Myocardial Substrate Metabolism in the Normal and Failing Heart

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Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, Ohio; Scuola Superiore Sant'Anna, Pisa, Italy; Department of Physiology, New York Medical College, Valhalla, New York; and Department of Pediatrics, University of Alberta, Edmonton, Canada

Stanley, William C., Fabio A. Recchia, and Gary D. Lopaschuk. Myocardial Substrate Metabolism in the Normal and Failing Heart. *Physiol Rev* 85: 1093–1129, 2005; doi:10.1152/physrev.00006.2004.—The alterations in myocardial energy substrate metabolism that occur in heart failure, and the causes and consequences of these abnormalities, are poorly understood. There is evidence to suggest that impaired substrate metabolism contributes to contractile dysfunction and to the progressive left ventricular remodeling that are characteristic of the heart failure state. The general concept that has recently emerged is that myocardial substrate selection is relatively normal during the early stages of heart failure; however, in the advanced stages there is a downregulation in fatty acid oxidation, increased glycolysis and glucose oxidation, reduced respiratory chain activity, and an impaired reserve for mitochondrial oxidative flux. This review discusses *1*) the metabolic changes that occur in chronic heart failure, with emphasis on the mechanisms that regulate the changes in the expression of metabolic genes and the function of metabolic pathways; *2*) the consequences of these metabolic changes on cardiac function; *3*) the role of changes in myocardial substrate metabolism on ventricular remodeling and disease progression; and *4*) the therapeutic potential of acute and long-term manipulation of cardiac substrate metabolism in heart failure.

I. INTRODUCTION

Cardiovascular disease is the leading cause of death and disability in the industrialized world, and although there has been a reduction in mortality from acute myocardial infarction over the last 30 years (215), there has been a concomitant rise in mortality attributable to heart failure (HF). The syndrome of HF was described by Hippocrates over two millennia ago and presented as shortness of breath and peripheral edema (214, 215). Autopsies performed in the 17th and 18th centuries revealed an enlarged ventricular chamber and increased heart mass in

HF patients (215). In the last century a myriad of structural and biochemical cardiac abnormalities were shown to be associated with HF, from defects in mitochondria to abnormal adrenergic signal transduction. At the end stages of HF, the myocardium has low ATP content due to a decreased ability to generate ATP by oxidative metabolism, and thus is unable to effectively transfer the chemical energy from the metabolism of carbon fuels to contractile work (12, 98, 213, 341). The consequences of metabolic dysfunction in HF are poorly understood, but there is growing evidence to support the concept that the alterations in substrate metabolism seen in HF contribute to contractile dysfunction and to the progression of left ventricular (LV) remodeling that are characteristic of the HF state.

Today HF is clinically defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" (179). Heart failure severely reduces exercise capacity and may or may not cause fluid retention and pulmonary congestion. Many HF patients have minimal edema or pulmonary congestion, thus the term *heart failure* is preferred over the older term *congestive heart failure* (179). Approximately two-thirds of all HF patients have a history of ischemic heart disease, and the remainder do not (215). HF presents as both systolic and diastolic LV dysfunction, with diastolic dysfunction being more common in a patient with a history of hypertension and/or diabetes in the absence of myocardial ischemia (6, 14, 117). Current medical therapies for HF are aimed at suppressing neurohormonal activation (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, β-adrenergic receptor antagonists, and aldosterone receptor antagonists), and treating fluid volume overload and hemodynamic symptoms (diuretics, digoxin, inotropic agents). These pharmacotherapies for HF can improve clinical symptoms and slow the progression of contractile dysfunction and expansion of LV chamber volume; nevertheless, there is still progression, and the prognosis for even the optimally treated patient remains poor (39, 63, 67). Moreover, there is recent evidence that intense suppression of the neurohormonal systems does not provide further benefit compared with more modest therapy (64, 385, 444). Thus there is a need for novel therapies for HF, independent of the neurohormonal axis, that can improve cardiac performance and prevent or reverse the progression of LV dysfunction and remodeling (38, 116, 381, 452).

Agents that act through optimization of cardiac substrate metabolism are particularly attractive because they could work additively with current therapies, while not exerting negative hemodynamic effects (38, 116, 381, 431). Emerging evidence suggests that disturbances in myocardial substrate utilization have adverse effects in the failing myocardium (212, 213) and that shifting the substrate preference of the heart away from fatty acids towards carbohydrate oxidation can improve pump function and slow the progression of HF (23, 27, 28, 38, 53, 116, 428). Almost a century ago the observation was made that acute ingestion of cane sugar relieved symptoms in patients with cardiac dysfunction, presumably of ischemia origin (45, 140). The optimization of cardiac substrate metabolism to improve cardiac function and slow progression in HF, without causing any direct negative hemodynamic or inotropic effects, remains a conceptually attractive therapeutic approach (38). To date, the role of myocardial substrate metabolism in the natural history of HF has not been thoroughly evaluated. Human, canine, and rodent studies show that in late-stage failure there is downregulation of myocardial fatty acid oxidation and accelerated glucose oxidation (79, 332, 359, 362, 389). However, the time course and the molecular mechanisms for this switch in substrate oxidation are not well understood (251, 388, 428).

It is important to keep in mind that HF is not a specific disease, but rather an extremely complex syndrome that is dependent on etiology, duration, underlying coronary artery disease and ischemia, endothelial dysfunction, and the co-occurrence of complicating disorders such as diabetes, hypertension, and obesity. In Europe and North America, ~20–30% of HF patients are diabetic, which in itself greatly alters myocardial substrate use (434, 449, 510) and affects the development of HF and LV remodeling after myocardial infarction (424). There is tremendous heterogeneity among the published data from patients and animals models of HF that may be attributed to the etiology, severity, and duration of HF and, in the case of animal models, the species studied. Moreover, studies in animal models demonstrate that the changes in myocardial metabolism and cardiac function often occur late in the development of HF. Thus one must use caution in drawing generalities from a single time point or from a single animal model. In addition, within a given failing heart there is likely gross and micro heterogeneity in the metabolic changes within the LV.

Despite these caveats and limitations, it remains of fundamental importance to identify the abnormalities in myocardial substrate metabolism that occur over the course of the development and progression of HF, and to understand the impact they have on left ventricular function and remodeling. This review discusses *1*) the metabolic changes that occur in chronic HF, with emphasis on the mechanisms that regulate the changes in the expression of metabolic genes and the function of metabolic pathways; *2*) the consequences of these changes on cardiac function; *3*) the role of changes in myocardial substrate metabolism in ventricular remodeling and disease progression; and *4*) the therapeutic potential of acute and long-term manipulation of cardiac energy metabolism in HF.

It is important to note that this review focuses on myocardial substrate metabolism in HF, and not on the well-documented HF-induced abnormalities in the transfer of energy from mitochondrial ATP to systolic and diastolic work. The reader is referred to recent reviews on this topic (98, 190, 477).

II. OVERVIEW OF MYOCARDIAL SUBSTRATE METABOLISM

To understand myocardial metabolism in HF, it is important to first have a solid understanding of myocardial metabolism in the normal heart and to understand the complex pathophysiology of HF. The reader is referred to textbooks and reviews on myocardial metabolism (270, 331, 433, 448, 473) and the pathophysiology of HF (215).

A. Regulation of Metabolic Pathways in the Heart

Under nonischemic conditions almost all (>95%) of ATP formation in the heart comes from oxidative phosphorylation in the mitochondria (Fig. 1), with the remainder derived from glycolysis and GTP formation in the citric acid cycle. The heart has a relatively low ATP content (5 μmol/g wet wt) and high rate of ATP hydrolysis (~0.5 μmol $\cdot$ g wet wt^{-1} $\cdot$ s^{-1} at rest), thus there is complete turnover of the myocardial ATP pool approximately every 10 s under normal conditions (188, 331). Approximately 60–70% of ATP hydrolysis fuels contractile shortening, and the remaining 30–40% is primarily used for the sarcoplasmic reticulum Ca^{2+}-ATPase and other ion pumps (128, 440). In the healthy heart the rate of oxidative phosphorylation is exquisitely linked to the rate of ATP hydrolysis so that ATP content remains constant even with large increases in cardiac power (17, 18, 153), such as occur during intense exercise or acute catecholamine stress. Mitochondrial oxidative phosphorylation is fueled with energy from electrons that are transferred from carbon fuels by dehydrogenation reactions that generate NADH and FADH$_2$ produced primarily in the fatty acid β-oxidation pathway, the citric acid cycle, and to a lesser extent from the pyruvate dehydrogenase reaction

and glycolysis (Figs. 1 and 2). There is a stoichiometric link between the rate of oxidation of carbon fuels, NADH and FADH$_2$ reduction, flux through the electron transport chain, oxygen consumption, oxidative phosphorylation, ATP hydrolysis, actin-myosin interaction, and external contractile power produced by the heart (Figs. 1 and 2). Thus an increase in contractile power results in a concomitant increase in all of the components in the system.

The regulation of myocardial metabolism is linked to arterial carbon substrate concentration, hormone concentrations, coronary flow, inotropic state, and the nutritional status of the tissue (331, 433, 448). The citric acid cycle is fueled by acetyl-CoA formed from decarboxylation of pyruvate and from β-oxidation of fatty acids (Fig. 2). The reducing equivalents (NADH and FADH$_2$) that are generated by either the dehydrogenases of glycolysis, the oxidation of lactate and pyruvate and fatty acid β-oxidation, or the citric acid cycle deliver electrons to the electron transport chain, resulting in ATP formation by oxidative phosphorylation. 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.

The rates of flux through the various metabolic pathways are controlled by both the degree of expression of key metabolic proteins (enzymes and transporters) and complex pathway regulation that is exerted by both allosteric regulation of enzymes and substrate/product relationships. The metabolic machinery in the heart is designed to generate large amounts of ATP to support high rates of external cardiac power. At maximal cardiac work loads in vivo this metabolic machinery consumes oxygen at 80–90% of the mitochondrial capacity for electron transport chain flux and oxygen consumption (315). At rest, however, the heart operates at ~15–25% of its maximal oxidative capacity, thus the expression or maximal activity of a key metabolic enzyme can be greatly reduced or increased without necessarily affecting ATP production or flux through the relevant pathway under resting conditions (106, 107). This is because flux through metabolic pathways can be rapidly turned on or off by allosteric modification of regulatory enzymes, changes in the
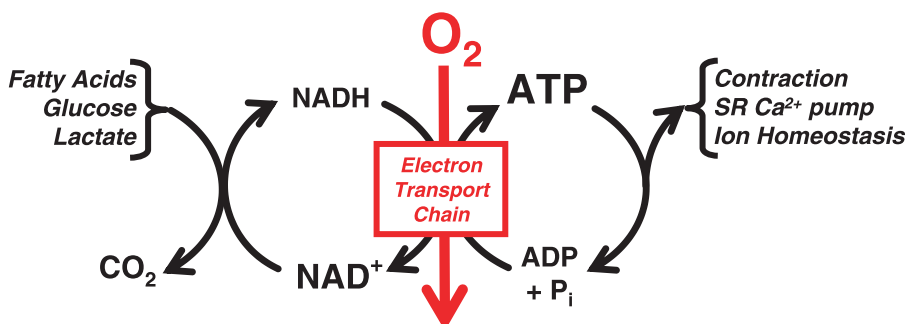

FIG. 1. Linkages between cardiac power, ATP hydrolysis, oxidative phosphorylation, and NADH generation by dehydrogenases in metabolism. SR, sarcoplasmic reticulum.
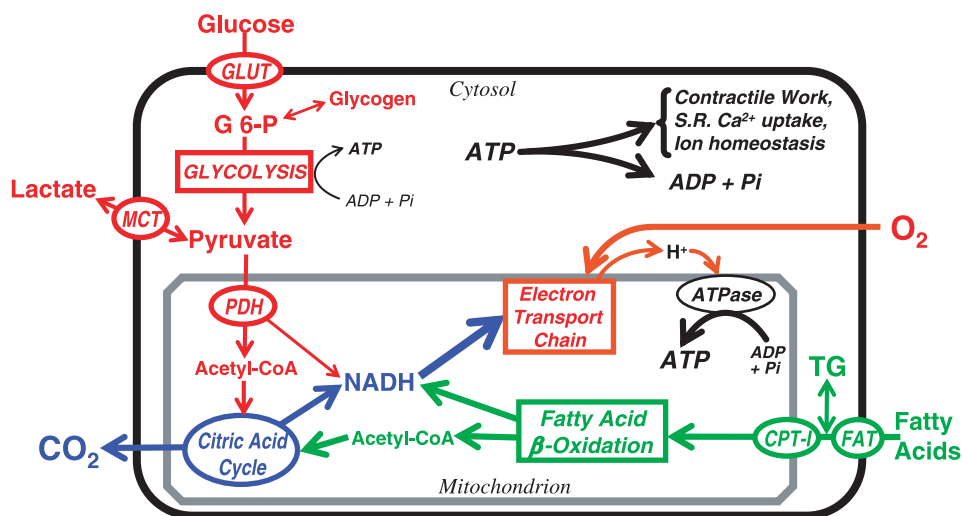
FIG. 2. The pathways and regulatory points of myocardial substrate metabolism. CPT-I, carnitine palmitoyltransferase-I; FAT, fatty acid transporter/CD36; G 6-P, glucose 6-phosphate; GLUT, glucose transporters; MCT, monocarboxylic acid transporters; PDH, pyruvate dehydrogenase.

concentration of inhibitory or stimulatory metabolites, or translocation of metabolic proteins to their site of function. These mechanisms allow for the rapid adaptation to acute stresses such as exercise, ischemia, or fasting.

B. Carbohydrate Metabolism

In the well-perfused heart, $\sim60-90\%$ of the acetyl-CoA comes from β-oxidation of fatty acids, and $10-40\%$ comes from the oxidation of pyruvate (126, 433, 492, 493, 495) that is derived in approximately equal amounts from glycolysis and lactate oxidation (126, 433, 492, 493, 495). The glycolytic pathway converts glucose 6-phosphate and 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 CO_2 and NAD^+ and complete the process of aerobic oxidative glycolysis or converted to lactate and NAD^+ in the cytosol (nonoxidative glycolysis).

The healthy nonischemic heart is a net consumer of lactate even under conditions of near-maximal cardiac power (204, 292, 426). 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 (85, 331, 433) or poorly controlled diabetes (15, 145, 434). There is a high rate of bidirectional lactate transmembrane flux and conversion to pyruvate (125, 141, 204, 293, 492, 493). Lactate transport across the cardiac sarcolemma is facilitated by the monocarboxylic acid transporter-1 (MCT-1) (Fig. 2; Refs. 118, 203).

Glycolytic substrate is derived from exogenous glucose and glycogen stores. Glucose transport into cardiomyocytes is regulated by the transmembrane glucose gradient and the content of glucose transporters in the sarcolemma (mainly GLUT-4, and to a lesser extent GLUT-1)

(Fig. 2). There is a translocation of glucose transporters from intracellular vesicles to the sarcolemmal membrane in response to insulin stimulation, increased work demand, or ischemia (433, 506, 507), which increases the membrane capacitance for glucose transport and the rate of glucose uptake. Translocation of GLUT-4 into the sarcolemma is also stimulated by activation of AMP-activated protein kinase (AMPK) (379, 506), which occurs during exercise stress in the rat heart (71). Mice with cardiac-specific overexpression of a dominant negative mutant of AMPK have depressed rates of glucose uptake (499), suggesting a critical role for AMPK in regulating basal glucose uptake in the heart. Russell et al. (380) recently demonstrated that transgenic mice expressing inactive AMPK have normal GLUT4 expression as well as baseline and insulin-stimulated cardiac glucose uptake, but fail to increase glucose uptake and glycolysis during ischemia (380), illustrating a key role for AMPK in mediating insulin-independent ischemia-induced glucose uptake.

An additional source of glucose 6-phosphate for the heart is intracellular glycogen stores. The glycogen pool in the heart is relatively small (~30 μmol/g wet wt compared with ~150 μmol/g wet wt in skeletal muscle) (35, 331, 429) and has a relatively rapid turnover despite stable tissue concentrations (155). Glycogen concentrations are increased by an elevated supply of exogenous substrate and/or hyperinsulinemia (235, 246, 433), and glycogenolysis is activated by adrenergic stimulation (e.g., increases in cAMP and Ca^{2+}), a fall in the tissue content of ATP, and a rise in inorganic phosphate such as occur with ischemia or intense exercise (133, 176, 433). Recently, there has been considerable interest focused on the role of AMPK in regulating glycogen content in the heart (9, 71, 499). Constitutively active AMPK due to a mutation in a regulatory subunit of the enzyme was recently shown to be associ-

ated with glycogen accumulation and hypertrophic cardiomyopathy (8, 9, 134). In contrast, acute activation of AMPK has been shown to activate glycogenolysis (267, 346). Clinically, patients with a mutation in the gamma-2 regulatory subunit of AMPK have Wolff-Parkinson-White syndrome and conduction system disease in the absence of cardiac hypertrophy (134, 135, 330), although the cellular mechanisms linking abnormal AMPK activity and the electrophysiological abnormalities are unclear.

Phosphofructokinase-1 (PFK-1) is a key regulatory enzyme in the glycolytic pathway and catalyzes the first irreversible step (Fig. 3). PFK-1 utilizes ATP to produce fructose 1,6-bisphosphate and is activated by ADP, AMP, and P_i and inhibited by ATP, thus accelerating flux through glycolysis when the phosphorylation potential falls. PFK-1 can also be inhibited by fructose 1,6-bisphosphate and by a fall in pH. The extent of $[H^+]$ inhibition of PFK-1 depends on ATP levels, with the inhibition being greatest when ATP levels are high (see Ref. 209 for review). As AMP accumulates, the sensitivity of PFK-1 to $[H^+]$ decreases. PFK-1 can also be stimulated by fructose 2,6-bisphosphate (F2,6BP), which is a feedforward activator of the enzyme (177). Citrate is a negative allosteric regulator of PFK-1 and links changes in mitochondrial oxidative metabolism to glycolysis. Accumulation of citrate was first proposed by Philip Randle to contribute to the decrease in glycolysis that occurs in various tissues when fatty acid oxidation increases (119, 325, 351, 352).

F2,6BP is a potent stimulator of PFK-1 and is formed from fructose 6-phosphate by the bifunctional enzyme phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2) (Fig. 3) (176, 177). Synthesis of F2,6BP by PFK-2 results in an activation of PFK-1. F2,6BP increases PFK-1 by increasing the affinity of the enzyme for fructose 6-phos-

phate and by decreasing the inhibitory effects of ATP on PFK-1. The production of F2,6BP itself is highly regulated (Fig. 3), with PFK-2 activity controlled by three main mechanisms: *1*) by allosteric modulation of PFK-2 activity, *2*) by phosphorylation control of PFK-2 activity, and *3*) by transcriptional control of enzyme activity (249, 368). PFK-2 is allosterically inhibited by citrate, which by decreasing F2,6BP levels is a second mechanism by which citrate can inhibit PFK-1 activity. A number of hormones that activate glycolysis, including insulin, glucagon, epinephrine, norepinephrine, and thyroid hormone, exert phosphorylation control on PFK-2 (209). In addition, AMPK can also phosphorylate PFK-2 (175, 288). Phosphorylation and activation of PFK-2 by AMPK is an attractive mechanism to explain AMP-induced acceleration of glycolysis.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyzes the conversion of glyceraldehyde 3-phosphate to 1,3-diphosphoglycerate and produces the NADH molecules that originate from glycolysis. GAPDH is a major regulatory step in the glycolytic pathway, since the accumulation of NADH within the cytoplasm of cells inhibits the GAPDH reaction rate. In contrast, an increase in NAD^+ activates GAPDH activity. High concentrations of lactate inhibit the regeneration of NAD^+ from NADH and thus reduce the flux through GAPDH, as do high concentrations of the product of the reaction, 1,3-diphosphoglycerate. During myocardial ischemia, an accumulation of lactate and NADH can result in GAPDH becoming the main rate-controlling reaction in glycolysis. For instance, severe ischemia in heart muscle will result in the cessation of oxidative metabolism, and the subsequent accumulation of NADH in the cytosol, and accumulation of lactate within the cell.

Cell fraction studies demonstrate that glycolytic enzymes are clustered near the sarcoplasmic reticulum and sarcolemma (103, 344, 486, 500), suggesting that glycolytic reactions are not distributed throughout the cytosol, but rather occur in a subdomain outside around the perimeter of the cardiomyocyte. Further support for this concept comes from in silico studies of the transition from normal to ischemic conditions, which shows that compartmentation of glycolysis to ~10% of the cytosolic space is required to simulate the burst of glycolysis that occurs with the onset of ischemia in vivo (519). Studies assessing the effect of inhibition of glycolysis suggest that glycolytically generated ATP is perferentially used by the sarcoplasmic reticulum to fuel Ca^{2+} uptake (103) and by the sarcolemma to maintain ion homeostatis (487, 488). Furthermore, inhibition of glycolysis impairs relaxation in ischemic and postischemic reperfused myocardium, suggesting that glycolytic ATP may be essential for optimal diastolic relaxation (197, 240, 486).

The pyruvate formed from glycolysis has three main fates: conversion to lactate, decarboxylation to acetyl-CoA, or carboxylation to oxaloacetate or malate. Pyru-

Fructose 6-phosphate

Citrate

H^+

ATP

Citrate

⊖

Phosphofructokinase-2

⊕ ···· *AMPK*

PKC, PKA

PI3 Kinase

Phosphofructokinase-1

⊕ ⊕

AMP
ADP
Pi

Fructose 2,6-bisphosphate
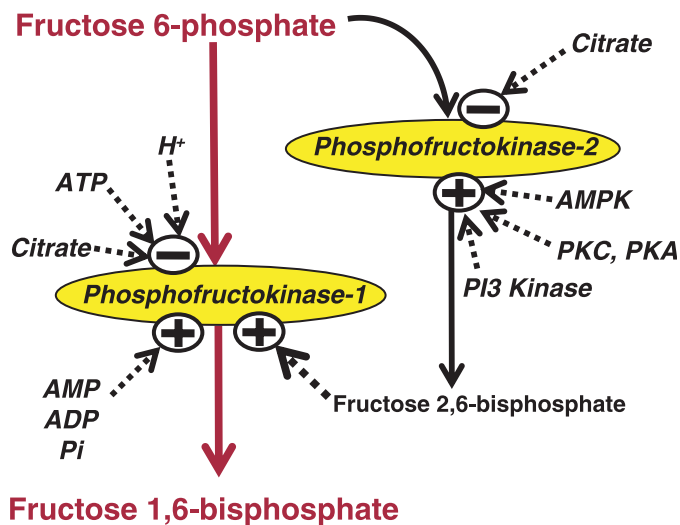
Fructose 1,6-bisphosphate

FIG. 3. Regulation of phosphofructokinase-1 (PFK-1) by PFK-2 and fructose 2,6-bisphosphate. PKA, protein kinase A; PKC, protein kinase C; PI3K, phosphatidylinositol 3-kinase.

vate decarboxylation is the key irreversible step in carbohydrate oxidation and is catalyzed by pyruvate dehydrogenase (PDH) (Fig. 4) (350), a multienzyme complex located in the mitochondrial matrix. PDH is inactivated by phosphorylation on the E_1 subunit of the enzyme complex by a specific PDH kinase (PDK) and is activated by dephosphorylation by a specific PDH phosphatase (219, 350, 355, 491) (Fig. 4). PDK is inhibited by pyruvate and by decreases in the acetyl-CoA/free CoA and NADH/NAD$^+$ ratios (219, 355, 490) (Fig. 4). There are four isoforms of PDK; PDK4 is the predominant form in heart, and its expression is rapidly induced by starvation, diabetes, and peroxisome proliferater activated receptor-α (PPARα) ligands (36, 150, 496), suggesting that its expression is controlled by the activity of the PPARα promoter system (see sect. IIIA). High circulating lipid and intracellular accumulation of long-chain fatty acid moieties, such as occur with fasting or diabetes, enhance PPARα-mediated expression of PDK4, resulting in greater phosphorylation inhibition of PDH and less oxidation of pyruvate derived from glycolysis and lactate oxidation (172, 496). The PDH complex also contains a PDH phosphatase that dephosphorylates and activates PDH. The activity of PDH phosphatase is increased by Ca^{2+} and Mg^{2+} (295). Adrenergic stimulation of the heart increases the cytosolic Ca^{2+} transient, and mitochondrial Ca^{2+} concentration results in activation of PDH (294, 296), thus explaining the activation of PDH and greater pyruvate oxidation in response to a β-adrenergic-induced increase in cardiac power (66, 126, 139, 294), despite no changes in any of the activators of PDK4 activity (416).

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. In addition, pyruvate oxidation is enhanced by suppression of fatty acid oxidation, as observed with a decreased plasma FFA levels, or by a direct inhibition of fatty acid oxidation (61, 164, 165, 235, 270, 410, 433). As discussed above, high rates of fatty acid oxidation also inhibit PFK-1 and PFK-2 (and thus glycolysis) via an increase in cytosolic citrate concentration (Fig. 4) This "glucose-fatty acid cycle" was first described by Philip Randle and colleagues in the 1960s (119, 353, 354), and thus is generally referred to as the "Randle cycle." The maximal rate of pyruvate oxidation at any given time is set by the degree of phosphorylation of PDH; however, the actual flux is determined by the concentrations of substrates and products in the mitochondrial matrix as these control the rate of flux through the active dephosphorylated complex (148).

In addition to lactate formation and oxidation by PDH, pyruvate enters the citric acid cycle (CAC) via carboxylation to either malate or oxaloacetate (442). This reaction is "anaplerotic" (127, 231) and acts to maintain the pool size of CAC intermediates and CAC function in the face of the small but constant loss of CAC intermediates through efflux of citrate and, to a lesser extent, succinate and fumarate from the heart (55, 69, 102, 244, 456, 458, 479). Pyruvate carboxylation accounts for $\sim$2–6% of the CAC flux under normal flow aerobic conditions (69, 336), and it is reduced relative to CAC flux when $M\dot{V}O_2$ is reduced in acutely hibernating swine myocardium (335). Another source of anaplerotic flux into the CAC is via transamination of glutamate to α-ketoglutarate, as demonstrated by the low but persistent uptake of glutamate in the human heart (318, 457–459). Studies using ^{13}C-labeled glutamate in perfused rat hearts suggest that conversion to α-ketoglutarate may be critical for the
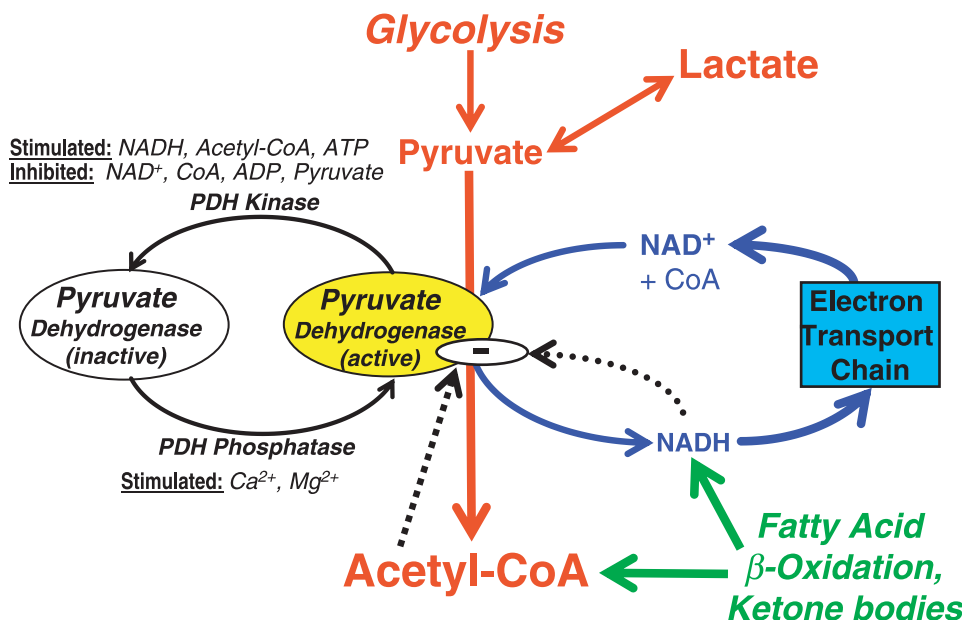

FIG. 4. Regulation of the oxidation of glucose and lactate by pyruvate dehydrogenase (PDH). The activity of PDH is inhibited by product inhibition from acetyl-CoA and NADH (dashed arrows), and by phosphorylation by PDH kinase and dephosphorylation by PDH phosphatase.
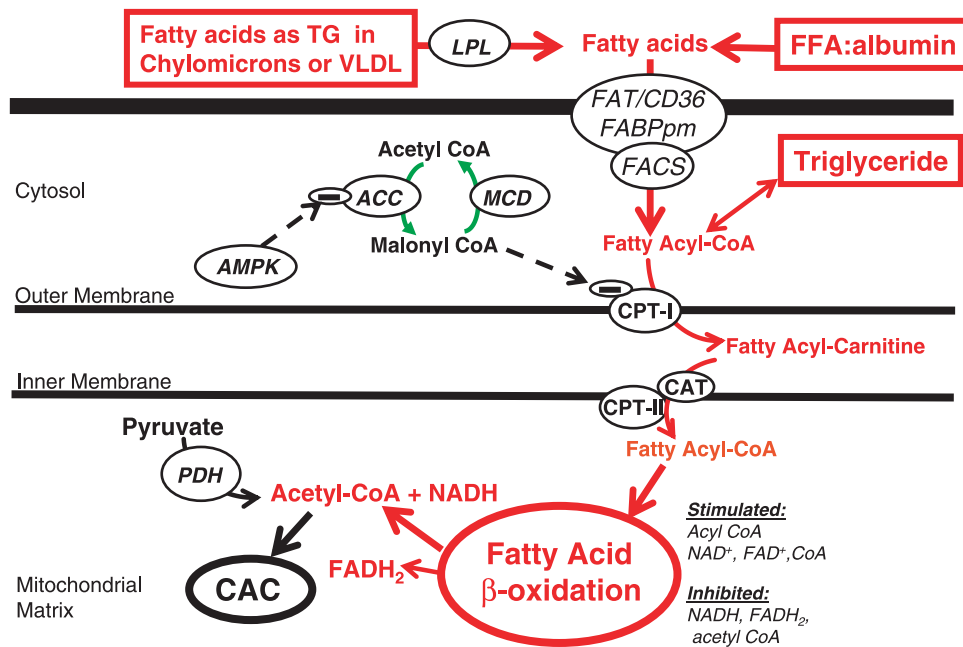
FIG. 5. Schematic depiction of myocardial fatty acid metabolism. ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; CAT, carnitine acyltranslocase; CPT-I, carnitine palmitoyltransferase-I; CPT-II, carnitine palmitoyltransferase-II; FABP$_{PM}$, plasma membrane fatty acid binding protein; FAT, fatty acid transporter; FFA, free fatty acids; LPL, lipoprotein lipase; MCD, malonyl-CoA decarboxylase; TG, triglyceride; VLDL, very-low-density lipoproteins.

regulation of the initial span of the CAC, particularly during ischemia (68). Another anaplerotic pathway is the formation of succinyl-CoA from propionyl-CoA that is generated from the terminal three carbons of odd chain length fatty acids (127, 258, 284, 290, 367). Plasma levels of propionate and other odd-chain-length fatty acids are low in humans; thus this is not a major pathway under normal conditions. However, a recent small clinical study in patients with deficiencies in long-chain fatty acid oxidation have clinical improvement and reversal of cardiac dysfunction with dietary supplementation with heptanoate, perhaps due to increased anaplerosis (369).

Pyruvate can also contribute to anaplerosis by transamination with glutamate to form alanine and the CAC intermediate α-ketoglutarate. The rate of alanine output by the myocardium is relatively low in dogs, pigs, and humans (15, 142, 305, 412, 459, 495) and is unaffected by acute ischemia (142) or when glycolysis is accelerated with hyperinsulinemia and hyperglycemia (495). Studies in stable coronary artery disease patients showed elevated alanine output compared with healthy people (318).

C. Fatty Acid Metabolism

The rate of fatty acid uptake by the heart is primarily determined by the concentration of nonesterified fatty acids in the plasma (32, 270, 494), which can vary over a fourfold range in healthy humans during the course of the day (from ~0.2 to 0.8 mM). Under conditions of metabolic stress, such as ischemia, diabetes, or starvation, plasma FFA concentrations can increase to much higher levels (>1.0 mM) (271). 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. They are transported in the plasma in the nonesterified form attached to albumin, or covalently bound in triglyceride, contained with chylomicrons or very-low-density lipoproteins. Plasma fatty acid concentration is regulated by their net release from triglycerides in adipocytes, which reflects the net balance between triglyceride breakdown by hormone-sensitive lipase and synthesis by glycerolphosphate acyltransferase (270). Hormone-sensitive lipase is activated by catecholamines and inhibited by insulin. Thus, with fasting, when insulin is low and catecholamines are high, the plasma FFA concentration is elevated, resulting in a high rate of fatty acid uptake and oxidation by the heart. Fatty acids are also released from triglyceride in chylomicrons and in very-low-density lipoproteins that are hydrolyzed by lipoprotein lipase bound to the outside of capillary endothelial cells and cardiomyocytes (13, 306, 501, 505).

Fatty acids enter the cardiomyocyte by either passive diffusion or by protein-mediated transport across the sarcolemma (Fig. 5) (473) involving either a fatty acid translocase (FAT), or a plasma membrane fatty acid binding protein (FABP$_{pm}$) (131, 401, 473). A specific 88-kDa FAT protein called CD36 is abundantly expressed in skeletal and cardiac muscle and appears to be the predominant form of FAT in the heart (401, 473). People with mutations in the CD36 gene have lower rates of uptake of the long-chain fatty acid analog ^{123}I-15-(p-iodophenyl)-3-methylpentadecanoic acid compared with normal people (226), suggesting that CD36 partially regulates the rate of myocardial fatty acid uptake in humans. Once transported

across the sarcolemma, the nonesterified fatty acids bind to FABP and are then activated by esterification to fatty acyl-CoA by fatty acyl-CoA synthase (FACS) (Fig. 5). FABPs are abundant in the cytosol and appear to be the primary intracellular carrier of nonesterified fatty acids. Recent studies show that there are FABP and FACS protein associated with CD36 on the cytosolic side of the sarcolemmal membrane, thus raising the possibility that fatty acids transported across the membrane can also be immediately esterified to fatty acyl-CoA (401). Inhibitable fatty acid transport is greater in electrically stimulated isolated cardiomyocytes compared with unstimulated conditions, suggesting that there is a translocation of FAT/CD36 into the sarcolemma from an intracellular site in response to contraction or increased energy demand (277–279). A similar phenomenon was observed in response to insulin stimulation (279). Translocation of FAT/CD36 has not been demonstrated in response to increased cardiac energy expenditure or insulin stimulation in the intact heart (277); thus it remains to be seen if translocation of FAT/CD36 regulates myocardial fatty acid transport under physiologically relevant conditions.

The product of FACS, long-chain fatty acyl-CoA, can either be esterified to triglyceride by glycerolphosphate acyltransferase (65, 270, 473) or converted to long-chain fatty acylcarnitine by carnitine palmitoyltransferase I (CPT-I) (Fig. 5) (270). Studies in normal humans, coronary artery disease patients, and large animals demonstrate that 70–90% of the $[^{14}C]$- or $[^{3}H]$oleate or palmitate that is taken up by the heart is immediately released into the venous effluent as $^{14}CO_2$ or $^{3}H_2O$ (51, 54, 245, 494). This suggests that in the healthy normal heart 70–90% of the fatty acids entering the cell are converted to acylcarnitine and immediately oxidized, and 10–30% enter the intracardiac triglyceride pool (270, 391, 392). The myocardial triglyceride pool is an important source of fatty acids, with the rate of lipolysis of myocardial triglycerides and its contribution to overall myocardial ATP production being inversely related to the concentration of exogenous fatty acids (72, 75, 339, 391). Triglyceride turnover can be rapidly accelerated by adrenergic stimulation (73, 74, 76, 138, 139, 233, 443) and is increased in uncontrolled diabetes (339, 393) and during reperfusion of ischemic hearts (392).

Fatty acid β-oxidation occurs primarily in the mitochondria and to a small extent in peroxisomes (238, 409). The primary products of fatty acid oxidation are NADH, $FADH_2$, and acetyl-CoA (Fig. 5). Before mitochondrial β-oxidation, the cytoplasmic long-chain acyl-CoA must first be transported into the mitochondrial matrix. Because the inner mitochondrial membrane is not permeable to long-chain acyl-CoA, the long-chain fatty acyl moiety is transferred from the cytosol into the matrix by a carnitine-dependent transport system (220, 270). First, CPT-I catalyzes the formation of long-chain acylcarnitine from long-chain acyl-CoA in the compartment between the inner and outer mitochondrial membranes. Next, carnitine acyltranslocase transports this long-chain acylcarnitine across the inner mitochondrial membrane in exchange for free carnitine. Lastly, carnitine palmitoyltransferase II (CPT-II) regenerates long-chain acyl CoA in the mitochondrial matrix (Fig. 5). Of the three enzymes involved in the transmitochondrial membrane transport, CPT-I serves the key regulatory role in controlling the rate of fatty acid uptake by the mitochondria (220, 270).

The activity of CPT-I is strongly inhibited by malonyl-CoA, which binds to CPT-I on the cytosolic side of the enzyme (Fig. 5) (220, 302, 513). There are two isoforms of CPT-I: CPT-Iα predominates in the liver, and CPT-Iβ is the main isoform in the heart (300, 302). CPT-Iβ is 30-fold more sensitive to malonyl-CoA inhibition than is CPT-Iα (300, 302, 485). Malonyl-CoA is a key physiological regulator of fatty acid oxidation in the heart. A fall in malonyl-CoA increases fatty acid uptake and oxidation (2, 143, 236), and an increase suppresses fatty acid oxidation (390, 430). Malonyl-CoA is formed from the carboxylation of acetyl-CoA by acetyl-CoA carboxylase (ACC) (137, 143, 145, 236, 375, 390, 454) and has a rapid rate of turnover in the heart (364, 366). Most of the acetyl-CoA in cardiomyocytes resides in the mitochondria (185); however, CPT-I activity is regulated by malonyl-CoA that is formed from carboxylation of extramitochondrial acetyl-CoA. There is indirect evidence to suggest that extramitochondrial acetyl-CoA is derived from citrate via the ATP-citrate lyase reaction (345, 395) and from the export for mitochondrial acetyl-CoA as acetylcarnitine (281, 390). More recently, results from studies with ^{13}C-labeled substrates and isotopomer analysis of malonyl-CoA provided direct evidence that in the perfused rat heart malonyl-CoA is derived from acetyl-CoA formed in peroxisomal β-oxidation of long-chain fatty acids (365). Furthermore, the data were consistent with long-chain fatty acids undergoing only a few cycles of β-oxidation in peroxisomes, followed by the generation of C_{12} and C_{14} fatty acyl-CoAs that are subsequently oxidized to acetyl-CoA in the mitochondria (365).

The activity of ACC is inhibited by phosphorylation by AMPK (236, 319, 394); thus activation of AMPK can result in reduced malonyl-CoA formation and acceleration of fatty acid oxidation (94, 95). It was recently shown there is an increase in AMPK activity in rats with LV hypertrophy produced by aortic banding (462), although the metabolic consequences of this activation are unclear. As discussed in section IIB, mutations in the gamma-2 regulatory subunit of AMPK result in glycogen accumulation and hypertrophic cardiomyopathy in mice (8, 9) and Wolffe-Parkinson-White syndrome in patients (135, 135, 330). To our knowledge, the effect of HF on AMPK expression and activity are not known. As discussed above, AMPK activation in the heart also stimulates glucose transporter translocation and glucose uptake (71, 379, 499); thus activation of AMPK can effect an increase in both carbohydrate and fatty acid metabolism. Thus, when

the metabolic rate of the heart is increased, as occurs during exercise, increased AMPK activity would increase acetyl-CoA production from both carbohydrates and lipids, and thus ensure an adequate supply of substrate to the mitochondria (71).

The degradation of malonyl-CoA is regulated by the activity of malonyl-CoA decarboxylase (MCD), which converts malonyl-CoA back to acetyl-CoA and CO_2 in the cytosol and mitochondrial (Fig. 5) (93, 146, 221, 225, 394). In general, situations where MCD activity is high results in low myocardial malonyl-CoA content and high rates of fatty acid oxidation (48, 92, 93). We have recently shown that pharmacological inhibition of MCD activity increases myocardial malonyl-CoA content, and (93) MCD activity regulates fatty acid oxidation. In addition, inhibition of MCD activity reduces malonyl-CoA turnover (366) and increases glucose oxidation under aerobic, ischemic, and postischemic conditions and improves postischemic recovery of contractile function (93), as has been previously observed with CPT-I inhibitors (163, 164, 427). An increase in cardiac power induced by β-adrenergic receptor stimulation results in a fall in myocardial malonyl-CoA content and accelerated fatty acid uptake and oxidation; however, this effect is not due to activation of AMPK or reduced ACC activity (137, 143) but has been associated with a reduction in the K_m of MCD(137), although this has not been a consistent finding (366).

Once taken up by the mitochondria, fatty acids undergo β-oxidation, a process that repeatedly cleaves off two carbon acetyl-CoA units, generating NADH and $FADH_2$ in the process (Fig. 5). The β-oxidation process involves four reactions, with specific enzymes for each step, and each reaction has specific enzymes for long-, medium-, and short-chain length fatty intermediates (30, 32). The first step is catalyzed by acyl-CoA dehydrogenase, followed by 2-enoyl-CoA hydratase, and then 3-hydroxyacyl-CoA dehydrogenase. The final step is 3-ketoacyl-CoA thiolase (3-KAT), which regenerates acyl-CoA for another round of β-oxidation and releases acetyl-CoA for the citric acid cycle. Acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase generate $FADH_2$ and NADH, respectively, and the acetyl-CoA formed from β-oxidation generates more NADH and $FADH_2$ in the CAC.

D. Ketone Body Metabolism

The heart extracts and oxidizes ketone bodies (β-hydroxybutyrate and acetoacetate) in a concentration-dependent manner (56, 114, 152, 441). Plasma ketone bodies are formed from fatty acids in the liver, and the arterial plasma concentration is normally very low, thus they are normally a minor substrate for the myocardium. During starvation or poorly controlled diabetes, plasma ketone body concentrations are elevated secondary to low insulin and high fatty acids, and they become a major substrate for the myocardium (15, 145). As with fatty acids, the uptake and oxidation of glucose and lactate are inhibited by elevated plasma ketone bodies (32, 436, 441, 467), with the inhibitory effect presumably mediated through product inhibition on PDH (see sect. IIF).

Oxidation of ketone bodies inhibits myocardial fatty acid oxidation (56, 114, 152, 243, 261, 436, 474). Diabetic myocardium has a high rate of β-hydroxybutyrate uptake and relatively low rates of fatty acid uptake (145), suggesting that in diabetic patients elevated plasma ketone concentrations can act to inhibit fatty acid uptake and oxidation. Clinical studies demonstrate that HF results in an increase in plasma ketone body concentration that appears to be secondary to elevated fatty acid levels (264–266); however, data on myocardial ketone body metabolism have not been reported from animals or patients with HF. The biochemical mechanisms responsible for inhibition of fatty acid β-oxidation by ketone bodies are not well understood, but do not appear to be related to changes in malonyl-CoA or the acetyl-CoA-to-free CoA ratio (436). Elevated rates of β-hydroxybutyrate and acetoacetate oxidation could inhibit fatty acid β-oxidation by increasing the intramitochondrial ratio of NADH to NAD^+, which would inhibit the ketoacyl-CoA dehydrogenase step of the fatty acid β-oxidation spiral (219, 238). Hasselbaink et al. (152) recently showed that palmitate oxidation was significantly enhanced in isolated cardiomyocytes from streptozotocin diabetic rats in the absence of acetoacetate; however, when measurements were made with the addition of ketone bodies, the rate of palmitate oxidation was not affected by diabetes. They also noted greater fatty acid uptake in the myocytes from diabetic rats and suggested that ketone-induced impairment of fatty acid oxidation might be responsible for the greater triglyceride storage in the heart with diabetes (82).

E. Interregulation of Fatty Acid and Carbohydrate Oxidation

The primary physiological regulator of flux through PDH and the rate of glucose oxidation in the heart is the rate of fatty acid oxidation (Fig. 4). High rates of fatty acid oxidation inhibit PDH activity via an increase in mitochondrial acetyl-CoA/free CoA and NADH/ NAD^+, which activates PDH kinase causing phosphorylation and inhibition of PDH (Fig. 4). In addition, in isolated heart mitochondria elevated rates of fatty acid oxidation inhibit flux through PDH at a given PDH phosphorylation state (148). Conversely, inhibition of fatty acid oxidation increases glucose and lactate uptake and oxidation by *1*) decreasing citrate levels and inhibition of PFK and *2*) lowering acetyl-CoA and/or NADH levels in the mitochondrial matrix,

thereby relieving the inhibition of PDH (165) (Figs. 4 and 5). This effect has been demonstrated with *1*) lowering plasma free fatty acid concentration by administering an inhibitor of lipolysis in adipocytes (229, 230, 245, 438), *2*) inhibition of CPT-I (51, 164, 165), *3*) inhibition of malonyl-CoA decarboxylase (which elevates malonyl-CoA content and inhibits CPT-I activity)(93, 366), and *4*) direct inhibitors of fatty acid β-oxidation (207, 297). It is important to note that partial inhibitors of myocardial fatty acid oxidation have been shown to lessen ischemic dysfunction and tissue damage in animal models of ischemia and reperfusion and have clear benefits in clinical trials in patients with chronic stable angina (26, 50, 78, 195, 340, 406, 445); this effect has been attributed to increased pyruvate oxidation and less lactate accumulation and efflux, and decreased proton accumulation (29, 164, 165, 427, 433).

F. Effects of Substrate Selection on Contractile Function and Efficiency

Several lines of evidence suggest that the contractile performance of the heart at a given $M\dot{V}_{O_2}$ is greater when the heart is oxidizing more glucose and lactate, and less fatty acids (47, 183, 227, 232, 243, 309, 310, 421). Studies in isolated rat hearts demonstrate that the mechanical power of the LV is less at a given rate of oxygen consumption when fatty acids rather than glucose are the sole exogenous substrate (47). Classic studies by Ole Mjøs in closed-chest dogs demonstrated that increasing the rate of fatty acid uptake by the heart with an infusion of heparin and triglyceride emulsion resulted in a 26% increase in myocardial oxygen consumption without changing the mechanical power of the LV (309, 310). A similar decrease in cardiac mechanical efficiency with elevated plasma FFA concentration was observed in healthy humans (421) and pigs (232), as well as during ischemia of moderate severity in dogs (227, 311). Furthermore, inhibition of fatty acid β-oxidation by 4-bromocrotonic acid decreased $M\dot{V}_{O_2}$ and improved mechanical efficiency of the LV of the working rat heart (183); a similar response was observed following acute administration of the fatty acid oxidation inhibitor ranolazine in dogs with HF (53). Korvald et al. (232) compared the relationship between $M\dot{V}_{O_2}$ and the LV pressure-volume loop over a wide range of work loads in anesthetized pigs. Treatment with insulin and glucose resulted in a 39% reduction in noncontractile basal $M\dot{V}_{O_2}$ [estimated from the intercept of the $M\dot{V}_{O_2}$-pressure-volume loop relationship (232)] compared with pigs subjected to high plasma fatty acids. Importantly, they did not observe a difference in the slope of this relationship, suggesting that under these conditions fatty acids did not affect excitation-contraction coupling or the ATP requirement for contractile power.

The mechanisms for impaired mechanical efficiency with high fatty acid oxidation are unclear. On a theoretical basis, fatty acid oxidation requires a greater rate of oxygen consumption for a given rate of ATP synthesis than do carbohydrates (428). The theoretical ATP-to-oxygen ratio for glucose or lactate are 3.17 and 3.00, respectively, while for palmitate and oleate the values are 2.80 and 2.86, respectively (209, 428). The actual values in vivo may be much lower due to constitutive leakage of protons across the inner mitochondrial membrane (37, 370, 371, 439). Fatty acid concentrations uncouple oxidative phosphorylation (decrease the P/O) and cause wasting of O_2 by mitochondria (34, 348). This would require a greater $M\dot{V}_{O_2}$ for a given rate of ATP formation by oxidative phosphorylation when fatty acids are the substrate (34, 348). These effects would alter the $M\dot{V}_{O_2}$ requirement for ATP production for both basal metabolism and for generating contractile power and relaxation (i.e., ATP hydrolysis to support Ca^{2+} uptake into the sarcoplasmic reticulum). In addition, high concentrations of long-chain fatty acids can also activate sarcolemmal Ca^{2+} channels, which would increase the entry of extracellular Ca^{2+} into the cytosol and increase the rate of ATP hydrolysis required to maintain normal cytosolic Ca^{2+} cycling (173).

It has been proposed that fatty acids waste ATP (and hence O_2) through the extrusion of long-chain fatty acids out of the mitochondria via uncoupling protein 3 (UCP3) (166, 408). In this scheme high rates of intramitochondrial fatty acyl-CoA production would result in formation of FFA by mitochondrial thioesterase-1, which would be transported out of the mitochondria by UCP3 and reesterified by FACS to long-chain fatty acyl-CoA in the cytosol (a reaction that consumes two ATP) (166, 178). Garlid and co-workers (120–123, 193, 198–201) observed that UCP3 can translocate the FA^- out of the mitochondrial matrix; once in the intramembranous space, the FA^- can associate with a proton. The resulting neutral FA species is able to "flip-flop" back into the mitochondrial matrix, where it relinquishes the proton. The net effect is a leak of protons, as with classic uncoupling, but with no net flux of fatty acids (120–123, 193, 198–201). While this clearly occurs, it may not play a major role in the energy-wasting effects of fatty acid observed in vivo, as many studies show no effect of UCP3 content on the P/O in isolated mitochondria (60, 62, 222, 408, 478). Studies in isolated skeletal muscle mitochondria show that lipid substrate (palmitoylcarnitine or palmitoyl-CoA) causes a UCP3-dependent decrease in state 4 respiration with no change in state III respiration or P/O, an effect that is not observed with nonlipid substrates (222). In addition, skeletal muscle mitochondria isolated from mice lacking UCP3 show a decreased in state 4 respiration (478) and mice overexpressing UCP3 show an increase in state 4 respiration (60) with no effect on state 3 respiration (60, 478). Thus exposure of the myocardium to high plasma

concentrations of FFA could waste ATP via this UCP3-mediated futile cycle.

G. Role of Nitric Oxide in Regulation of Myocardial Energy Substrate Metabolism

In 1989, Brune and Lapetina demonstrated that nitric oxide (NO) can enhance ADP-ribosylation of a 37-kDa cytosolic protein (43), later identified as GAPDH (90, 91, 313, 475), a key enzyme of the glycolytic pathway. Zhang and Snyder documented a similar action of NO in neuronal cells (517). These seminal studies on the direct effects of NO on glucose metabolism were followed by others that described inhibitory actions of NO on phosphofructokinase of pancreatic islets (465) and an indirect stimulatory action of NO on 6-phosphofructo-2-kinase in neurons (4). Although the mechanisms are still poorly defined, convincing evidence has been provided that NO also plays an important role in the regulation of myocardial substrate metabolism. Depre et al. (83) observed a decreased glucose uptake in isolated hearts during 8-bromo-cGMP infusion. They concluded that NO, via its second messenger cGMP, probably inhibits glucose transport into cardiomyocytes and that this could explain their previous findings of a cardioprotective action of NO synthase (NOS) inhibition during myocardial ischemia (84, 87), when cardiac function is highly dependent on glycolytic flux. In hearts isolated from endothelial cell NOS knockout mice, Tada et al. (447) found that basal cardiac glucose uptake is markedly increased and can be inhibited by 8-bromo-cGMP. It is possible that all of these findings in vitro were affected by nonphysiological conditions of substrate and oxygen supply. This was not the case, however, since we found that cardiac glucose uptake and oxidation are increased after systemic NOS inhibition in conscious dogs (360, 361). Conversely, under the same experimental conditions, fatty acid uptake and oxidation are reduced. On the other hand, we did not observe this shift in substrate oxidation with NOS inhibition in isolated rat hearts (239). An interesting paradox is that NO/cGMP exerts opposite effects on glucose transport and metabolism in skeletal muscle (512). Additional research is needed to elucidate the mechanisms underlying the regulation of myocardial substrate metabolism by NO.

It has been suggested that the activity of cardiac NOS during metabolic stress is regulated by a possible feedback mechanism involving AMPK (57). Chen et al. (57) found that AMPK coimmunoprecipitates with cardiac eNOS and activated it by phosphorylating Ser-1177, but only in the presence of Ca^{2+}-calmodulin, both in tissue homogenates and in ischemic isolated rat hearts. Because NO is a main regulator of vascular tone and cardiac function, these findings lead to the intriguing hypothesis that the stimulatory effect exerted by AMPK on eNOS may represent a link between metabolic adaptations and cardiovascular function under conditions of stress. Li et al. (255) also observed coprecipitation of AMPK and eNOS and demonstrated that activation of AMPK with 5-amino-4-imidazole-1-β-carboxamide ribofuranoside (AICAR) results in activation of eNOS, GLUT4 translocation and greater glucose uptake in isolated papillary muscles. AICAR treatment also results in increased glucose uptake (255), which is in contrast with previous studies showing decreased glucose uptake with NOS inhibition or 8-bromo-cGMP (83, 84, 87, 360, 361). Additional research is needed to elucidate the mechanisms underlying the complex interactions between myocardial substrate metabolism and NO.

III. REGULATION OF MYOCARDIAL METABOLIC PHENOTYPE

Myocardial metabolic phenotype can be defined as the substrate preference by the heart at a given metabolic milieu (e.g., arterial concentrations of glucose, lactate, fatty acids, insulin, catecholamines, oxygen), hemodynamic condition (heart rate, preload, afterload, coronary blood flow), and inotropic state. This phenotype is primarily dependent on the content of the proteins (enzymes and transporters) that facilitate flux through the metabolic pathways and the structure and integrity of key cellular organelles, such as mitochondria, that are responsible for energy metabolism. To affect metabolic phenotype, however, it is important that the protein that is modified exerts a key regulatory role in metabolism. Many metabolic enzymes in a pathway are redundant or expressed in great excess and therefore do not regulate flux through the pathway. It is therefore possible to have dramatic changes in expression of some proteins without much effect on substrate flux. In other words, changes in flux cannot simply be inferred from changes in enzyme activity or expression. Therefore, in evaluating the effects of heart failure on myocardial substrate metabolism, it is important to assess several aspects of the metabolic pathway of interest, specifically: *1*) the rate of flux through metabolic pathways under physiologically relevant conditions; *2*) the expression, activity, and characteristics of key regulatory proteins (e.g., V_{max}, K_m, allosteric modification of an enzyme); and *3*) the tissue content of regulatory metabolites.

There have been a variety of investigations into the metabolic phenotype changes that occur in response to chronic cardiac stress like cardiac hypertrophy and HF. These studies have used a variety of methodological approaches but have mainly been aimed at the assessment of flux through the metabolic pathway [either in vivo using invasive (30, 31, 338, 493, 494) or noninvasive tech-

niques, e.g., positron emission tomography (PET)] (79, 81, 237, 453, 480), or in isolated perfused hearts (24, 224, 269), or they have sampled the myocardium to evaluate mRNA levels using real-time quantitative polymerase chain reaction (86, 356, 357, 509) or gene chip microarrays (307, 451). It is more complex to assess changes in the protein expression, activity, and rate of turnover. Nevertheless, in studying the effects of HF on metabolic phenotype, the goal has been to understand the relative importance of changes in the function of selected proteins on the flux through various metabolic pathways, on cardiac function, and on the progression of HF. At present, much emphasis is placed on understanding the mechanisms that signal changes in the expression of genes encoding proteins that regulate substrate metabolism and, in turn, affect cardiac function and progression in HF. However, as discussed, care should be taken in interpreting these data without parallel measurements of metabolic flux.

A. Control of the Expression of Metabolic Enzymes in the Heart

Regulation of the expression of the multitude of enzymes and transporters involved in myocardial energy metabolism is complex and not well understood. In HF, recent interest has focused on altered expression of both glycolytic and mitochondrial enzymes. In general, the overall capacity for oxidative metabolism in a cell is dependent on the volume density and composition of mitochondria. However, over the last decade it has become clear that mitochondrial fuel selection can be altered by differential expression of enzymes of the fatty acid oxidation pathway relative to enzymes that oxidize pyruvate (PDH and PDK) or acetyl-CoA (e.g., citrate synthase), or those in the electron transport chain. Mitochondria have a circular DNA genome that encodes for the 13 subunits of the respiratory complexes I, III, IV, and V (400). The remaining respiratory subunits and all of the proteins required for carbon substrate metabolism are encoded by nuclear genes. It is becoming clear that both nuclear and mitochondrial transcription alterations are important in the metabolic phenotype changes observed in HF (124, 477).

An important nuclear gene transcription control that regulates the capacity for myocardial mitochondrial fatty acid oxidation is regulated by the ligand-activated transcription factors, named peroxisome proliferator-activated receptors, or PPARs (25, 180). These transcription factors control gene expression by first forming heterodimers with retinoid X receptors and then binding to specific response elements (PPAR response elements, or PPREs) located within promoter regions of many genes encoding metabolic enzymes (Fig. 6). In addition, the PPAR/RXR complex is positively regulated by the cofactor PPARγ coactivator-1 (PGC-1) (25, 180, 476). Cardiac overexpression of PGC-1 increases the mRNA of numerous mitochondrial genes and triggers mitochondrial biogenesis (181, 250, 476). Once bound to the PPRE, the PPAR/RXR/PGC-1 complex increases the rate of transcription of fatty acid oxidation genes and PDK-4 (the inhibitory kinase of PDH) (129, 150, 172, 251). In addition, stimulation of gene transcription is inhibited by the bind-
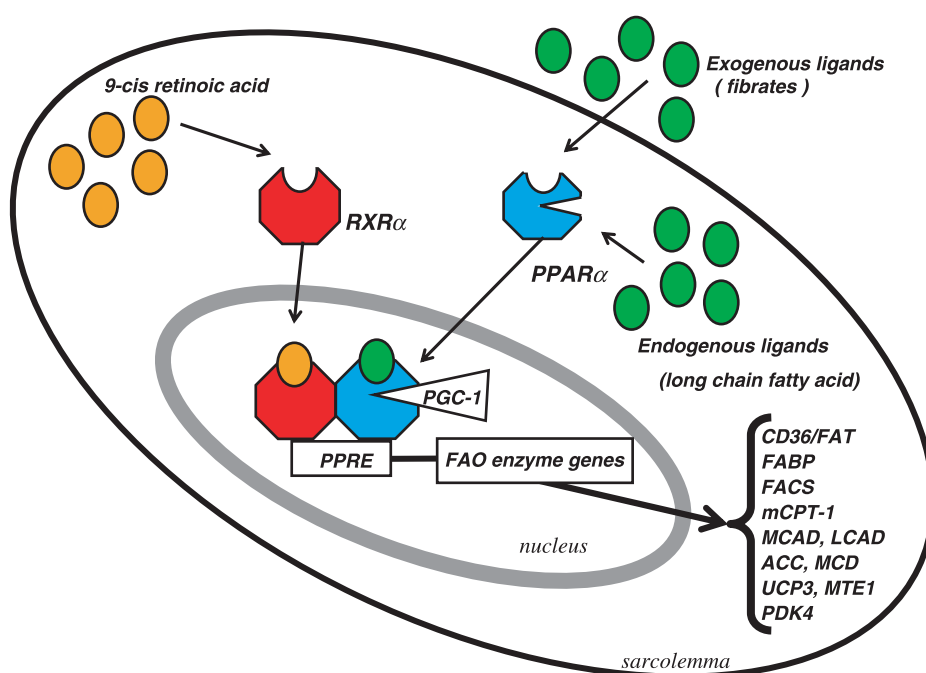
FIG. 6. Regulation of expression of metabolic genes in cardiomyocytes by stimulation of the peroxisome proliferator activated receptor α (PPARα). Note that PPARδ has similar, but less well described, effects on gene expression (see text). ACC, acetyl-CoA carboxylase, mCPT-I, muscle isoform of carnitine palmitoyltransferase-I; FABP, fatty acid binding protein; LCAD, long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; MCD, malonyl-CoA decarboxylase; MTE1, mitochondrial thioesterase 1; PDK4, pyruvate dehydrogenase kinase 4; PPRE, peroxisome proliferator activated receptor response element; RXRα, retinoid X receptor α; UCP3, uncoupling protein 3.

ing of several cofactors such as COUP and SP1 (251). The activity of PPAR/RXR heterodimers is increased by fatty acids and eicosanoids; thus PPAR/RXR heterodimers act as lipid sensors in the cell, resulting in a greater capacity for fatty acid catabolism in response to a greater cell exposure to lipid (Fig. 6) (25, 180).

There are three isoforms of PPARs: PPARα, PPAR β/δ, and PPARγ (25, 129, 180, 251, 472). PPARα expression is high in tissues that have high rates of fatty acid oxidation (heart, liver, brown fat, kidney) and regulates the expression of key components of fatty acid uptake, esterification, and oxidation by transcriptional activation of genes encoding for key proteins in the pathway (Fig. 6). In the heart, PPARα forms a heterodimer with RXRα; the natural activating ligand for RXRα is 9-cis-retinoic acid (25). Activation of PPARα by pharmacological ligands (e.g., fenofibrate, clofibrate, or WY-14,643) increases the expression of fatty acid oxidation enzymes (129, 180, 509) and the rate of fatty acid oxidation in cardiomyocytes (129). Consistent with these findings is the observation that PPARα knockout mice have low expression of fatty acid oxidation enzymes and suppressed fatty acid oxidation (48). It was also recently demonstrated that PPARα regulates the expression of UCP3 (511) and mitochondrial thioesterase 1 (437) in the heart and thus plays a role in regulating the extrusion of fatty acyl-CoA from the mitochondria (166).

PPARδ [also referred to as PPARβ/δ (129)] is also expressed in cardiomyocytes and stimulates the expression of proteins in the fatty acid oxidation pathway in a manner similar to PPARα (58, 129). Gilde et al. (129) showed that exposure of isolated neonatal rat cardiomyocytes to PPARδ agonists results in upregulation of the mRNA for fatty acid oxidation enzymes and increased fatty acid oxidation. Cheng et al. (58) recently showed that mice with a cardiomyocyte-restricted deletion of PPARδ downregulated the expression of the mRNA and protein for fatty acid oxidation enzymes and had reduced myocardial oxidation of fatty acids. The mice had progressive LV dysfunction and hypertrophy, but had myocardial lipid accumulation and increased mortality late in life. These recent findings suggest that PPARδ may play a role that is similar to PPARα in the regulation of cardiac fatty acid metabolism.

PPARγ mRNA is expressed at very low levels in cardiomyocytes, and at higher rates in a broad range of tissues including skeletal muscle, colon, small and large intestines, kidney, pancreas, and spleen. Although PPARγ does not appear to play a direct role regulating fatty acid oxidation in the heart (129, 216), it can indirectly regulate fatty acid oxidation by decreasing the fatty acid concentration to which the heart is exposed. The effective insulin-sensitizing agents, the thiazolidinediones, are PPARγ ligands and act to sequester fatty acids in adipocytes, lower circulating fatty acids, and triglycerides and there-fore reduce the exposure of the myocardium to fatty acids (25). Thus the thiazolidinediones ("PPARγ agonists") can decrease myocardial fatty acid oxidation in vivo by decreasing plasma fatty acid levels and thus myocardial fatty acid uptake and oxidation. Furthermore, the action of PPARγ agonists on adipocytes likely reduces ligand stimulation of the PPARα/RXR complex in cardiomyocytes, and thus reduces the expression of proteins regulating fatty acid uptake and oxidation in the heart.

Recent studies in isolated neonatal cardiomyocytes suggest that the orphan nuclear receptor estrogen-related receptor α (ERRα) interacts with PGC-1 and binds to the PPRE to increase the expression of PPARα-regulated genes and increased fatty acid uptake, accumulation, and oxidation (181, 182). Overexpression of ERRα also resulted in an increase in the mRNA for proteins that are not regulated by PPARα, including contractile proteins and enzymes involved in carbohydrate metabolism and mitochondrial respiration (182). The endogenous ligand(s) for ERRα have not been identified.

B. Cardiac Lipotoxicity

Recent evidence from animal studies demonstrates that obesity and elevated plasma fatty acid and triglycerides can result in a cardiac specific "lipotoxicity," characterized by accumulation of neutral lipids (triglycerides) and ceramides, which are associated with increased apoptosis, and contractile dysfunction (109, 301, 402, 468, 469, 501, 505, 520). For instance, Zhou et al. (520) showed that mature obese Zucker diabetic rats develop cardiac dilatation and reduced contractility that correspond with elevated myocardial triglycerides, ceramide, and DNA laddering, an index of apoptosis. Suppression of plasma triglyceride with the PPARγ agonist troglitazone lowers myocardial triglyceride and ceramide content, which was associated with complete prevention of DNA laddering and loss of cardiac function. Cardiac overexpression of FACS results in lipid accumulation, cardiac hypertrophy, gradual development of LV dysfunction, and premature death (59). Cardiac overexpression of human lipoprotein lipase with a glycosylphosphatidylinositol anchoring sequence that localizes the enzyme to the surface of cardiomyocytes causes LV chamber enlargement and impaired contractile function compared with wild-type mice (501). The mechanism for lipid-induced cardiac remodeling and dysfunction in this model is unclear but could be due to apoptotic cell loss (162, 260, 333, 425, 520) and/or a decrease in cardiac mechanical efficiency with very high rates of fatty acid oxidation and impaired carbohydrate oxidation (227, 232, 309, 310, 421).

The toxic effects of lipid accumulation in the heart can be demonstrated in small animal models; however, the clinical significance of these findings is not yet clear in

type 2 diabetes, obesity, and HF. Epidemiological studies show that obese people have a decrease in life expectancy and greater mortality from cardiovascular disease (113, 174) and a greater risk for developing HF (218). However, once a patient is diagnosed with HF, there is a paradoxical reduction in the rate of mortality in obese compared with lean patients (80, 171, 247, 248). These observations are complicated by the fact that cachexia is a positive predictor of mortality in HF, and weight loss is strongly associated with poor outcome (7, 80). The clinical complexities of the HF and obesity, and the paucity of data, make it impossible to draw conclusions at this point regarding mechanistic interactions between the two syndromes.

C. Regulation of Phenotype Switch from Fetal to Adult State: Implications for Heart Failure

One of the hallmarks of HF is a reexpression of fetal forms of genes expressing contractile proteins, specifically myosin (411). A similar reexpression of some fetal metabolic genes has been noted in HF; however, there is not a clear recapitulation of the fetal metabolic phenotype (see discussion below) (356, 362, 374, 388, 389). Nonetheless, much can be learned about the regulation of metabolic phenotype by studying the rapid transformation in enzyme pathways and substrate use that occurs during the transition from the fetal to neonatal state. During the fetal stages of the developing mammalian heart, glucose is the primary energy substrate for energy transduction, while rates of fatty acid oxidation are very low (130). In the fetal and immediate newborn period, the heart is very reliant on glycolysis as a source of energy (110, 272) due both to higher activities of the enzymes in the glycolytic pathway (110, 169, 282, 372) and altered pathway regulation (272, 460) in fetal hearts. Direct measurements of glycolysis in perfused rabbit hearts demonstrate that in the immediate newborn period, 44% of the ATP production is derived from glycolysis (274); however, within days of birth glycolysis decreases and provides only 7% of ATP production, values similar to those seen in the adult rabbit heart (273, 274). Even though glycolysis is high in the fetal and newborn heart, these hearts still have a considerable mitochondrial oxidative capacity (273, 274, 482, 483). Fetal hearts readily extract (110–112) and oxidize lactate (489), and because circulating lactate levels are very high in the fetus (130), lactate oxidation accounts for the majority of myocardial oxygen consumption (110, 111). While glycolytic rates are high in the immediate newborn period, glucose oxidation is very low and is not a major source of ATP production (274, 275). The capacity to oxidize glucose increases as the heart matures (192, 272, 273).

In the fetal and newborn heart, fatty acid oxidation rates are low and provide only a small proportion of overall ATP production (130, 132, 273, 274). In the imme-

diate newborn period, <20% of the heart's ATP requirements are met by the oxidation of fatty acids (274). However, after birth, there is a dramatic 10-fold increase in fatty acid oxidation, which is accompanied by a parallel decrease in glycolytic rates (192, 274). This is opposite to the switch towards reduced fatty acid oxidation and increased glucose oxidation observed in some forms of severe HF. Interestingly, if the newborn heart is subjected to a volume overload hypertrophy, the expression and activity of key enzymes controlling fatty acid oxidation remain in the "fetal state" (208).

A number of key enzymes involved in fatty acid oxidation are altered in the transitions from fetal to adult metabolism. In the fetal heart there is a greater proportion of CPT-Iα relative to CPT-Iβ, a phenomenon similar to what is observed in cardiac hypertrophy (41, 304, 461, 497). However, one of the most dramatic differences in fatty acid oxidation control in the newborn period is the levels of malonyl-CoA, and the control of malonyl-CoA levels (275, 282). In the immediate newborn period, malonyl-CoA content in the heart is very high, but then rapidly decreases within days of birth (92, 275, 282). This dramatic drop in malonyl-CoA is an important contributor to the maturation of fatty acid oxidation following birth (275) and is due to both decreased synthesis by ACC and increased degradation by MCD (92, 275). The decrease in ACC activity with maturation is due to an increase in AMPK activity following birth (92), which phosphorylates and inhibits ACC activity (275). An increase in AMPK activity has also been observed with cardiac hypertrophy in the rat, illustrating that there is not a simple switch to fetal metabolic regulation in response to chronic cardiac stress (462). The increase in MCD activity in the newborn period is primarily due to an increase in MCD expression (92), which may be due to activation of PPARα, a known transcriptional regulator of MCD (48, 508). The role of PPARα in HF is discussed below.

D. Effects of Aging on Substrate Metabolism

It is important to consider that the incidence of HF is directly related to age (33) and that the progression from adulthood to senescence affects cardiac contractile properties and LV chamber size (241, 242, 422), myocardial flow reserve (471) and cardiac mitochondria function (104, 147, 253, 276), and affects myocardial substrate metabolism independent of HF. Recent studies using PET show that with aging (~69 vs. 29 years of age), humans have a decrease in myocardial fatty acid uptake and oxidation, with no change in glucose uptake under resting conditions (211). However, when M$\dot{V}_{O_2}$ is increased by an infusion of dobutamine, there is a similar increase in myocardial fatty acid uptake in both young and old subjects, and an increase in glucose uptake in the young

subject but not in the old subjects. This is in contrast to studies in perfused rat hearts, where there was no difference between 6 and 24 mo in palmitate oxidation for a given M$\dot{V}O_2$ at either low or high work loads (3). Old rats have a decrease in myocardial GLUT4 mRNA and protein content that is not affected by exercise training by treadmill running (144). McMillin et al. (303) observed a decrease palmitoylcarnitine oxidation, CPT-I activity, and carnitine exchange in isolated mitochondria from old rats compared with adult animals. In addition, old animals did not exhibit fatty acid suppression of glucose oxidation that was evident in the adult rat heart, consistent with the concept of an aging defect in long-chain fatty acid oxidation (303). Iemitsu et al. (186) found a decrease in mRNA and protein expression for PPARα in 23- compared with 4-mo-old rats and that this decrease was prevented by swim training from 21 to 23 mo. Aging resulted in a decrease in the activity of cytochrome oxidase, citrate synthase, and 3-hydroxylacyl-CoA dehydrogenase, which was also prevented by 2 mo of swim training (186). Most animal studies investigating the pathophysiology of HF are performed in juvenile or young adult animals, and thus the effects of age are not present, suggesting that one should be cautious in interpreting such data.

IV. METABOLIC PHENOTYPE IN HEART FAILURE

A. Considerations Regarding the Etiology of Heart Failure

The etiology of HF can be divided into two broad categories: those patients with a history of myocardial ischemia/coronary artery disease (approximately two-thirds of all patients) and those without a history of coronary disease ("idiopathic cardiomyopathy") (215). The early stages of HF are often clinically asymptomatic due to physiological compensatory mechanisms (e.g., activation of the renin-angiotensin system, greater sympathetic nervous system activity, and development of cardiomyocyte hypertrophy); however, these same mechanisms also contribute to the progression of HF by precipitating ventricular remodeling (increased LV chamber volume, wall thinning, and myocardial fibrosis). It is important to note that inborn errors in mitochondrial metabolism and the electron transport chain can result in cardiomyopathy and present as clinical HF (49, 156, 217, 285); however, this area is outside the scope of the present review.

Due to the difficulties in obtaining myocardial tissue samples and assessing substrate flux in humans, little is known about myocardial substrate metabolism in HF patients. Furthermore, analysis of data from patients is complicated by the diverse etiology of the HF syndrome, the numerous pharmacotherapies used to treat these pa-

tients, the presence of complicating disorders (diabetes, insulin resistance, obesity), and the clinical stage. At present, there are few measurements of myocardial substrate metabolism in HF patients. Several studies have assessed levels of mRNA and protein expression in myocardium from hearts explanted from HF patients undergoing transplantation. However, these studies are compromised by the lack of a proper "normal" control group (the HF samples are rapidly obtained, while the control tissue is generally obtained from donor hearts that were unacceptable for transplantation and thus are usually on ice from several hours before processing). Despite these limitations, there is clear agreement between animal and human studies on many of the effects of HF on changes in the expression of key metabolic enzymes (see below).

The greatest impediment to understanding myocardial metabolism in HF is the limitations of existing animal models of HF (10, 317, 347, 386). Human HF of ischemic origin usually develops slowly following a myocardial infarction, affecting areas of the ventricle remote from the infarcted regions that have normal myocardial blood flow. While transient HF can occur during the acute phase of a myocardial infarction or with unstable angina, chronic HF slowly develops after establishment of the infarct, with evolution of LV remodeling and adverse changes in both the infarcted and the noninfarcted regions. Several animal models have been developed to mimic this condition, specifically the rat infarct model (263, 342, 343), the canine direct-current shock model (299), and the pig infarct model (262). Like in humans, in these models infarction does not always result in true HF (i.e., decreased LV systolic function, chamber dilation, or elevated LV end-diastolic pressure), although a predictable number of animals progress to a state similar to human HF. A particularly robust and well-characterized canine model of HF has been developed by Sabbah et al. (386), where HF is produced by repeated bouts of ischemic injury induced by microembolizations caused by intracoronary injections of 90-μm-diameter microspheres ~4–7 times 1 wk apart, which generates diffuse infarcts and progressive LV dysfunction, chamber dilation, and HF (384, 418).

Clinically, HF can develop in the absence of coronary artery disease in patients with a history of LV hypertrophy due to hypertension or aortic stenosis, though unlike HF in patients with a history of ischemic heart disease, LV chamber dilation develops relatively late in hypertensive patients who progress to HF (215). Animal models of LV hypertrophy have been developed using chronic aortic constrictions in rats, dogs, and pigs (504, 516). There are numerous studies on the effects of LV hypertrophy in rodents on myocardial substrate metabolism in the absence of HF (16, 251, 291, 396, 516, 518); however, there are few studies where the animals actually progressed from concentric LV hypertrophy to overt HF (e.g., decreased cardiac output, LV ejection fraction, and increase

LV end-diastolic pressure). In dogs and pigs subjected to aortic constriction, HF develops after 6–12 mo in ~40% of the animals, whereas the remaining animals hypertrophy but do not progress to failure (167, 504).

Another widely used model that does not involve myocardial ischemic injury is the rapid pacing-induced model in dogs, where the heart rate is increased to >220 beats/min, resulting in decompensated end-stage failure after 4–6 wk of pacing. This model is highly reproducible and has also been produced in pigs, sheep, and rabbits (10, 317, 347). The mechanisms that precipitate HF in the model are related to neurohormonal activation secondary to poor cardiac function, presumably due to poor diastolic filling and increased metabolic stress and decreased phosphorylation potential (314, 420).

B. Electron Transport Chain and Oxidative Phosphorylation Defects in Heart Failure

The focus of this review is on the metabolism of carbon substrates in HF. However, the ultimate fate of the reducing equivalents generated from intermediary metabolism is the electron transport chain (ETC) and oxidative phosphorylation, making it important to briefly address this topic (Fig. 7) [the reader is referred to several recent reviews that more specifically address mitochondrial and ETC defects in HF (49, 98, 253, 287, 477)]. In addition, HF generates defects in the transfer of the energy from mitochondrial ATP to the site of ATP hydrolysis and the function of the creatine phosphate system (97–99, 190, 257, 322–324, 463, 477); however, this topic is outside the scope of this review.

Studies in patients and animal models show that there is a decrease in tissue ATP content, a rise in ADP, and a fall in the phosphorylation potential (21, 22, 189, 257, 298, 314, 322–324, 420, 463, 470), thus impairing the kinetics for ATP utilization for cell contraction (myosin ATPase) and relaxation (sarcoplasmic reticulum Ca^{2+}-ATPase). In addition, HF impairs the capacity for the creatine kinase system to transfer mitochondrial ATP to

the myofibril (88, 97, 98, 257, 463, 477, 504). An impaired ETC could also affect the mitochondrial and cytosolic redox state ($NADH/NAD^+$) and the concentrations of ATP, ADP, and P_i, which could influence the rate of flux through key metabolic enzymes such as PDH or phosphofructokinase.

Mitochondria in the failing heart are characterized by a greater occurrence of membrane disruption and matrix depletion (383, 403, 417, 419), a lower capacity for respiration with a variety of substrates (136, 170, 334, 383, 397–399, 419), defects in complexes of the ETC (44, 49, 196, 286, 287, 298, 349, 404), and a decreased capacity for oxidative phosphorylation (49, 253, 262, 286, 349). In rats with infarct-induced HF, there is a decrease in myocardial ATP and creatine phosphate and in ADP stimulated respiration in isolated permeabilized myocyte bundles with glutamate and malate as substrates at 12 wk after coronary ligation (397–399). Myocardial homogenates from cardiomyopathic Syrian hamster have a decreased ability to oxidize fatty acids (19, 205), which was subsequently shown by Hoppel et al. (170) to reflect a generalized defect in oxidative metabolism that is not specific for fatty acids. This defect in oxidative phosphorylation was found in interfibrillar mitochondria, and not in subsarcolemmal mitochondria (170). To our knowledge, this is the only study to investigate the effects of HF on select populations of cardiac mitochondria (253).

Studies in patients and animals with HF show a reduced activity of several ETC complexes. Jarreta and co-workers (49, 196) measured the activity of complexes I-IV in myocardial biopsies from HF patients. They observed that the activity of complex III was reduced by 35% with no changes in the other complexes in patients with either idiopathic dilated cardiomyopathy or a history of ischemic heart disease compared with donor hearts with normal cardiac function. The only genetic defects they found were neutral polymorphisms in the cytochrome *b* gene, strongly suggesting that the decreased activity in the respiratory chain complex III activity was not due to expression of an abnormal gene (196). This observation is
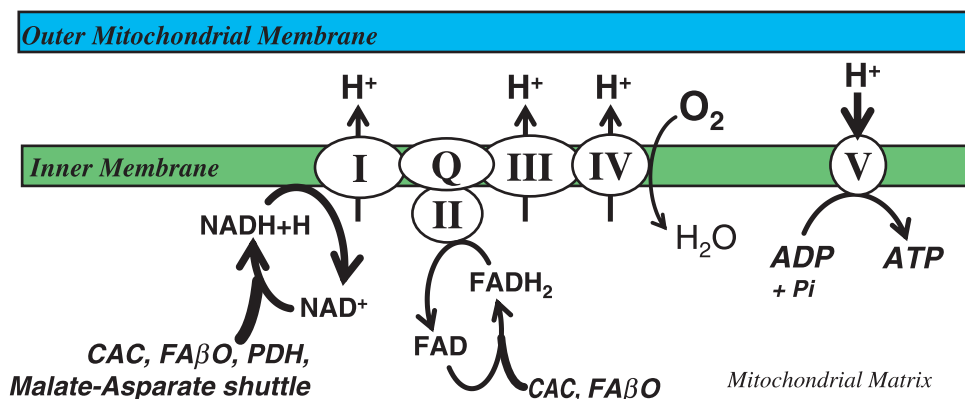
FIG. 7. The electron transport chain. Studies in heart failure (HF) patients show conflicting results, with reduced activity of either complex I (404), complex III (49, 196), or complexes III and IV (44). Conflicting results are also reported in the canine rapid pacing model of HF, with defects observed in either complex I activity (184) or in complexes III and V (286). CAC, citric acid cycle; FAβO, fatty acid β-oxidation; PDH, pyruvate dehydrogense.

Mitochondrial Matrix

further supported by the fact that patients with a congenital complex III defect do not present with cardiomyopathy (316). Depressed complex III activity could not be attributed to mitochondrial DNA damage or depressed mitochondrial gene expression (196). Buchwald et al. (44) measured the activity of the ETC complexes in isolated mitochondrial particles from transplant recipients with dilated cardiomyopathy (DCM) and from unused donor hearts. Cytochrome c content and the activity of complexes III and IV were decreased by 21, 24, and 28% compared with donor hearts, with no differences in the activities of complexes II and V. On the other hand, similar measurements of respiratory complex activities in HF patients by Scheubel et al. (404) showed a 28% decrease in complex I activity compared with donor hearts, but no changes in complexes II-IV or of the CAC enzyme citrate synthase.

Defects in the ETC have also been identified in the canine rapid pacing model of HF. Marin-Garcia et al. (286) showed that in severe end-stage decompensated pacing-induced HF (LV end-diastolic pressure of 38 mmHg), there was no decrease in the activities of complexes I, II, or IV, but a highly significant decrease in the activities of complexes III (81% reduction) and V (70% reduction), with no change in the activity of citrate synthase. They also observed a similar reduction in the activities of these enzymes, although to a lesser extent, in skeletal muscle. The defects in ETC complexes were correlated to plasma concentration of tumor necrosis factor-α (286), and treatment of dogs with etanercept, a soluble tumor necrosis factor receptor fusion protein, partially prevents the defect, suggesting the possibility that tumor necrosis factor-α somehow regulates ETC complexes III and IV (312). In contrast, using the same pacing-induced canine model of HF, Ide et al. (184) reported a 50% decrease in complex I activity in cardiac submitochondrial particles, which was associated with greater production of reactive oxygen species.

Regardless of such differences among studies, these findings are consistent with the concept that in HF there is a major lesion in oxidative metabolism at the level of the ETC. On the other hand, there is a large disparity among the clinical and experimental studies regarding the sites of the lesions in the respiratory chain. It is also unclear if *1*) these effects are isolated to a subpopulation of cardiomyocytes, or if they occur uniformly throughout all cells, or *2*) they are localized to either subsarcolemmal or intrafibrillar populations of mitochondria. In addition, the consequences of these lesions on cardiac metabolism, oxidative damage, and contractile function are not clear. One possibility is that impairment in the ETC reduces the in vivo capacity for myocardial ATP generation and thus limits cardiac contractile function during high work states, such as exercise or acute adrenergic stress. Nikolaidis et al. (328) recently observed a reduced $M\dot{V}O_2$ response to increased cardiac power in dogs with pacing-induced HF that was due to a limitation in oxygen extraction, but not in myocardial blood flow. These finding are consistent with the concept of impaired mitochondrial respiratory capacity in HF, resulting in reduced ability to generate ATP in response to increased demand for cardiac power.

Recent studies demonstrate that downregulation of fatty acid oxidation enzymes can be triggered by a defect in the ETC in the mouse heart (149). Hansson et al. (149) knocked out mitochondrial transcription factor A and observed a progressive decline in ETC activities and mitochondrial ATP production. The downregulation of enzymes of fatty acid oxidation occurred early in the development of mitochondrial dysfunction and was accompanied by an upregulation of hexokinase with no change in other glycolytic enzymes. The mechanisms that link impaired respiratory chain function to changes in the expression of metabolic genes are unclear. Nevertheless, these findings suggest the possibility that the metabolic switch in HF could be secondary to impaired ETC function.

C. Substrate Metabolism in Heart Failure

1. Results from HF patients

While numerous studies in patients and animal models show that HF reduces the capacity to transduce the energy from foodstuffs into ATP, less is known about the effects of HF on myocardial substrate metabolism and fuel selection. There are few measurements of myocardial substrate oxidation in HF patients, and the results are somewhat conflicting. In general, the data support the concept that in the early stages of HF there is a normal (or slightly elevated) rate of fatty acid oxidation, and in advanced or end-stage HF there is downregulation of fatty acid oxidation. Paolisso et al. (338) found increased extraction and uptake of plasma FFA and decreased glucose uptake in congestive HF patients [$n = 10$; New York Heart Association (NYHA) classes II and III] compared with age-matched healthy individuals. In addition, the rate of myocardial lipid oxidation, as estimated from the transmyocardial respiratory quotient, increased by 50% in HF patients. In these patients there was a corresponding 60% decrease in cardiac carbohydrate oxidation compared with healthy controls. It should be noted that these indirect measurements of substrate oxidation do not differentiate between lactate, glucose, or glycogen oxidation. HF patients had increased plasma norepinephrine (5.2 ± 0.2 vs. 1.4 ± 0.3 pmol/ml) which corresponded to increased plasma FFA concentrations (1.0 ± 0.1 vs. 0.66 ± 0.08 mM, presumably due to greater β-adrenergic stimulation). However, the HF patients also had significantly higher plasma insulin levels, which would likely stimulate glucose uptake and oxidation by the heart. The alterna-

tions in plasma substrate and norepinephrine concentrations make if difficult to separate HF-induced changes in myocardial metabolic pathways from changes in the metabolic milieu.

Using PET, Taylor et al. (453) found greater myocardial uptake of a radiolabeled fatty acid analog and less radiolabeled deoxyglucose uptake in class III HF patients compared with healthy subjects. On the other hand, patients with idiopathic dilated cardiomyopathy appear to have greater myocardial glucose uptake and less fatty acid uptake compared with normal people. Yazaki et al. (503) found a reduced retention of the radiolabeled fatty acid analog ^{123}I-beta-methyl-iodophenylpentadecanoic acid (BMIPP) in circumscribed cardiac regions of patients with severe idiopathic dilated cardiomyopathy, consistent with impaired fatty acid utilization; however, the kinetics of BMIPP are complex and not validated in failing myocardium (228, 234, 363). A recent PET study by Dávila-Román et al. (79) showed decreased fatty acid utilization and increased myocardial glucose metabolism in patients with idiopathic dilated cardiomyopathy. It is important to note that with PET one can estimate glucose uptake from the accumulation of ^{18}F-deoxyglucose 6-phosphate in the tissue during infusion of ^{18}F-deoxyglucose tracer, or from estimations derived from the decay in tissue ^{11}C content following injection of [^{11}C]glucose; however, it is not possible to directly measure the rate of glucose oxidation, as done with invasive studies using [^{14}C]glucose and myocardial production of ^{14}CO$_2$ (492, 493). The discrepancy among these clinical investigations may be attributable to the severity of HF, supporting the idea that in the early stages of HF there is a normal (or slightly elevated) rate of fatty acid oxidation, with a dramatic downregulation of fatty acid oxidation in advanced or end-stage HF.

2. Results from animal models of HF

Studies in the canine rapid pacing model of heart failure by Recchia et al. (359) support the concept that there is relatively normal myocardial substrate metabolism in the early and middle stages of the development of HF, but a sharp switch away from fatty acid towards carbohydrate oxidation in end-stage HF (e.g., LV end-diastolic pressure ≥25 mmHg). The substrate switch was evidenced by a sharp rise in glucose uptake and a fall in fatty acid uptake that coincided with a steep elevation in LV end-diastolic pressure and cardiac decompensation, all occurring during the last week of pacing. Further support for this late switch comes from the transmyocardial respiratory quotient (an estimate of substrate oxidation from CO$_2$ production and MV̇O$_2$, with 0.7 reflecting 100% fat oxidation, and 1.0 100% carbohydrate oxidation), which did not change significantly from the prepacing value (0.73 ± 0.06) at 3 wk of pacing (0.80 ± 0.04), but increased sharply with the onset of decompensation

(0.87 ± 0.09, 0.96 ± 0.08, and 1.02 ± 0.06 at 24, 27, and 29 days of pacing). Nikolaidis et al. (329) observed a similar fall in fatty acid uptake in end-stage HF in this model despite a rise in plasma fatty acid concentration, but also found decreases in glucose and lactate uptake despite no change in MV̇O$_2$. Studies using isotopic tracers to directly measure substrate oxidation showed a significant increase in glucose oxidation and decrease in fatty acid oxidation in end-stage pacing-induced failure compared with normal dogs (252, 332).

Interestingly, the metabolic changes in canine pacing-induced HF are paralleled by a fall in cardiac production of NO metabolites. Whether reduced NO synthesis and a switch in substrate metabolism, in the failing heart, are linked by a cause-effect relationship is presently unknown. Convincing evidence indicates that NO exerts a direct action on cardiac substrate utilization (83, 84, 358, 360, 361, 447), but only one of those studies (447) determined the effects of permanent reduction in NO synthesis in hearts isolated from endothelial cell NOS knock-out mice, while the others tested short-term effects (see sect. II*G*). Molecular alterations in the failing heart, including downregulation of metabolic enzymes (see sect. IV) and of NOS (423), occur over long periods of time. Ideally, the relationship between lack of cardiac NO and substrate selection should be tested by reestablishing a normal NO production selectively in the heart and during the progression of HF, a difficult task to perform with the pharmacological tools presently available. A further element of complexity is that the lack of NO in the failing heart might *1*) lead to excessive mitochondrial O$_2$ consumption (498) and *2*) contribute to coronary microcirculatory dysfunction (464), therefore causing subliminal myocardial ischemia in the absence of coronary macrovascular disease, resulting in metabolic adaptations. In fact, as mentioned in section IV*D*, pacing-induced HF, similar to human dilated cardiomyopathy, is characterized by regional myocardial perfusion abnormalities, detectable only with careful assessment of regional flow distribution (154, 321).

Studies in early-stage HF in the canine microembolization model suggest that the changes in substrate use are a late-stage phenomenon. Chandler et al. (52) measured myocardial substrate oxidation in dogs with well-compensated microembolization-induced HF using isotopic tracers and found no differences in myocardial glucose, lactate, or fatty acid metabolism compared with normal dogs. These results support the concept that there is not a decrease in fatty acid oxidation early in HF and that the dramatic downregulation of fatty acid oxidation enzymes and the switch to carbohydrate metabolism occurs only in more severe or decompensated HF.

Studies in rats 8 wk after myocardial infarction showed an elevated LV end-diastolic pressure (12 vs. 3 mmHg) and decreased developed pressure (69 vs. 78 mmHg compared with sham rats in vivo) (362). When hearts were isolated and perfused with erythrocyte con-

taining buffer, there was no difference in M$\dot{V}_{O_2}$ between groups; however, there was an 84% increase in glucose oxidation with no significant change in palmitate oxidation (362). These results suggest that early in the development of HF in this model there is activation of glucose metabolism but not a reduction in exogenous fatty acid oxidation.

D. Alterations in Expression and Function of Metabolic Proteins in Heart Failure

Studies describing the expression of metabolic enzymes in HF have primarily focused on advanced end-stage failure and have provided consistent evidence for a downregulation of myocardial fatty acid oxidation enzymes, which is consistent with the switch in substrate metabolism away from fatty acid oxidation toward greater glucose oxidation. Sack et al. (389) showed that explanted hearts from transplant recipients had a dramatic downregulation of the enzymes of the fatty acid oxidation pathway compared with unused donor hearts. The failed hearts had significantly reduced mRNA for the fatty acid oxidation enzymes long-chain acyl-CoA dehydrogenase (LCAD) and medium-chain acyl-CoA dehydrogenase (MCAD), as well as protein levels of MCAD, with no downregulation of the mRNA for the glycolytic enzyme GAPDH. Karbowska et al. (210) found a 54% reduction in PPARα protein level in ventricular biopsies from five patients with compensated end-stage HF compared with control donor hearts. This suggests that the downregulation of the mRNA, protein expression, and activity of PPARα regulated genes in end-stage HF is due to less PPARα/RXRα heterodimer activity. The expression of RXRα has not been reported in HF patients.

Studies in dogs with end-stage pacing-induced HF found a similar downregulation of enzymes involved in fatty acid oxidation; there was a 40% reduction in the activity and expression of MCAD and in the activity of CPT-I, which correlated with a 40% decrease in the rate of fatty acid oxidation and a 155% increase in the rate of glucose oxidation measured in vivo (252, 332). Surprisingly, MCAD downregulation was not paralleled by reduced expression of PPARα, the nuclear receptor that controls the expression of many key enzymes of the fatty acid oxidative pathway (Fig. 6) (332). On the other hand, consistent with impaired fatty acid oxidation, we found a reduced availability of RXRα, the obligate cofactor of PPARα, which significantly correlated with MCAD expression and activity. Based on previous findings in vitro (96), we hypothesized that RXRα downregulation was due to sustained hypoxia in the paced ventricle consequent to supply/demand mismatch, even if we could not detect significant changes in mean coronary blood flow and in the rate of nonoxidative glycolysis. This hypothesis is supported by the finding that pacing-induced HF is characterized by a reduced subendocardial blood flow, especially in the LV free wall, when the pacemaker is activated (154). Similar regional myocardial perfusion abnormalities have been observed with PET in patients with idiopathic dilated cardiomyopathy (320, 321).

Measurements of the mRNA expression in myocardium from dogs with end-stage pacing-induced HF suggest that not only the mRNA levels of key enzymes of the fatty acid oxidation pathway are downregulated, but also GLUT-1, GLUT-4, GAPDH, PDH (E$_2$ subunit), and PDK-4 were reduced in failing hearts compared with normal myocardium (252, 356). This suggests that the failing heart represses the expression of all metabolic enzymes, rather than selectively suppressing fatty acid oxidation enzyme and potentiating the carbohydrate pathway.

Studies in less advanced HF suggest that the change in the expression of metabolic genes is a late-stage phenomenon. Chandler et al. (52) analyzed the myocardium from dogs with well-compensated microembolization-induced HF. Mitochondria were isolated for the measurement of CPT-I activity and the ability of malonyl-CoA to inhibit CPT-I activity. As discussed above, the heart expresses two isoforms of CPT-I: liver (CPT-Iα) and heart (CPT-Iβ), with CPT-Iα not as sensitive to malonyl-CoA inhibition as CPT-Iβ (223, 300, 302). This has potential significance in HF since Depre et al. (86) showed that in human end-stage HF and in cardiac hypertrophy in the rat heart there is a significant reduction in the mRNA for CPT-Iβ, but no change in the mRNA for CPT-Iα. This could translate into predominance of the liver isoform in the failing heart and loss of malonyl-CoA sensitivity (357). However, we did not observe any difference in the maximal activity of CPT-I between groups, or in the sensitivity of CPT-I to malonyl-CoA inhibition in isolated mitochondria (52, 337), which suggests there was not a relative switch from the muscle form of CPT-I to the malony-CoA insensitive liver form. We did, however, observe a 22% decrease in the myocardial content of malonyl-CoA in HF, suggesting less in vivo inhibition of CPT-I activity (52). In addition, the total activity and the activation state of PDH, the key enzyme regulating myocardial pyruvate oxidation (and hence glucose and lactate oxidation), was not affected by HF. These data further support the concept that in the early stages of HF the myocardium primarily relies on fatty acid as an oxidative substrate, and that there is not yet a switch to greater glucose oxidation and less fatty acid oxidation.

Similar to our observations in dogs with HF, Martin et al. (289) found that the activity of CPT-I was not different between myocardial biopsies obtained from HF patients undergoing transplantation compared with nonfailing donor hearts. However, they did find that the activity of CPT-II was significantly reduced. Consistent with this observation, the myocardial content of long-chain

acylcarnitine was increased over fourfold, and the free carnitine content was reduced by one-half in the HF patients. This study did not measure mitochondrial volume density or the activity of marker enzymes (e.g., citrate synthase), so it is unclear if the HF patients had a general reduction in mitochondrial density.

Studies in the rat infarct model of HF found that 20 wk after coronary artery ligation there is a decrease in the mRNA expression of selected fatty acid oxidation enzymes (fatty acid binding protein, MCAD, and very-long-chain acyl-CoA dehydrogenase) with no change in CPT-I or long-chain acyl-CoA dehydrogenase (362, 374). HF develops in this model (e.g., increase in LV end-diastolic volume and decrease in LVEF) at ~12 wk after infarction (263, 342, 343, 362, 374). There was also decreased protein expression for MCAD (362, 374), suggesting a response similar to patients in end-stage HF (20, 388, 389) or dogs with decompensated pacing-induced HF (332, 359). Iemitsu et al. (186) found approximately an 80% reduction in the mRNA expression of PPARα and of the fatty acid oxidation enzymes hydroxyacyl-CoA dehydrogense and CPT-1 6 mo after infarction in the rat; however, protein expression or enzyme activities were not reported.

Recent studies by Miyamoto et al. (308) in a rabbit model of volume overload hypertrophic HF induced by a carotid-jugular shunt found that after 6 wk there was no downregulation of PPARα protein expression, or in the expression of enzymes fatty acids β-oxidation (308). Volume overload resulted in eccentric hypertrophy, as documented by an increase in LV end-diastolic dimension without an increase in anterior or posterior wall thickness. The myocardial uptake of the fatty acid analog ^{125}I-iodophenyl 9-methylpentadecanoic acid was increased in the volume-loaded animals, suggestive of a greater fatty acid uptake and oxidation. Thus, in the early stages of cardiac failure in this model, there is no downregulation of the fatty acid oxidation pathway, but rather evidence for enhanced fatty acid oxidation without upregulation of the pathway (308).

There is little evidence for upregulation of the proteins involved in the carbohydrate utilization pathway (glucose transporters, glycolytic enzymes, or the PDH complex) in HF. Paradoxically, there is a decrease in glycolytic enzyme activity and expression despite increased glycolysis in severe rapid pacing HF in dogs (97, 252) and in patients with either hypertrophic or dilated cardiomyopathy (206). Studies in the rat infarct model of HF found an increased protein expression of GLUT-1 and downregulation of GLUT-4 compared with sham hearts (374). We recently observed that at end-stage pacing-induced HF in dogs, there is downregulation of mRNA for GLUT-1, GLUT-4, and GAPDH, with no change in the GLUT-1 and GLUT-4 protein content in the sarcolemmal membrane, but a decrease in the protein expression and activity of GAPDH (252). Paradoxically, there was an increase in glucose uptake and oxidation despite downregulation of the pathway (252, 332). Studies in Syrian hamsters found reduced activity of PDH in two cardiomyopathic strains (reduction of 68–84% compared with normal hearts) (89). When the hearts were perfused with 5 mM dichloroacetate (DCA) to inhibit PDK and convert the enzyme to the dephosphorylated active form, there was an increase in PDH activity and a significant increase in systolic function of the heart, but the maximal activity of PDH was still significantly less in cardiomyopathic animals (32 and 38% reduction from values obtained from normal hamsters). These results suggest that in this model of HF there is less total PDH enzyme present and greater phosphorylation inhibition that contributes to contractile dysfunction. We recently observed greater protein expression of PDK4 and less PDH E2 subunit, and no change in PDH activity in dogs with end stage pacing-induced HF compared with normal dogs, yet the rate of glucose oxidation was elevated by 2.5-fold (252). Taken together, these results suggest that any increase in glycolytic flux and glucose oxidation with HF is due to alterations in pathway regulation that are secondary to suppression of fatty acid oxidation, and are not due to upregulation of proteins involved in glucose uptake, glycolysis, or pyruvate oxidation.

Little is known about the effect of HF on myocardial lactate metabolism. Recent studies in the rat infarct model of HF demonstrated upregulation of the lactate transporter MCT-1 that corresponded to an increase in the V_{max} for lactate uptake in isolated cardiomyocytes (202). A similar increase in MCT-1 expression and myocardial lactate transport was observed in rats with HF caused by chronic volume overload induced by an arterial-venous fistula (11). The effects of HF on MCT-1 expression have not been reported in large animal HF models or patients, nor have the effects of HF on myocardial lactate uptake been assessed under conditions of cardiac stress or elevated arterial lactate concentrations.

V. THERAPEUTIC POTENTIAL FOR MANIPULATION OF SUBSTRATE METABOLISM

A. Short-Term Metabolic Therapy to Optimize Cardiac Function

On the basis of our previous discussion, increasing the flux through PDH may improve myocardial contractile function in HF. While this effect might not be effective in advanced end-stage HF, where the metabolic substrate preference has already switched to reduced fatty acid oxidation and accelerated glucose oxidation (252, 332, 359, 389, 428), it could be effective in the earlier stages of HF, when substrate oxidation is relatively normal (52,

338). In support of this, Bersin and co-workers (27, 28) observed improved contractile function in ten HF patients (NYHA classes III and IV) treated with intravenous DCA to inhibit PDH kinase, activate PDH, and increase pyruvate oxidation. DCA was infused at $1.67 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 min, and cardiovascular measurements made during the treatment period were compared with values obtained immediately before infusion. Myocardial lactate uptake increased during DCA infusion despite a significant fall in arterial lactate concentration. Consistent with a stimulation of PDH, during treatment with DCA there was a significant increase in stroke volume and stroke work, and an increase in LV mechanical efficiency from 15.2 to 20.6%. Although rates of glucose or FFA uptake and oxidation were not measured, these results suggest that DCA increases pyruvate oxidation and mechanical efficiency by switching the heart towards the more efficient fuel. However, one should use caution in interpreting these results because of the lack of a vehicle-treated control group. To establish the mechanism of action of DCA in improving ventricular function in HF patients, it is important to show that DCA increases the rates of glucose and lactate oxidation and decreases fatty acid oxidation. We observed a similar increase in LV pump function without an increase in LV energy expenditure in response to acute treatment with the fatty acid oxidation inhibitor ranolazine in dogs with microembolization-induced HF (53, 382).

In vitro studies demonstrate that high concentrations of pyruvate increase contractile function and potentiate the contractile effects of β-adrenergic stimulation in normal myocardium (46, 160, 283) and in isolated samples of failing human myocardium (151, 157, 161). Hermann et al. (159) evaluated the effects of an acute intracoronary infusion of sodium pyruvate on LV function in NYHA class III HF patients with dilated cardiomyopathy (ejection fraction <25%). The estimated pyruvate concentration in the coronary artery was between 3 and 6 mM (well above the normal levels of ~0.1 mM). Pyruvate infusion resulted in a rapid increase in LV peak dP/dt, ejection fraction, and cardiac output that immediately reversed upon cessation of the infusion (158, 159). The mechanism for this response is unclear but could be due to greater pyruvate oxidation, increased cytosolic phosphorylation potential, or effects on the Ca^{2+} transient (151, 157, 161, 283). From a practical standpoint, it is not feasible to intravenously infuse sodium pyruvate to attain high arterial pyruvate concentrations due to the high sodium load that accompanies infusion of the sodium salt. It is possible to avoid this problem by infusing glycerol esters of pyruvate, which was recently shown to elevate arterial pyruvate concentrations and reduce myocardial infarct size during reperfusion in pigs (432); however, this approach has not been evaluated in HF.

Another means to rapidly enhance glucose oxidation and inhibit fatty acid oxidation in humans is to raise plasma insulin concentration. The effects of insulin on the heart are complex in that insulin directly stimulates myocardial glucose uptake (42, 194), but also dramatically suppresses lipolysis in adipocytes and thus indirectly stimulates myocardial glucose uptake and oxidation via the Randle cycle (42, 108, 495). Cottin et al. (70) observed an improved wall motion score and LV ejection fraction in patients with ischemic heart disease and LV dysfunction when they were treated with an infusion of insulin under normoglycemic conditions (LV ejection fraction increased from 38.1 ± 6.4 to 53.3 ± 11.6 after 1 h); however, the study was not blinded, and there was no control group. Nikolaidis et al. (326) recently demonstrated that a continuous infusion of the insulinomimetic glucagon-like peptide-1 (GLP-1) over a 2-day period improved LV function and increased myocardial glucose uptake in conscious dogs with advanced pacing-induced HF (326). Moreover, treatment with GLP-1 increased myocardial glucose uptake and increased LV mechanical efficiency (327).

Taken together, there is evidence from small clinical and animal studies to support the concept that acutely stimulating myocardial carbohydrate oxidation and inhibiting myocardial fatty acid oxidation can rapidly improve LV function and mechanical efficiency. The cellular mechanisms responsible for this effect are unclear but are likely due to the various effects described in section IIF. While the clinical data are intriguing, they are not definitive, and large-scale controlled clinical trials are needed before conclusions regarding clinical benefit can be drawn.

B. Long-Term Metabolic Therapy to Slow Heart Failure Progression and Improve Function

Chronic inhibition of myocardial FFA oxidation has been investigated with the fatty acid oxidation inhibitor trimetazidine (105) in HF patients (23, 115, 373) and rodent models (88a, 446). Trimetazidine is an effective generic antianginal drug used extensively outside of North America (78, 254, 427, 435, 445) and is a potent and selective inhibitor of long-chain 3-ketoacyl thiolase (207, 268). In addition, studies in rats and isolated myocytes show that trimetazidine alters myocardial phospholipid metabolism, stimulating the turnover and accumulation of long-chain fatty acids into phospholipid (413, 414), decreasing the fraction of phospholipids containing linoleic acid, and increasing the content of phospholipids comprised of oleic and stearic acids (415). Studies in cardiomyopathic Syrian hamsters (a HF model with severely decreased PDH activity; Ref. 89) found that chronic treatment with trimetazidine extended the average survival

time on treatment from 364 to 560 days (88a). At the time this study was performed, trimetazidine was not known to be an inhibitor of fatty acid oxidation; therefore, the relationship between metabolic alterations and HF progression was not investigated.

A small clinical trial showed that 2 mo of treatment with trimetazidine resulted in significant improvement in LV ejection fraction at rest and enhanced LV wall motion during a dobutamine stress test compared with placebo in NYHA classes II and III HF patients (23). In two recent small clinical studies trimetazidine was shown to improve systolic LV function in patients with diabetes and ischemic cardiomyopathy compared with placebo (115, 373). Interestingly, 6 mo of trimetazidine improved diastolic function, as assessed by an increase in the peak E/A ratio on mitral flow (from 0.68 ± 0.1 to 0.89 ± 0.3), while there was no change in the patients treated with placebo (373). Trimetazidine has not been evaluated in patients with HF from other than an ischemic origin, nor have large-scale clinical trials been conducted.

Another approach to suppression of myocardial fatty acid oxidation is inhibition of CPT-I. Studies by Rupp and co-workers (376–378, 466, 515) demonstrated that chronic treatment with etomoxir to rats with LV hypertrophy secondary to aortic banding results in improved LV function and sarcoplasmic Ca^{2+} handling, increased expression of SERCA2, and attenuated the transition from compensated to failing cardiac hypertrophy. We recently tested the hypothesis that pharmacological inhibition of CPT-I with oxfenicine can prevent ventricular remodeling and slow the progression of pacing-induced HF in dogs (259). Treatment with oxfenicine significantly attenuated LV dilation and hemodynamic dysfunction at 28 days of pacing (Fig. 8) and significantly extended the duration of pacing needed to reach terminal failure (LV end-diastolic pressure = 25 mmHg). In addition, oxfenicine completely prevented LV wall thinning and the activation of matrix metalloproteinases. Interestingly, inhibition of CPT-I resulted in increased expression of PPAR-α regulated genes and prevented the HF-induced fall in the mRNA for metabolic enzymes. As recently noted by Rupp and co-workers (378, 514), inhibition of CPT-I results in not only a reduction in the rate of myocardial fatty acid oxidation, but may also simultaneous stimulate the PPARα/RXRα complex through the build up of long-chain fatty acyl-CoA in the cytosol. This could result in a paradoxical stimulation of the expression of the enzymes of fatty acid oxidation but decrease flux through the pathway. Rupp and co-workers (377, 378) noted that inhibition of CPT-I in rats with aortic banding partially prevented both the contractile dysfunction and the downregulation of SERCA2, which they speculated could be due to PPARα/RXRα regulation of SERCA2 expression, noting similarities between the SERCA2 regulatory region and the PPARα response element (PPRE). Thus chronic inhibition of myo-
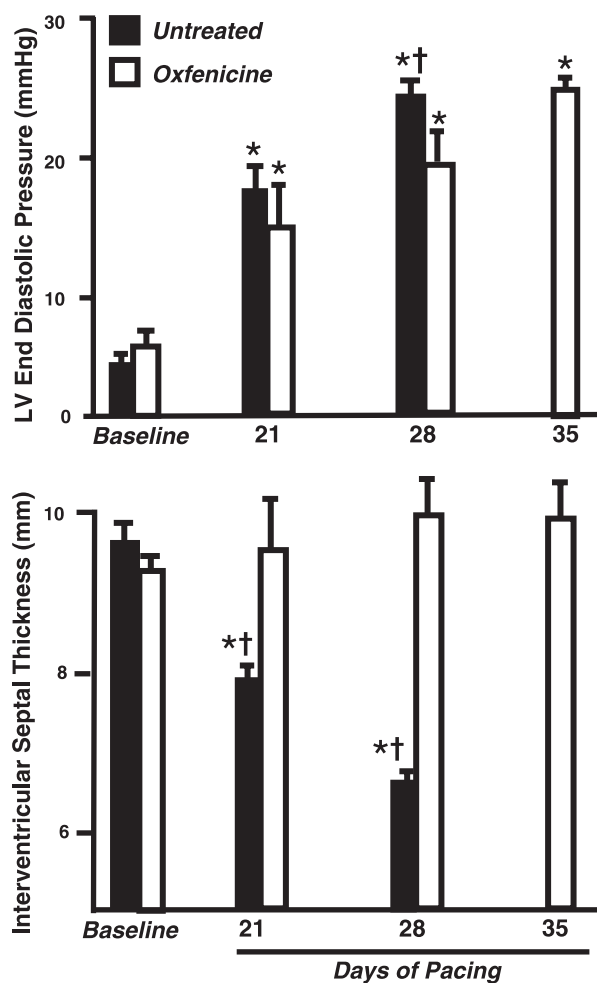

FIG. 8. Effects of the CPT-I inhibitor oxfenicine (60 mg/kg po once daily) on left ventricular (LV) end-diastolic pressure (*top*) and end-diastolic interventricular septal thickness (*bottom*) in dogs subjected to rapid pacing-induced heart failure. Treatment was initiated on the first day of pacing. *$P < 0.05$ compared with baseline. †$P < 0.05$ compared with oxfenicine-treated group at the same time point. [Drawn from data presented in Lionetti et al. (259).]

cardial fatty acid oxidation at the level of CPT-I in HF could have very different results than a similar suppression of fatty acid oxidation with trimetazidine (which acts directly on mitochondrial fatty acid β-oxidation at the level of long-chain 3-keto-acylthiolase). The effects of CPT-I inhibition with etomoxir were assessed in an open label pilot study in class II-III HF patients, showing improved LV function and exercise performance following 3 mo of treatment (38, 405). The results of controlled trials with CPT-I inhibitors have not been reported.

Conceptually, another means to switch substrate metabolism would be to directly stimulate glucose uptake or pyruvate oxidation; however, pharmacological agents are not currently available for the chronic inhibition of PDK, or activation of glucose transport or glycolysis. Studies in transgenic mice provide insight for the potential for this approach. Cardiac specific overexpression of GLUT-1 pre-

vented LV dysfunction in response to ascending aortic constriction and reduced mortality and depletion of high energy phosphates (256), and GLUT-4 ablation in mice results in LV hypertrophy (1). These results suggest that pharmacological activation of carbohydrate oxidation has potential as a drug target for the treatment of HF.

Dietary supplementation with either coenzyme Q or carnitine has been proposed for the treatment of HF. Acute and chronic administration of carnitine can increase glucose oxidation in the isolated perfused rat heart by increasing the acetylcarnitine concentration and decreasing the acetyl-CoA concentration, and thus relieving acetyl-CoA inhibition on PDH (see Fig. 3) (40, 407). A randomized double-blind trial in 472 myocardial infarction patients showed that oral carnitine therapy (6 g/day) initiated within 24 h after the onset of chest pain failed to effect clinical outcome or LV injection fraction over the course of 1 yr of treatment; however, it did significantly reduce the rate of increase in the LV end-diastolic volume (187). Controlled trials in HF patients have not been reported. The rationale for supplementation with coenzyme Q is that this will overcome possible lesions in the ETC, as discussed in section IV*B*. While improved LV function was suggested in small uncontrolled trials in HF patients (191, 387), a double-blind crossover trial of oral coenzyme Q versus placebo in 32 HF patients (LV ejection fraction of 26%) showed that 3 mo with oral coenzyme Q did not affect resting LV systolic function or the patient's quality of life despite more than a doubling of the plasma levels of coenzyme Q (484).

Long-term β-adrenergic receptor antagonists reduce mortality and improve LV function in HF patients (39, 168), and in clinical studies this improvement is associated with a switch in myocardial metabolism away from fatty acid uptake and oxidation towards more glucose uptake and carbohydrate oxidation (100, 101, 480), and greater lactate uptake (5). The mechanisms for these effects are not known, nor have they been demonstrated in large-scale clinical trials. We observed that 3 mo of metoprolol treatment in dogs with coronary microembolization-induced heart failure improved LV function and a significant 28% decrease in CPT-I activity (337), suggesting that the shift in substrate metabolism observed in the clinical studies could be due to downregulation of this enzyme.

Despite the clear beneficial effects of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists in slowing the progression of HF, there are little data on the metabolic consequences of suppression of the effects of angiotensin in HF. Indirect measurement of myocardial fatty acid metabolism using noninvasive imaging of the fatty acid analog BMIPP shows that HF patients have less cardiac accumulation of BMIPP and a faster washout rate from the myocardium than in healthy controls and that 6 mo of treatment with either enalipril

or candesartan improved cardiac function and increases the accumulation and slows the rate of BMIPP washout (450, 502), suggestive of greater fatty acid uptake and clearance after treatment. The interpretation of these findings is complicated by difficulties in quantitatively relating BMIPP kinetics to myocardial fatty acid uptake and oxidation (228, 234, 363). Nevertheless, these findings are consistent with the idea that improvement in cardiac function following chronic suppression of the renin-angiotensin system also alters myocardial fatty acid metabolism; however, it is not possible to draw a conclusion on the nature of these alterations.

Studies in infarct-induced HF in the rat show a decrease in myocardial ATP and creatine phosphate and in ADP stimulated respiration and that treatment with either an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist partially prevents this defect (397–399). Lygate et al. (280) recently used this model to compare the effects of chronic treatment with the PPARγ activator rosiglitazone, captopril, and rosiglitazone plus captopril for 8 wk after infarction (280). LV ejection fraction was moderately but significantly increased by rosiglitazone treatment, and the increase in LV end-diastolic pressures and reduced +dP/dt(max) was partially prevented by rosiglitazone treatment either alone or in combination with captopril. On the other hand, captopril prevented LV dilatation when given alone or in combination with rosiglitazone, while rosiglitozone alone did not. Importantly, mortality at 8 wk was 26 and 19% for the rosiglitazone and rosiglitazone plus captopril groups, respectively. Clinically, PPARγ agonists are associated with edema in HF patients and are generally contraindicated (455, 481). Further study is required before the effects of pharmacological stimulation of the various PPARs on cardiac function, remodeling, and progression in HF are understood.

VI. CONCLUSIONS

The alterations in myocardial substrate metabolism that occur in HF, and the causes and consequences of these abnormalities, are poorly understood. There is evidence to suggest that impaired substrate metabolism contributes to contractile dysfunction and to the progressive LV remodeling that are characteristic of the HF state. The general concept that has recently emerged is that myocardial substrate selection is relatively normal during the early stages of HF; however, in the advanced stages there is a downregulation in fatty acid oxidation, increased glycolysis and glucose oxidation, reduced respiratory chain activity, and an impaired reserve for mitochondrial oxidative flux. While recent work has described many of the molecular mechanisms responsible for the changes in myocardial metabolic phenotype that occur during nor-

mal physiology (e.g., maturation or fasting), we continue to have a poor understanding of the regulatory mechanisms that affect changes in the expression of metabolic proteins over the course of HF. Initial pharmacological studies suggest that manipulation of myocardial substrate metabolism has therapeutic potential for the treatment of HF. Taken together, we are just beginning to understand the complex role of energy substrate metabolism in HF, and there is a clear need for extensive work in this clinically important area.

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