

Despite treatment with haemodynamic drugs angina remains a significant health problem for many patients with ischemic heart disease. It has long been shown that haemodynamic anti-ischemic drugs do not have a significant additive effect while the combination of haemodynamic agents with drugs that improve cardiac metabolism is an effective treatment for myocardial ischemia.

## Hemodynamic combined therapy

| Study   | Combinations  | Findings   |
|---|---|--|
| Akras <i>et al</i> . <i>Lancet</i><br>1991;338:1036–1039                  | Atenolol<br>Atenolol + nifedipine SR<br>Atenolol + ISMN<br>Atenolol + ISMN +<br>Nifedipine SR | No substantial benefit to any combination over betablocker monotherapy           |
| Meyer TE <i>et al</i> .<br><i>Cardiovasc Drugs Ther</i><br>1993;7:909–913 | Atenolol<br>Nifedipine SR<br>Atenolol + nifedipine SR   | Combination therapy is no better than atenolol alone                             |
| Madjlissi-Simon T<br><i>Eur Heart J</i><br>1995;16:1780–1788              | Beta- blocker<br>Beta- blocker + amlodipine   | Combination provides no additional benefit in patients resistant to beta-blocker |

## Hemodynamic combined therapy

|   |  |   |
|---|--|---|
| TIBET. Fox K<br><i>Eur Heart J</i><br>1996;17:96–103                    | Atenolol<br>Nifedipine SR<br>Atenolol + nifedipine SR<br>Atenolol + nifedipine SR<br>608 patients included | No additive benefit from combined therapy.  |
| IMAGE. Savonitto<br><i>J Am Coll Cardiol</i><br>1996;27:311–316         | Metoprolol<br>Nifedipine SR<br>Combined therapy<br>249 inclusions  | No additional benefit when Calcium Channel blocker is adjuncted to A beta-blocker |
| CESAR. Knight C<br>and Fox KM<br><i>Am J Cardiol</i><br>1998;81:133–136 | Amlodipine + Atenolol vs<br>Diltiazem + Atenolol   | Exercise test parameters do not improve when adding a second hemodynamic drug     |

Under non-ischemic conditions the majority of ATP formation in the healthy heart comes from oxidative phosphorylation in the mitochondria, with the remainder derived from glycolysis and GTP formation in the citric acid cycle. The heart has a relatively low ATP content and has a complete turnover of the ATP pool approximately every 10 seconds. Approximately 60–70% of ATP is used for contractility, and the remaining 30–40% is primarily used for the sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase and other ion pumps.

The regulation of myocardial metabolism is linked to substrate availability, coronary flow, inotropic state, and hormonal regulation. The citric acid cycle is fuelled by acetyl-CoA formed from decarboxylation of pyruvate and from  $\beta$ -oxidation of fatty acids. In the healthy heart the rates of flux through the metabolic pathways linked to ATP generation are set by the requirement for external power generated by the myocardium and the rate of ATP hydrolysis.

In the normal heart, ~60–80% of the acetyl-CoA comes from  $\beta$ -oxidation of fatty acids, and 20–40% comes from the oxidation of pyruvate produced in nearly equal amounts from glycolysis and lactate oxidation. The glycolytic pathway converts glucose 6-phosphate and  $\text{NAD}^+$  to pyruvate and NADH and generates two ATP for each molecule of glucose. The NADH and pyruvate formed in glycolysis are either shuttled into the mitochondrial matrix to generate  $\text{CO}_2$  and  $\text{NAD}^+$  and complete the process of aerobic oxidative glycolysis or converted to lactate and  $\text{NAD}^+$  in the cytosol. The healthy nonischemic heart is a net consumer of lactate even under conditions of near-maximal cardiac power. The myocardium becomes a net lactate producer only when there is accelerated glycolysis in the face of impaired oxidation of pyruvate, such as occurs with ischemia or diabetes mellitus. The oxidation of glucose and pyruvate and the activity of PDH in the heart are decreased by elevated rates of fatty acid oxidation, such as occur if plasma levels of free fatty acids (FFA) are elevated or if the glucose uptake is impaired.

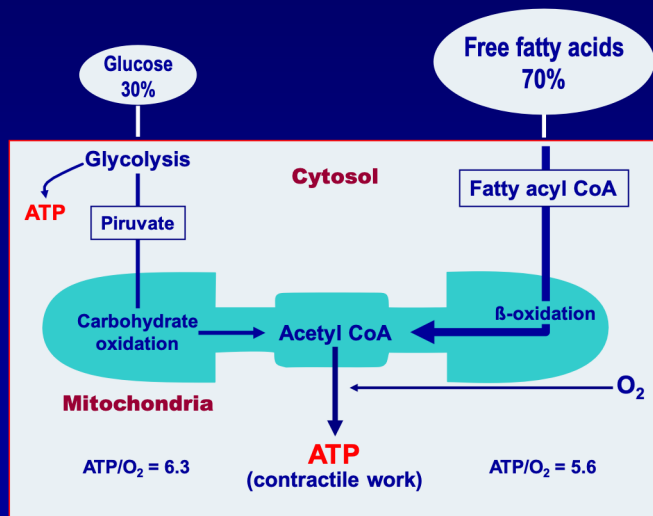
The rate of fatty acid uptake by the heart is primarily determined by the concentration of nonesterified fatty acids in the plasma. Under conditions of metabolic stress, such as ischemia, diabetes, or starvation, plasma FFA concentrations can increase to much higher levels ( $>1.0$  mM). Free fatty acids are highly hydrophobic and are never truly free in vivo but rather are associated with proteins or covalently bound to coenzyme A or carnitine. Fatty acid  $\beta$ -oxidation occurs primarily in the mitochondria and to a small extent in peroxisomes. The primary products of fatty acid oxidation are NADH,  $\text{FADH}_2$ , and acetyl-CoA. Once taken up by the mitochondria, fatty acids undergo  $\beta$ -oxidation. This process involves four reactions. The final step is modulated by 3-ketoacyl-CoA thiolase (3-KAT), which regenerates acyl-CoA for another round of  $\beta$ -oxidation and releases acetyl-CoA for the citric acid cycle.

The primary physiological regulator of the rate of glucose oxidation in the heart is the rate of fatty acid oxidation. High rates of fatty acid oxidation inhibit PDH activity via an increase in mitochondrial acetyl-CoA/free CoA and NADH/  $\text{NAD}^+$ , which activates PDH kinase causing phosphorylation and inhibition of PDH.

Conversely, inhibition of fatty acid oxidation increases glucose and lactate uptake and oxidation by decreasing citrate levels and inhibition of PFK and lowering acetyl-CoA and/or NADH levels in the mitochondrial matrix, thereby relieving the inhibition of PDH.

Therefore, the healthy adult human heart at rest is able to adopt substrate utilisation accordingly to circumstances but in general approximately 70% of energy production is derived from beta oxidation of fatty acids.

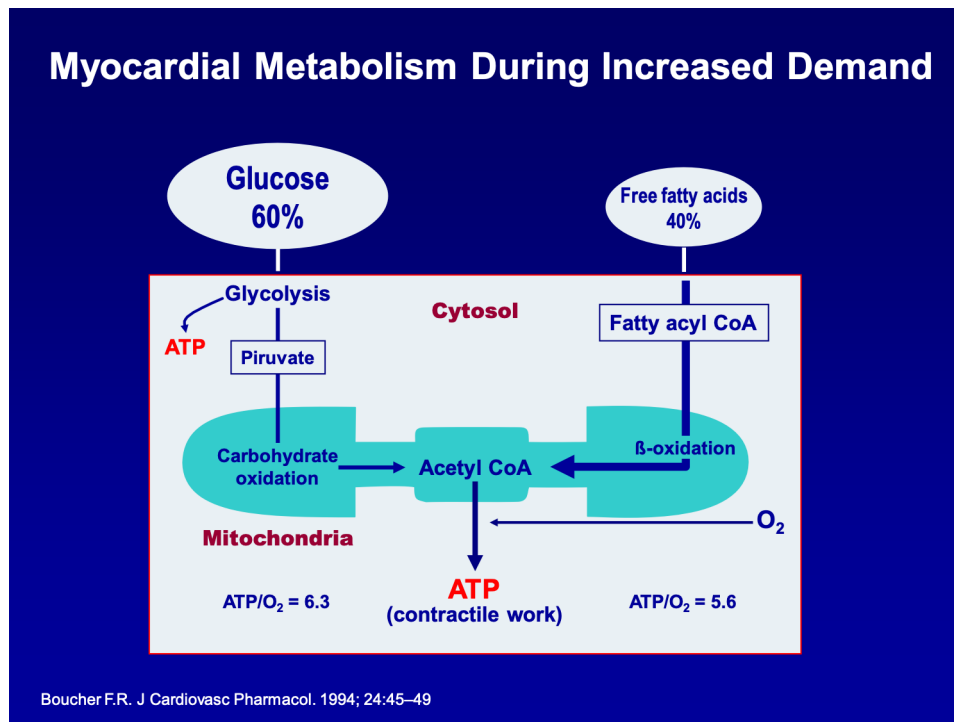
## Myocardial Metabolism at Rest



Boucher F.R. J Cardiovasc Pharmacol. 1994; 24:45–49

During increased metabolic demands, like in case of increased heart rate or blood pressure, in the normal human heart there is a shift towards greater glucose utilisation suggesting that the heart utilizes at rest the least effective source of energy production (FFA) in order to store glucose for periods of increased metabolic demands. Indeed, carbohydrate oxidation is more effective than

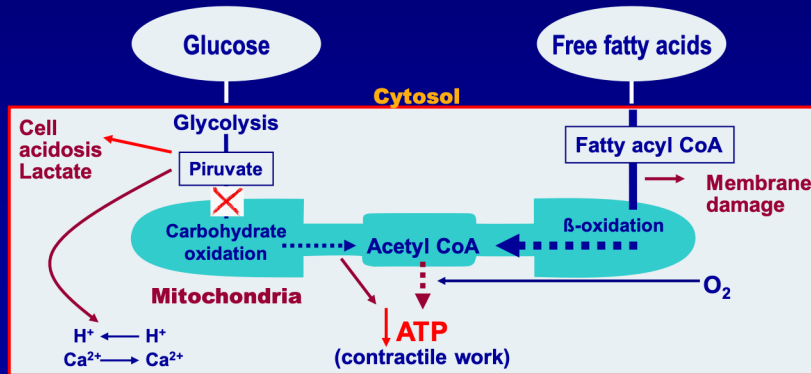
FFAs oxidation in producing ATP.



The changes that occur during increased metabolic demands also occur during ischemia or in patients with diabetes mellitus where there is a shift towards greater glucose utilisation, but free fatty acid utilisation is still around 50%.

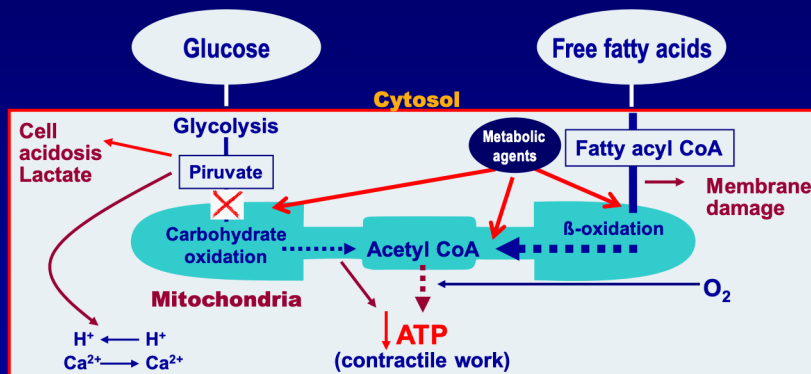
## Metabolic changes during chronic ischemia and diabetes

- ▶ Impaired capacity for glucose uptake and glycolysis
- ▶ Decrease in carbohydrate oxidation
- ▶ Increased FFA oxidation



The “Metabolic” antianginal drugs optimizing fatty acid metabolism induce a shift from free fatty acid towards glucose utilisation thereby increasing energy production for a given amount of oxygen.

## Sites of action of metabolic agents



## Classification of myocardial metabolic agents

- **FFA uptake inhibitors**

**Perhexiline**

**Oxfenicine**

**Etmoxir**

- **FFA  $\beta$ -Oxidation inhibitors**

**Trimetazidine**

- **Others**

**D-Ribose**

**Propionyl-L-Carnitine**

**Glucagon-like Peptide-1**

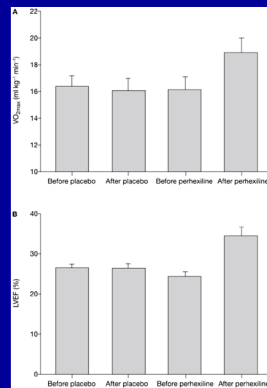
Only few substances proven effective in modulating cardiac metabolism are commercially available. Of these the only two drugs that have been shown to improve myocardial ischemia are parexhelline and trimetazidine

## Modulators of Cardiac Metabolism

|                 | Metabolic effect at pharmacological doses | Anti-ischemic effect | Major SE       | Marketed  |
|-----------------|---|----------------------|----------------|-----------|
| Trimetazidine   | FFA inhibitor                             | ++++                 | GI             | Worldwide |
| Perhexiline     | CPI inhibitor                             | +++                  | Liver toxicity | Australia |
| Etomoxir        | CPI inhibitor                             | ----                 | LVH, Lymphoma  | No        |
| Niacin          | Uptake inhibitor                          | ----                 |                | Worldwide |
| Ranolazine      | None                                      | +---                 | QT, Liver      | US        |
| Dichloroacetate | Inhib PDH kinase                          | +++                  |                | No        |

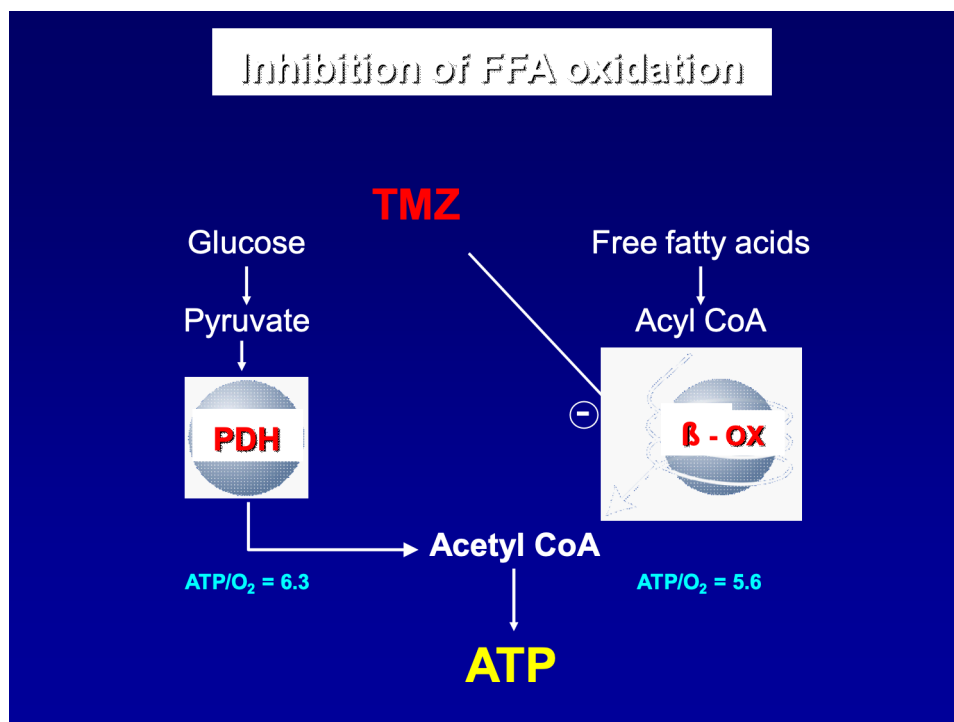
**Trimetazidine and Perhexiline are the only two metabolic agents with proven anti-ischemic effect**

## Effect of perhexiline treatment in patients with ischemic or nonischemic heart failure



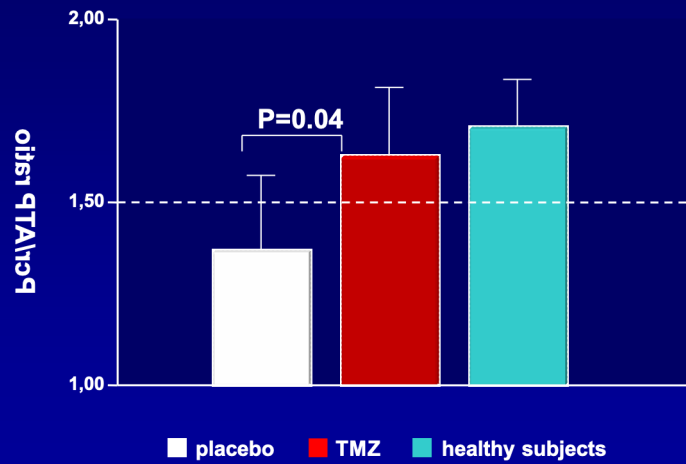
Reproduced from Lee L *et al.* (2005) Metabolic modulation with perhexiline in chronic heart failure: a randomized controlled trial of short-term use of a novel treatment. *Circulation* 112: 3280–3288. © (2005) Lippincott, Williams & Wilkins.

Trimetazidine has been shown to modulate cardiac metabolism through an inhibition of beta-oxidation at the 3-KAT enzyme. The inhibition of FFA oxidation leads to a greater use of glucose and glycogen as energy substrate with a greater mechanical efficiency during ischemia.



The metabolic effect of trimetazidine on myocardial energy production has been recently proven in vivo by Fragasso et al who showed that in patients with coronary artery disease trimetazidine normalizes the PCr/ATP (Phosphocreatine/ATP).

## Effect of Trimetazidine on PCr/ATP ratio in patients with CVD

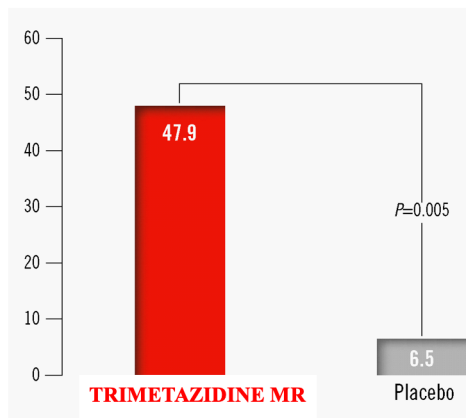


Fragasso G, et al. Eur Heart J 2006;27: 942-948

Trimetazidine is an effective anti-ischemic agent and several studies have shown that trimetazidine significantly prolongs both time to 1 mm ST depression and exercise time in patients with myocardial ischemia.

## Anti-ischemic Effect of Trimetazidine

Change in time to 1-mm ST-segment depression

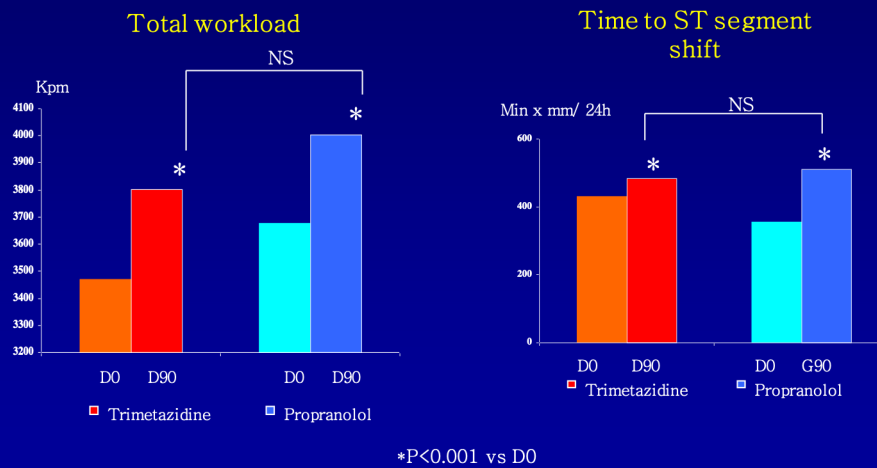


Sellier P et al. Cardiovasc Drugs Ther. 2001;15 :81.

Trimetazidine has been shown to have an anti-ischemic effect similar to that of beta-blockers.



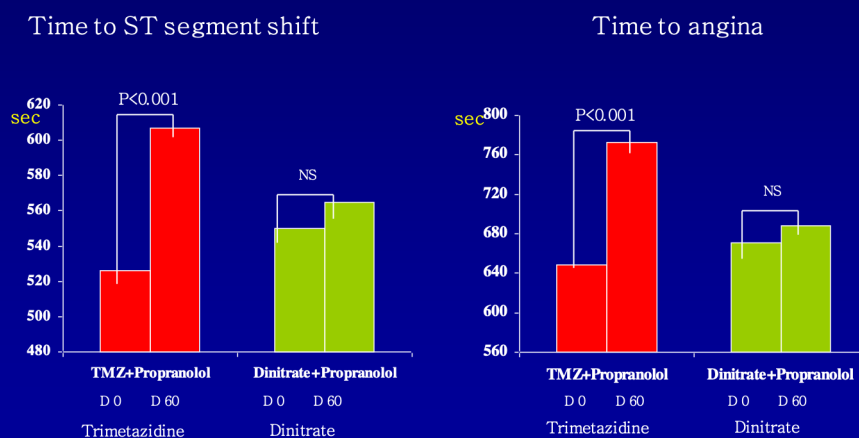
## Trimetazidine vs B-blockers



Detry JM et al, Br J clin Pharmac 1994; 37: 279-288

Conversely to nitrates and calcium channel blockers, Trimetazidine has been shown to improve time to 1 mm ST depression and exercise time in patients on background therapy with beta-blockers.

## Effect of Trimetazidine or Nitrates in Patients with Positive ETT despite B-blockers

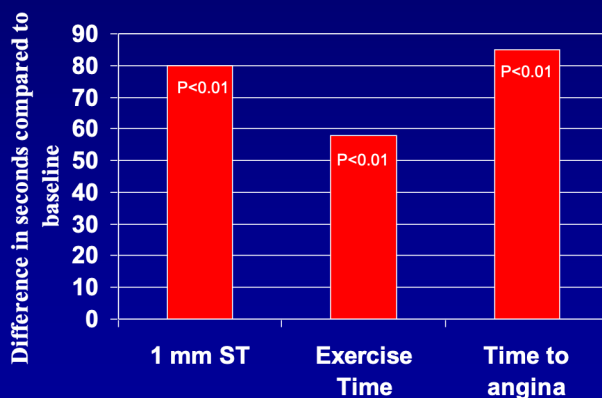


Michaelides A P et al. Clin Drug Invest 1997; 13 (1): 8 - 14

Trimetazidine has been shown to improve symptoms in patients with ischemic heart disease and in patients with resistant and recurrent angina.

## Efficacy of trimetazidine in patients with recurrent angina: a subgroup analysis of the TRIMPOL II study

To assess the efficacy of trimetazidine in the subpopulation of 94/426 patients with a history of PTCA or CABG, who were included in the TRIMPOL II study.



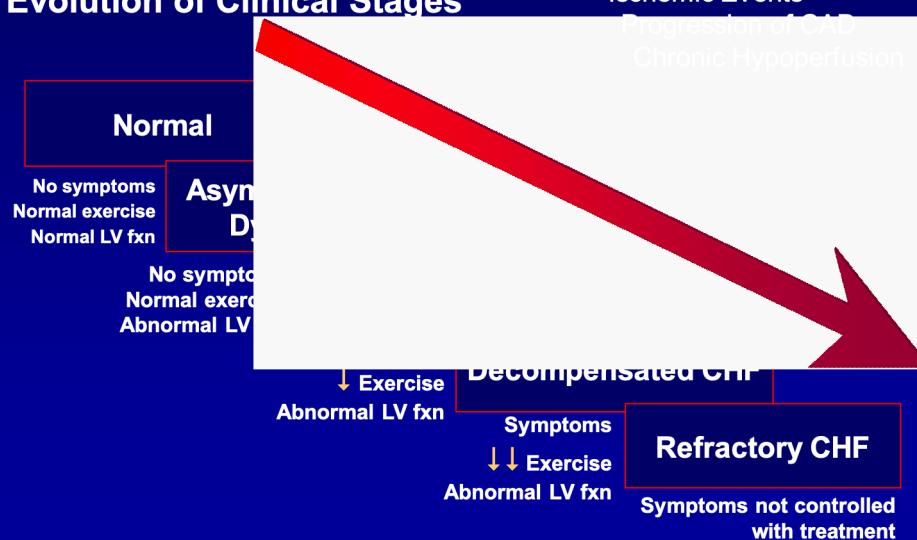
Curr Med Res Opin. 2004 Sep;20(9):1447-54

Further to the anti-ischemic effect, modulation of cardiac metabolism may represent an alternative approach to the treatment of ischemic and diabetic heart failure. Patients with ischemic heart disease and those with diabetes often develop left ventricular dysfunction because of the progression of coronary artery disease, chronic hypoperfusion and occurrence of new ischemic episodes.

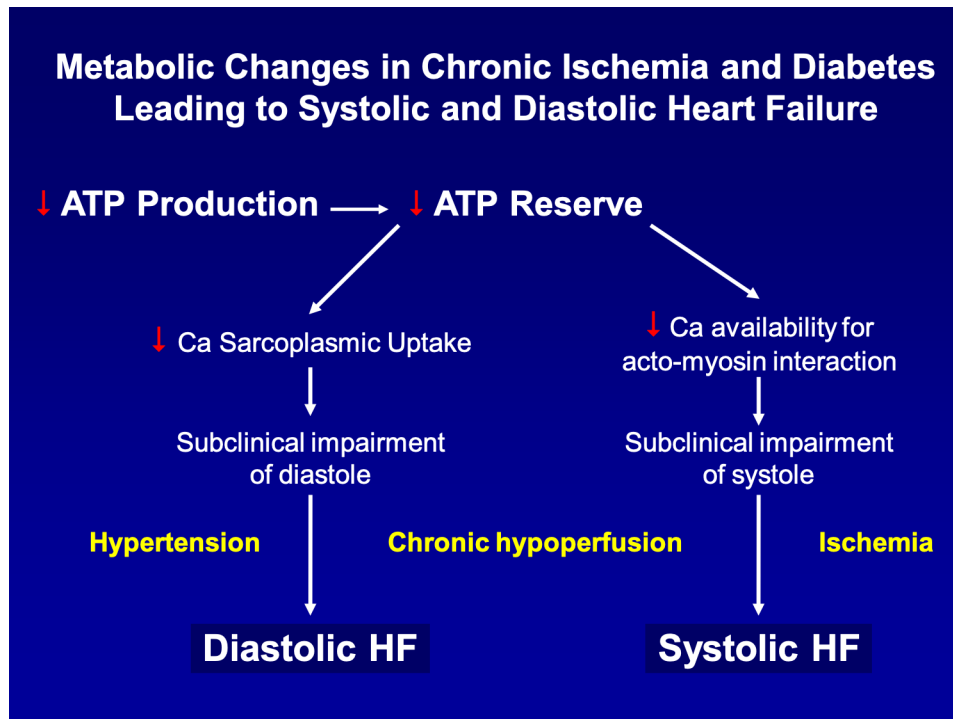
## Ischemic Heart Failure

### Evolution of Clinical Stages

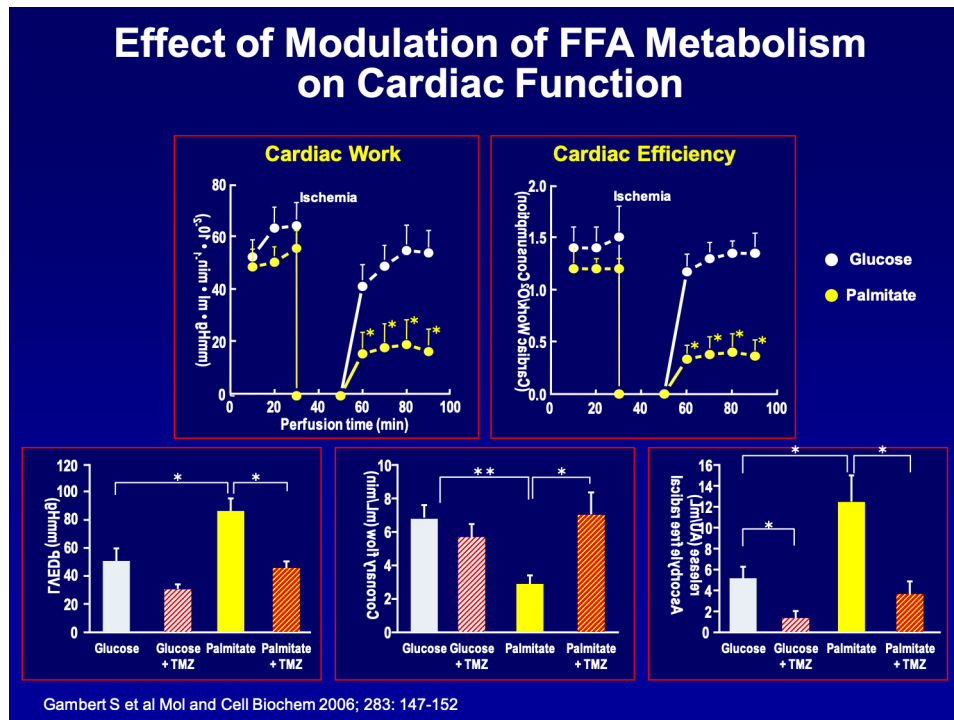
### Ischemic Events



The metabolic and functional effects of metabolic agents in the settings of heart failure is of particular relevance in patients with diabetes mellitus in whom glucose metabolism is impaired and myocardial metabolism is shifted towards a preferential utilization of fatty acids. Because of the preferential promotion of glucose and pyruvate oxidation, the improvement of glucose metabolism leads to an improved contractility and to an increased activity of the sodium-potassium ATPase and the calcium uptake pump of the sarcoplasmic reticulum, that are respectively responsible of left ventricular systolic depolarization and diastolic relaxation.



Studies on isolated and perfused hearts have shown that after coronary artery ligation, if the heart is perfused with fatty acids there is a modest recovery of left ventricular function while if glucose is used in the perfusate there is a prompt recovery of left ventricular function, thereby suggesting that glucose metabolism is more efficient for the recovery of left ventricular function after ischemia.



The metabolic effect of improved myocardial glucose metabolism modulation translates into a reduced total ischemic burden and into a better utilization of metabolic substrates that translates into a greater mechanical efficiency.

Intracoronary pyruvate was shown to acutely increase stroke volume and reduce pulmonary capillary wedge pressure, implying acute beneficial effects of a shift away from fatty acid metabolism in patients with heart failure. This finding drove interest in the potential beneficial effects of modifying substrate utilisation in chronic heart failure. A number of pharmacological agents have been shown to inhibit FFA utilisation in the heart, some of these agents have been tested in clinical trials.

As mentioned, Perhexiline is a reversible inhibitor of both CPT1 and CPT2 which are key enzymes involved in the transport of free fatty acids into the mitochondria. Perhexiline is used as antianginal agent, improves exercise tolerance, and ischemic threshold. Its use however is limited because of hepatotoxic effects and peripheral neuropathy. The risk of toxic effects is virtually eliminated by maintaining plasma concentrations at between 150 and 600 ng/ml, at this level the drug also remains efficacious. Perhexiline has been shown in a double-blind, randomized, placebo-controlled trial, to have shown short-term beneficial effects of in patients with ischemic or non-ischemic heart failure.

Oxfenicine is an irreversible inhibitor of carnitine palmitoyltransferase I (CPT1). Oxfenicine has been shown to delay development of terminal heart failure, attenuate adverse hemodynamic changes, prevent wall thinning. No human studies have been reported with use of Oxfenicine in heart failure.

Etomoxir an irreversible inhibitor of CPT1 introduced as an antidiabetic drug. In humans, a 3-month, open-label, trial in 10 patients with NYHA class II–III heart failure, etomoxir treatment in addition to standard therapy significantly improved left ventricular ejection fraction, cardiac output at peak exercise, and clinical status. Subsequently, a large randomized placebo controlled study was terminated prematurely because of the development of significant hepatotoxicity.

$\beta$ -adrenoreceptor blockade improves left ventricular function and prognosis in patients with heart failure. Wallhaus et al. demonstrated that carvedilol in patients with heart failure caused a 57%

reduction in myocardial free fatty acid uptake. In another study, Al-Hesayen and colleagues showed that after 4 months of carvedilol therapy, myocardial lactate consumption was increased and myocardial uptake of free fatty acids in patients with chronic heart failure was reduced. This suggests that carvedilol therapy may cause a significant shift in myocardial substrate use from free fatty acids to glucose. The effect does not seem to be related to an ancillary property of carvedilol but seems to be related to the metabolic changes of beta blockade on cardiac metabolism and therefore shared by most beta-blockers

Trimetazidine is the metabolic agent with the largest clinical evidence in heart failure. In a double-blind, placebo-controlled trial involving 47 patients with coronary artery disease and a reduced left ventricular function, limited by angina but not by heart failure, trimetazidine therapy improved left ventricular systolic and diastolic function and quality of life. A number of other studies also demonstrated benefits with Trimetazidine. Di Napoli et al demonstrated in an 18 months, open-label study a significant improvement in left ventricular function and survival in patients with ischemic cardiomyopathy with reduced left ventricular ejection fraction. Our group demonstrated improvements in left ventricular ejection fraction among patients with diabetes and coronary heart disease, and in elderly patients with ischemic left ventricular dysfunction all with a mean left ventricular function <35%. Fragasso et al demonstrated in patients with both ischaemic and non-ischaemic cardiomyopathy increase in LVEF and NYHA class with the use of Trimetazidine.

Ranolazine has been shown to be a partial inhibitor of fatty acid  $\beta$  oxidation [91;92], but this has not been reliably replicated in large experimental or human studies and is not present at therapeutic doses. The exact mechanism of action of this drug is at the present largely unknown although it has been suggested that ranolazine reduces sodium entry into ischemic myocardial cells and, therefore, is thought to indirectly reduce calcium uptake via the sodium–calcium exchanger, to preserve ionic

homeostasis. The drug has some anti-anginal properties but this issue is still controversial. So far there have been no studies looking at the effects of ranolazine in humans with chronic heart failure. There are reports that the drug prolongs the QT interval on electrocardiograms. This effect raises concerns about possible complications such as torsade de pointes polymorphic ventricular tachycardia and sudden cardiac death. Therefore, the long-term safety of ranolazine needs further investigations.

Glucagon-like peptide-1 (GLP-1) is an incretin that increases myocardial glucose uptake. In a dog model of heart failure, GLP-1 improved LV function and systemic haemodynamics. In small open label study, chronic infusion of GLP-1 significantly improved left ventricular function, functional status, and quality of life in patients with severe heart failure.

D-Ribose increases ATP production by entering the pentose phosphate pathway and bypassing rate limiting steps of glycolysis.

In a prospective, double blind, randomised, cross over design study, Omran et al showed an improvement in quality of life and diastolic function with ribose supplementation in patients with ischaemic cardiomyopathy.

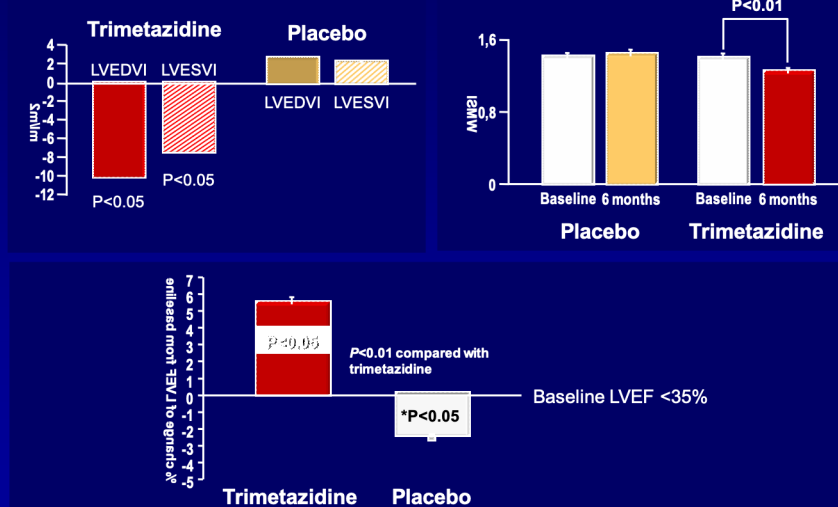
It is well known that carnitine deficiency may cause heart failure. Carnitine is an important co-factor in intermediary metabolism of the myocardium which improves utilisation of pyruvate in Krebs cycle. Studies with carnitine supplementation have shown mixed results.

| Metabolic Agent      | Author                                   | Study design                    | No Patient | Patient Characteristics   | Study duration | Outcome  |
|----------------------|--|---------------------------------|------------|---|----------------|--|
| <b>Perhexiline</b>   | Lee <i>et al</i> 2005                    | RC PCT*<br>D o u b l e<br>blind | 56         | EF $\leq$ 45<br>Non-ischemic and<br>Ischemic CHF<br>NYHA II-IV            | 2 months       | LVEF<br>V <sub>o2</sub> max<br>Improved quality<br>of life (QOL) |
| <b>Trimetazidine</b> | Vitale <i>et al</i> 2004                 | RC PCT                          | 47         | EF< 40%<br>Chronic stable angina<br>NYHA I-III                            | 6 months       | ↑ LVEF<br>Better QOL<br>Improved event<br>free survival          |
| <b>Trimetazidine</b> | Di Napoli <i>et al</i> 2005,<br>2007     | Open label                      | 61         | LVEF <40%<br>Ischeamic LV dysfunction<br>NYHA II-IV                       | 18 months      | ↑ LVEF<br>Improved –<br>NYHA<br>Improved event<br>free survival  |
| <b>Trimetazidine</b> | Fragasso<br>G <i>et al</i> 2006          | Open label                      | 55         | LVEF<45%<br>Ischaemic and Non-<br>ishchaemic CHF<br>NYHA II-III           | 13 months      | ↑ LVEF<br>Improved -<br>NYHA                                     |
| <b>Trimetazidine</b> | Rosano<br>G <i>et al</i> 2003            | RC PCT                          | 86         | EF< 40%<br>Chronic stable angina<br>NYHA I-III                            | 6 months       | ↑ LVEF<br>Better QOL<br>Improved<br>glucose tolerance            |
|                      | Fragasso<br>G <i>et al</i> 2003          | RC PCT                          | 61         |   | 3 months       |  |
| <b>Etomoxir</b>      | Schmidt-<br>Schweda<br><i>et al</i> 2000 | Open label                      | 10         | LVEF<40%<br>Dilated Cardiomyopathy<br>NYHA II-III                         | 3 months       | ↑ LVEF<br>Increased Stroke<br>volume during<br>exercise          |
| <b>Etomoxir</b>      | Holubars<br>ch CJ <i>et al</i> 2007      | RC PCT                          | 350        | LVEF<40%<br>Ischaemic and Non-<br>ischaemic moderate CHF<br>NYHA II-III   | 6 months       | Study stopped<br>prematurely<br>because of<br>hepatotoxicity.    |
| <b>D-Ribose</b>      | Omran<br><i>et al</i> 2003               | RC PCT<br>Cross over            | 15         | Ischaemic Cardiomyopathy<br>NYHA II-III                                   | 3 weeks        | Improved<br>functional<br>capacity and<br>diastolic function     |
| <b>L-Carnitine</b>   | Anand<br><i>et al</i> 1998               | RC PCT<br>S i n g l e<br>blind  | 30         | LVEF<40%<br>NYHA II-III<br>Ischaemic and non-<br>ischaemic cardiomyopathy | 4 weeks        | ↑ VO <sub>2</sub> max<br>No change in<br>LVEF                    |



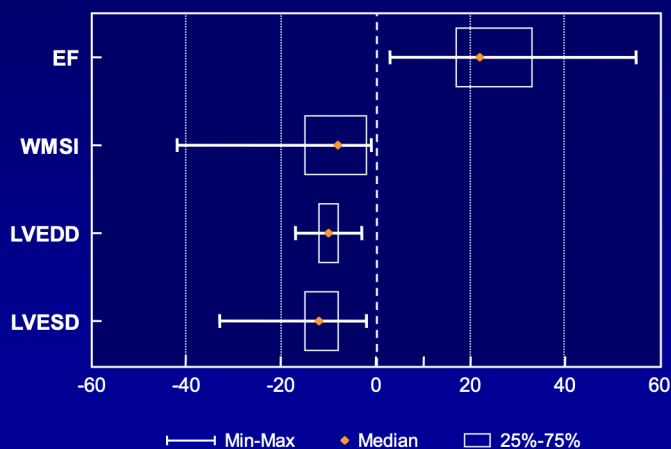
|                                |                         |            |    |             |         |                      |
|--------------------------------|-------------------------|------------|----|-------------|---------|----------------------|
| <b>Glucagon-like Peptide 1</b> | Sokos <i>et al</i> 2006 | Open label | 12 | NYHA III-IV | 5 weeks | LVEF<br>Improved QOL |
|--------------------------------|-------------------------|------------|----|-------------|---------|----------------------|

## Effect of Trimetazidine on LV Function in Type II Diabetic Patients with Ischemic Cardiomyopathy



Rosano G et al *Cardiovascular Diabetology* 2003; 2:16-24

## Effect of Trimetazidine Elderly Patients with Ischemic Cardiomyopathy



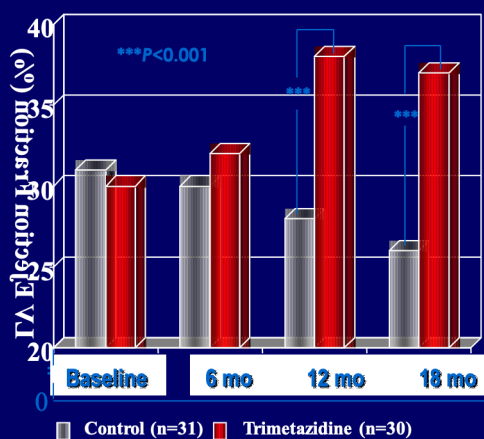
Vitali C et al. Eur Heart J 2004; 25:181-182

## Long-term Treatment with Trimetazidine Improves LV Function in Patients with ICM

61 CAD patients with dilated ICM (previous MI) and LVEF < 40%

Open label design. Pts. randomized to 18-month trimetazidine (20 mg tds) added to conventional treatment, or conventional treatment alone

**LV function (EF) assessed by echocardiography**

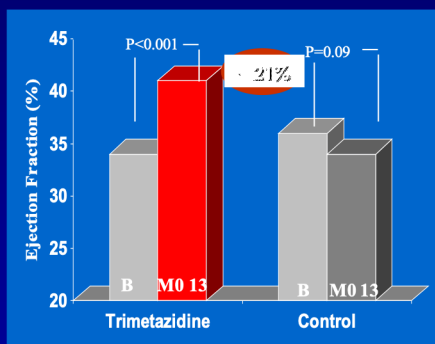


Di Napoli P, Taccardi AA, Barsotti A. Heart 2005; 91: 161-165

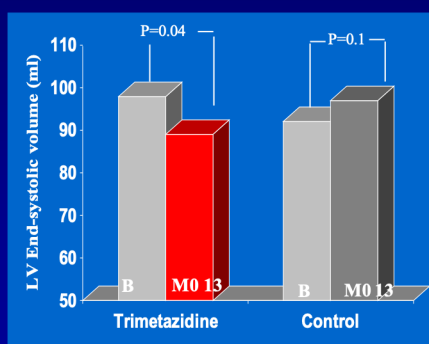
## Benefits of trimetazidine in heart failure

Long term treatment with Trimetazidine improves LV function

### ◆ LV Ejection Fraction



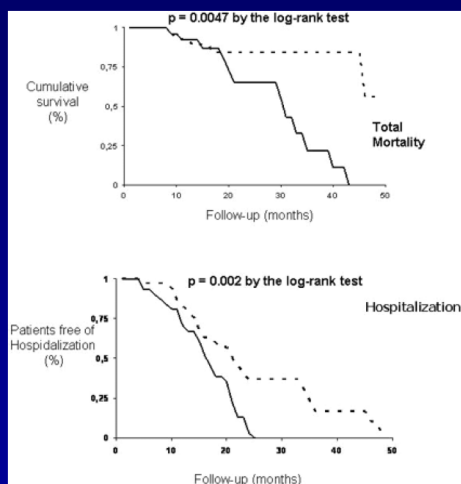
### ◆ LV end-systolic volume



A significant decrease in NYHA class ( $p<0.0001$ ) has also been observed

G Fragasso, et al. JACC 2006;48;992-998

## Effect of Metabolic Therapy in Heart Failure



Di Napoli et al. Circulation 2007; 116:331-334.

*“The heart is more than a pump. It is also an organ that needs energy from metabolism.*

*A metabolic disease, ischemia, should ideally be treated by metabolic therapy”*

*L. Opie*