The study of the process and control of the transitional cardiovascular physiology from the fetal to adult condition has brought enormous insight into the diagnosis, natural history and treatment of congenital, as well as acquired, cardiac abnormalities in children. It is now apparent that a remarkable passage also occurs in the metabolic maturation of the myocardium. The myocardial cell undergoes important changes in metabolic operations that include substrate preference, maintenance of cellular integrity, production and delivery of high energy phosphate, replication of the contractile apparatus as well as response to adverse metabolic and hemodynamic conditions. Remarkably, the functional capacity of the heart remains essentially constant throughout this period of differentiation. Indeed, the immature cardiovascular system demonstrates a striking capacity to accommodate severe physiologic burdens and metabolic alterations. These features, among others, have attracted the attention of numerous investigators from a variety of disciplines. Such diversity has resulted in a rich body of information which, in combination with newer techniques and theoretical approaches, bares many new questions relevant to the broader practice of cardiovascular medicine.

Surgical intervention for more complex anomalies in even the youngest individuals has brought neonatal cardiovascular surgery to a virtual specialty. Accuracy in preoperative diagnosis, advanced surgical skills, superior cardiopulmonary bypass techniques and exceptional postoperative management have led to remarkable reductions in mortality. However, some studies indicate that difficulties in providing cardioplegic protection may account for a significant proportion of present early hospital deaths occurring in the pediatric age group. It has become clear then that a clearer understanding of the special metabolic features of the immature myocardium could lead to improvement in myocardial protection, further reducing operative mortality in this age group.

The intent of this chapter is to review some specific aspects of the metabolic maturation of the myocardium. Functional and therapeutic correlates will be emphasized where possible. Important differences between the immature and adult myocardium that may influence their tolerance of adverse ambient conditions will be focused upon.

Substrate Utilization

Early investigations into developmental patterns of substrate utilization have, perhaps more than any other area, stimulated the study of the developmental biology of the heart. The importance of glycogen and glycolysis in the preservation of tissue viability under anaerobic conditions became apparent with the understanding of intermediary metabolism. Native tissue glycogen content of the heart seemed
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directly related to the preservation of function and individual survival [45]. However, other studies indicated that the variance in absolute glycogen content of the myocardium among species did not correlate well with the individual species resistance to anoxic insult [29]. Within a species, however, methods of augmenting glycogen content promotes improved function during and upon recovery from anoxic conditions [45].

Developmental changes in substrate preference have been documented in several laboratories and in a variety of mammalian species. Wildenthal [58] has emphasized that although the timing may vary among species the pattern is uniform. Data gathered by a variety of techniques including tissue homogenates, tissue culture, organ perfusion, isolated mitochondrial preparations and in vivo experiments have consistently demonstrated that glycolysis is the preferred metabolic pathway in the neonatal myocardium, rapidly giving way to non-esterified fatty acid oxidation in the early developmental period.

In a pivotal study, Wittels and Bressler [59] demonstrated that the neonatal myocardium has an impaired ability to utilize long chain fatty acids relative to the adult. These investigators also showed that the capacity for intramitochondrial beta-oxidation of fatty acids was not impaired in the immature heart. Neonatal and adult myocardial homogenates were equally capable of oxidizing short chain fatty acids (hexanoate). The long chain fatty acids, however, do not have direct access to the intramitochondrial space but must first be esterified to carnitine for transport across the mitochondrial membrane. This process is accomplished by acyl CoA-carnitine transferase located in the mitochondrial membrane and this appears to be the rate limiting step. The activity of this enzyme system in newborn rat preparations was about half that of the adult. In experiments using isolated mitochondrial preparations, Warshaw and Terry [53] demonstrated that while palmitoylcarnitine could be readily oxidized by fetal calf heart mitochondria, oxidation using palmitoyl-CoA was markedly reduced when compared with the six-week old calf heart. Similarly, cultured fetal mouse heart cells are capable of oxidizing octanoate as early as the end of the second trimester whereas utilization of long chain fatty acids was quite low and increased only a negligible amount toward term. The glycolytic pathway was found to be active and lactate release was nearly mole for mole in the second trimester preparations. Near term however the lactate release/glucose uptake ratio was substantially lower indicating oxidative pathways were becoming dominant [58]. It is of interest to note that this latter study also showed a decrease in glucose uptake as fetal cells closer to term were studied. This observation has been corroborated in the isolated fetal rat heart.

Fetal lamb mitochondria have been shown to have higher oxidative capacity for Krebs cycle intermediates than the newborn and the newborn greater than adult [56]. These observations challenged the presumptive primacy of anaerobic glycolysis in the myocardium at least toward term. Fisher and colleagues [9] examined this question in an ovine fetal in vivo model. At a mean gestational age of 121 days (term = 147), the fetal myocardial oxygen consumption was equivalent to the adult. Based on arteriovenous differences across the left ventricular free wall, it was shown that although glucose uptake was greater than in the adult it could account for only about a third of the total caloric needs. Lactate uptake was found also to be significantly greater than the adult and was calculated to supply 60% of the caloric needs of the heart. Pyruvate was found to make a "small but significant" contribution to the caloric requirements in both the fetus and adult [9]. Examining this question in a perfused working fetal pig heart, Werner and coworkers [57] used perfusion buffers containing glucose alone, glucose and octanoate or glucose with palmitate. Octanoate was found to have significant uptake, enough to account for the entire caloric needs of the heart. Under these conditions the tissue levels of citrate (as a Krebs cycle intermediate) rose, indicating the octanoate had undergone beta-oxidation to acetyl-CoA. Palmitate on the other hand had negligible uptake and tissue citrate levels were similar to those seen when glucose alone was the substrate. Glucose uptake, however, was suppressed by each fatty acid containing buffer, indicating that more than one mechanism may be operational. Carnitine levels have been shown to be somewhat lower in the immature myocardial preparation, however these levels could not account for the observed reduction in fatty acid metabolism. Further, carnitine supplementation does not provide any significant augmentation in long chain fatty acid oxidation.

The mechanism by which an increase in aerobic metabolism occurs in the perinatal period appears to be the increasing mass of mitochon-