per carbon atom, and ATP yield per oxygen atom.

Molecule	ATP Yield per Molecule	ATP Yield per Carbon Atom	ATP Yield per Oxygen Atom Taken Up (P/O ratio)
Glucose	38	6.3	3.17
Palmitic Acid	130	8.1	2.83

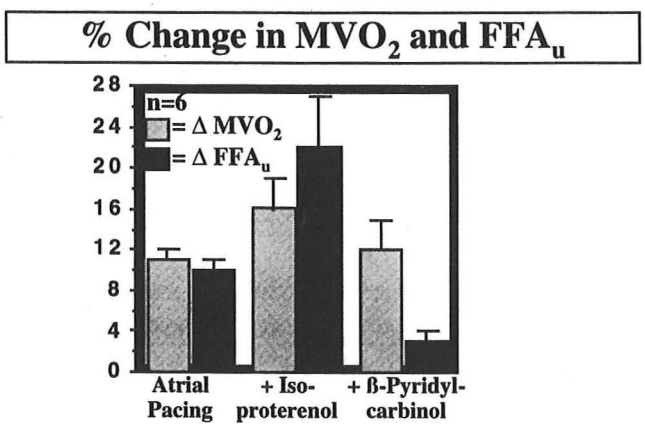
Figure 5

It is clear that fatty acids yield more ATP per carbon atom, but use more oxygen in doing so. Thus, free fatty acids are good when oxygen is unlimited. However, in ischemic states (coronary artery disease, heart failure, hypertrophy, etc), when oxygen is limited, glucose becomes a more efficient fuel. However, evolution has determined that in periods of stress or high adrenergic tone, free fatty acids are used preferentially.[79-83]

It has long been known that fatty acids and glucose provide the major substrates for myocardial energy metabolism and that excess utilization of free fatty acids by the heart increases myocardial oxygen consumption.[79-81] Several experimental observations

suggest that fatty acid substrate utilization by the heart is less efficient than glucose. In the oxygen limited heart, high concentrations of free fatty acids depress myocardial performance.[79,82] This effect is presumably due to the increased need for oxygen in the presence of fatty acid metabolism. In addition, the increase in plasma fatty acids at rest has been shown to have no effect on myocardial oxygen consumption.[83] However, when oxygen consumption is increased by atrial pacing or catecholamine induced stress, myocardial oxygen consumption is increased disproportionately in the presence of infused lipids and heparin as compared to a control state.[83]

In a study of patients with coronary artery disease, Simonsen and Kjekshus atrially paced patients below their angina threshold and then administered isoproterenol (Figure 6).[83] This resulted in an increase in myocardial oxygen consumption and free fatty acid uptake into the heart. When ß-pyridyl carbinol, an agent which inhibits free fatty acid uptake was then given, myocardial oxygen consumption and free fatty acid uptake both fell. These investigators found a linear relation between myocardial oxygen consumption and free fatty acid uptake. Thus, catecholamines increase free fatty acid utilization and myocardial oxygen consumption.

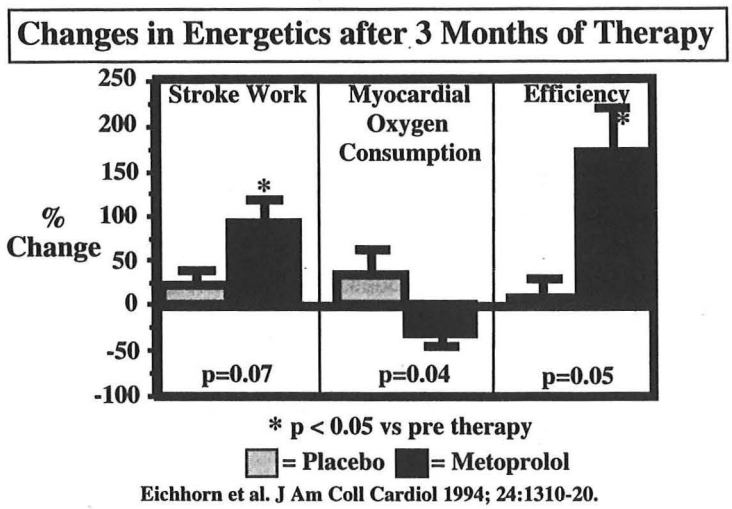


Simonsen S, Kjekshus JK. Circulation 1990; 81:484-490

Figure 6

It is clear that catecholamines stimulate release and utilization of fatty acids.[79,83] As congestive heart failure is a state of increased adrenergic stimulation, with elevated sympathetic nerve traffic and increased plasma norepinephrine levels [1], lipolysis and glycogenolysis are both stimulated.[84] In the dog, myocardial oxygen consumption which is increased by beta-agonist stimulation, is further increased by a beta-stimulated increase in

(i.e. a shift to) fatty acid utilization.[80] As myocardial work does not change or decreases when there is a shift from glucose to fatty acid utilization, this shift represents a reduction in myocardial efficiency.[80] Previous data from our laboratory has shown that beta-adrenergic blockade results in increased mechanical work in the absence of increased myocardial oxygen consumption (Figure 7).[14,15]



Eichhorn et al. J Am Coll Cardiol 1994; 24:1310-20.

Figure 7

This effect, which represents an increase in myocardial mechanical efficiency, may be due in part to a blockade of the adrenergic stimulation of fatty acid substrate utilization and a shift to glucose. Some support for this hypothesis comes from two early ß-blocker trials where transmyocardial lactate extraction was measured before and after ß-blockade.[14,85] In these studies, lactate extraction increased with therapy, suggesting increased pyruvate/glucose utilization. In addition, in our studies, there was a linear relationship between transmyocardial respiratory quotient (a measure of substrate utilization) and coronary sinus norepinephrine (a surrogate measure of cardiac adrenergic activation)(Figure 8).[14] These data suggested a relationship between activation of the adrenergic nervous system and a shift in substrate utilization toward free fatty acids.

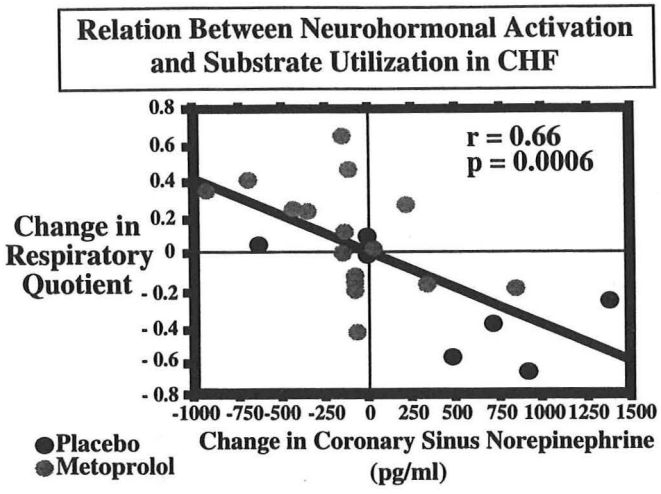


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Figure 8

Change in phenotype of contractile proteins and calcium regulatory proteins

Several lines of evidence suggest that shifts in substrate utilization, in the absence of alterations in the activation of the renin-angiotensin or adrenergic nervous systems, may alter both performance [86-89], efficiency [89,83], and phenotype [90-101] of the failing heart.

The process of hypertrophy increases the number of functioning contractile elements. Alterations in gene expression involve calcium handling by the sarcoplasmic reticulum and changes in contractile proteins or their regulatory elements producing an inefficient contractile element.[102-108] Some or all of these changes ultimately lead to progressive left ventricular dysfunction, best understood as a continued decline in systolic function.

Systolic dysfunction of individual cardiac myocytes is by definition due to a change in gene expression. In rodent systems the constellation of alterations in gene expression that accompanies cardiac hypertrophy and its transition to myocardial dysfunction has been termed activation of a "fetal" program, as the changes recapitulate embryonic or neonatal patterns.[1,8,102] Because humans do not exhibit major changes in gene expression during development they do not exhibit the dramatic fetal program activation that characterizes hypertrophy or failure in rodent hearts.[102] However, there are certain changes in human hearts that resemble fetal activation. These include an up-regulation in gene expression of atrial natriuretic peptide[103,104] and down-regulation in the expression of SR-calcium ATPase [102,105,106] and a myosin heavy chain.[107,108] Angiotensin-II, [57,58,109],

endothelins [109,110] and adrenergic stimulation [1,111] have been shown to be potent inducers of the fetal/hypertrophy gene program in model systems.

Reduction in systolic performance by alteration in phenotype leads to a decrease in myocardial efficiency. A reduction in efficiency, mandates either a reduction in mechanical work or an increase in oxygen utilization to maintain equal performance.

The treatment of a patient with heart failure with an ACE inhibitor and ß-blocker results in an attenuation or even a reversal of the pathological remodeling process, an increase in performance and contractility of the failing heart, and improvement in myocardial efficiency.[1,11,14,15,23] This reversal in pathological remodeling correlates with improved outcome in most cases.[24-34] The improvement in left ventricular performance with ACE inhibitors and ß-blockers is associated with a reversal in some of the phenotypical abnormalities which characterize the failing heart [108] as well as a shift in substrate utilization from fatty acids to glucose.[14,112]

Metabolic Altering Agents and Their Effect on Ventricular Function and Phenotype-

Figure 9 shows the metabolic pathways and their inhibitors. Acetyl CoA for oxidative phosphorylation is formed from either fatty acids or glucose utilization. Glucose entry into the cell can be inhibited by insulin deficiency. Once in the cell, glucose enters the glycolytic pathway and is broken down to pyruvate. The conversion of pyruvate to acetyl CoA is controlled by the enzyme pyruvate dehydrogenase (PDH) which is a regulatory enzyme controlling entry of glucose into the Krebbs cycle and oxidative phosphorylation. Free fatty acids may also enter the cell, but must be carried into the mitochondria by carnitine. The conversion of Acetyl CoA from acyl carnitine is controlled by the enzyme carnitine palmitoyl trasferase I (CPT 1). Thus, CPT1 is a controlling enzyme regulating free fatty acid entry into the Krebbs cycle.

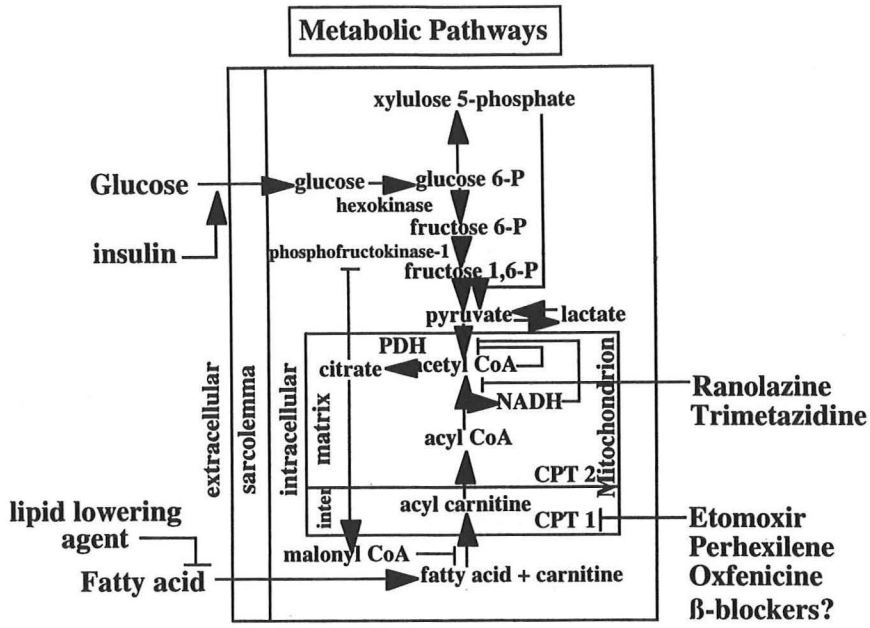


Figure 9

Several agents exist which regulate free fatty acid and glucose metabolism. These agents all shift metabolic utilization from free fatty acids to preferential glucose utilization. Trimetazidine inhibits 3-ketoacyl CoA thiolase and indirectly stimulates PDH. Ranolazine inhibits fatty acid oxidation through unclear mechanisms and indirectly stimulates PDH. Etomoxir, Perhexilene, and Oxfenicine inhibit CPT1.

The increase in adrenergic drive in heart failure results in greater free fatty acid utilization and a reduction in myocardial efficiency. These metabolic agents, which interfere with fatty acid utilization, produce two effects: 1) an early improvement in ventricular function due to increased glucose utilization and ATP production and a reduction in oxygen consumption relieving ischemia 2) a late effect on gene expression (see below).[86-101]

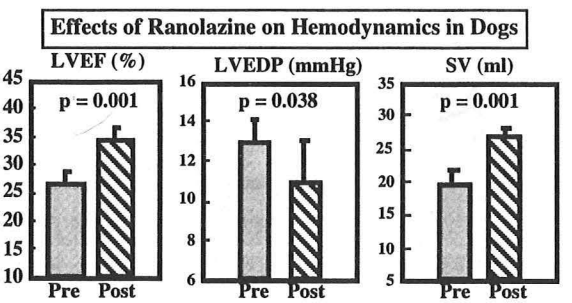
<u>Evidence of Early Improvement in ventricular function with metabolic altering agents</u>:

Liedtke and associates examined the effect of free fatty acid (Intralipid) and heparin (releases free fatty acids) administration on ventricular function in mildly ischemic pigs.[88] Free fatty acids progressively reduced systolic pressure and peak +dP/dt over time without changing diastolic pressures.

Bersin and associates examined the effect of dichloroacetate ((DCA) which stimulates PDH) and dobutamine on myocardial energetics in patients with heart failure.[89] They found that both agents improved stroke volume and stroke work. DCA increased lactate extraction (suggesting a shift to glucose metabolism) while dobutamine increased lactate production. Myocardial oxygen consumption increased with dobutamine while it decreased with DCA, suggesting improved efficiency.

Schmidt-Schweda and associates examined the effects of etomoxir on acute and chronic hemodynamics in 10 patients with heart failure.[86] Acutely, etomoxir had no effect on peak developed force, heart rate, cardiac output, systolic pressure, or systemic vascular resistance. After 3 months of therapy, etomoxir improved both resting and exercise stroke volume and lowered exercise pulmonary capillary wedge pressure.

Sabbah and colleagues examined the effect of ranolazine on acute hemodyanmics in a canine heart failure model.[87] After 40 minutes of infusion, they found no shift in heart rate or systolic blood pressure acutely, however, left ventricular end-diastolic pressure fell and stroke volume and ejection fraction increased (Figure 10). Both peak +dP/dt (contractile force) and peak -dP/dt (relaxation) improved with ranolazine.



Sabbah HN et al. Circulation 2000; 102 (suppl II): II-721

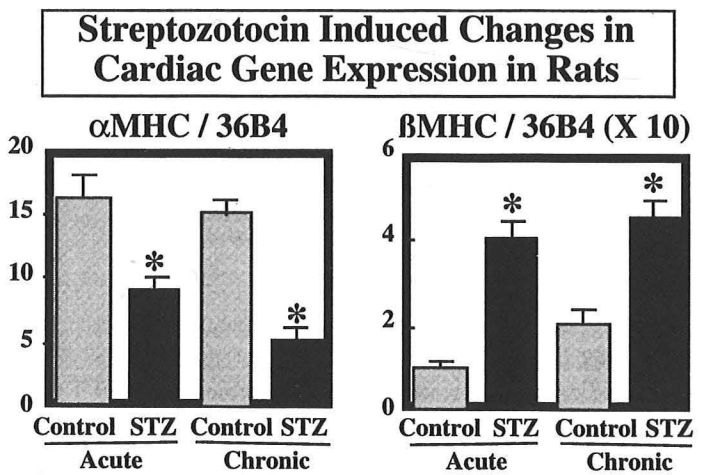
Figure 10

More recently, a multicenter study of ranolazine has been conducted to examine the efficacy of this drug to improve exercise duration in patients with ischemic heart disease and both with (n=29) and without (n=146) heart failure.[113] This was a double-blind, 4 period crossover study. Patients were exercised weekly at peak and trough levels of ranolazine. Ranolazine increased exercise duration in patients with and without heart failure compared to placebo ($p<0.001$). There was also a prolongation of time to 1 mm of ST depression on ranolazine compared to placebo ($p<0.001$).

These data all suggest a rather early onset of ventricular function and efficiency improvement when a metabolic agent is administered. This early effect may be a direct result of increased ATP due to a shift in glucose utilization.

Evidence of a late change in phenotype with metabolic altering agents:

Depre and Taegtmeyer examined changes in gene expression with rtPCR 1 week and 6 months after inducing glucose intolerance in rats given streptozotocin.[100] As expected, the streptozotocin treated rats had poor glucose control. After one week of therapy, there was a downregulation in the faster, adult αMHC and an upregulation of the slower, more fetal like ß-MHC (Figure 11). In addition, SERCA 2A and α-actin were downregulated, suggesting that alteration of substrates, even in non-failing hearts may alter gene expression.



Depre C and Taegtmeyer H. J Mol Cell Cardiol 2000; 32: 985-996.

Figure 11

In a similar study, Rupp and colleagues examined the effect of etomoxir (which inhibits fatty acid utilization) on Wistar rat gene expression.[90,114] Administration of 50 mg/kg of etomoxir reduced body weight and increased heart weight relative to body weight. The proportion of myosin V_1 (α-MHC) was increased with high dose etomoxir. Both low and high dose etomoxir increased Ca^{+2} uptake by SR vesicles suggesting upregulated SERCA activity/expression.

Zarain-Herzberg and Rupp examined SR gene expression in pressure overloaded rat hearts.[91] After 8 weeks of aortic constriction in rats, SERCA2, phospholamban, and

Ca^{+2} release channel mRNA was downregulated in pressure overloaded vs sham rats (Figure 12). In pressure overloaded rats treated with etomoxir, there was an upregulation (normalization) of SERCA2, phospholamban, and Ca^{+2} release channel mRNA. Thus, a shift from fatty acid to glucose utilization in the pressure overloaded rat results in upregulation in SR proteins controlling calcium flux and α-MHC.

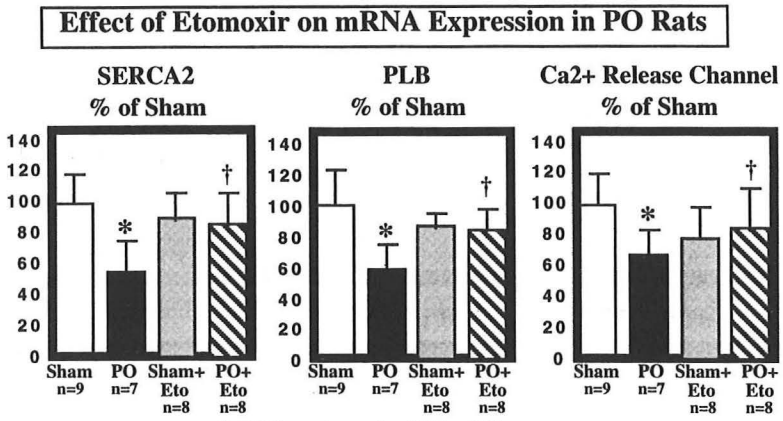


Figure 12

Effect of metabolic therapy on survival:

D'hahan studied calcium overload in cardiomyopathic hamsters.[115] In this study, cytosolic calcium was assessed by spectrofluorometry using fura 2. Cardiomyopathic hamsters had increased cytosolic calcium concentrations compared to non-failing hearts. However, use of trimetazadine normalized the amount of cytosolic calcium. Furthermore, Kaplan-Meier analysis of survival was better in the hamsters taking trimetazadine (Figure 13).

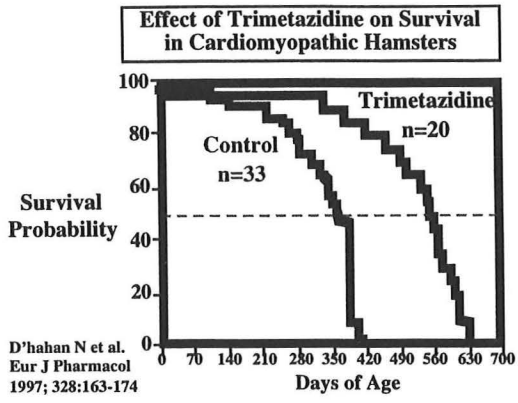


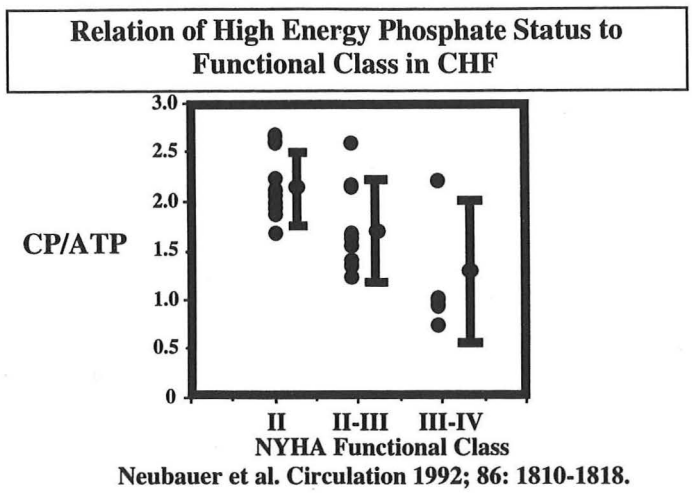
Figure13

Possible Adverse Effects of Long-Term Inhibition of Fatty Acid Oxidation:

Unger and associates studied genetically obese Zucker Diabetic Fatty (ZDF) rats (fa/fa) who have loss of function of the leptin receptor.[116] These rats have a metabolic syndrome similar to that seen in metabolic "Syndrome X". These rats have reduced fatty acid oxidation, excessive deposition of triacylglycerol (TG) in nonadipose tissues (steatosis) leading to an increased pool of fatty acyl-CoA which provides substrate for nonoxidative metabolic pathways, such as ceramide synthesis. This may lead to apoptotic cell death. In this study, the hearts of the ZDF rats were examined at 7, 14, and 20 weeks. Using rtPCR, these investigators found a down regulation of enzymes reponsible for fatty acid oxidation (CPT-1 and Acyl-CoA oxidase) in the heart, and an increase in triacyglycerol compared to wild type rats. There was also an increase in apoptosis and a reduction in fractional shortening by echocardiography. These results suggest that long-term inhibition of fatty acid oxidation with metabolic agents needs long term assessment in humans as fatty acid deposition in myocytes with inhibited fatty acid oxidation may result in cell death over time which would lead to remodeling and progressive failure. Thus, long-term studies are needed.

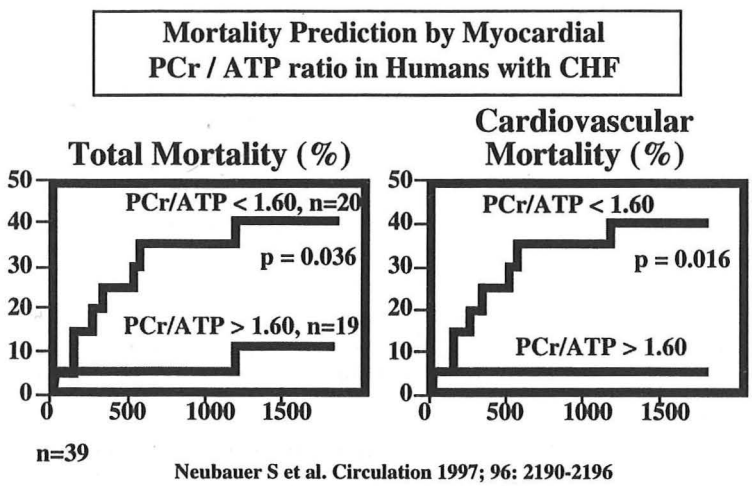
Summary

Heart failure leads to an energy depleted, ischemic state. This energy depleted state worsens as heart failure progresses (Figure 14) and may lead to or be a concomitant factor for a poor prognosis (Figure 15).



Neubauer et al. Circulation 1992; 86: 1810-1818.

Figure 14



Neubauer S et al. Circulation 1997; 96: 2190-2196

Figure 15

Newer therapies for heart failure in the future may include agents which alter substrate utilization. It is clear that in energy depleted states and ischemia, that glucose is a more energy efficient fuel in an oxygen depleted failing heart. Agents which force the heart to use glucose may improve hemodynamics and the energy state of the heart. This may lead to a shift in phenotype and perhaps a reversal in the pathological remodeling process. More studies are needed.

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