COMPENSATION OF DEFICIENT FATTY ACID OXIDATION IN LONG
CHAIN ACYL-CoA DEHYDROGENASE KNOCKOUT MICE

S.M. Houten1, A.J. Bakermans2, H.J. Herrema3, C. Wagg4, H. te Brinke1,
T.H. van Dijk3, M. van Weeghel1, F.A. Wijburg1, G.D. Lopaschuk4, J.J.
Prompers2, D.-J. Reijngoud3, R.J. Wanders1

1Laboratory Genetic Metabolic Diseases, Academic Medical Center, The
Netherlands; 2Biomedical Engineering, Eindhoven University of
Technology, Eindhoven, The Netherlands; 3Laboratory of Pediatrics,
University Medical Center Groningen, The Netherlands; 4Departments of
Pediatrics and Pharmacology, Heritage Medical Research Center,
University of Alberta, Edmonton, Canada

Background: Mitochondrial fatty acid β-oxidation (FAO) is the prime pathway for the
degradation of fatty acids. FAO is essential to maintain energy homeostasis in liver,
muscle and heart and is of particular importance during fasting. FAO is catalyzed by a
series of enzymes, for most of which inherited defects have been described. The main
pathological consequences associated with FAO defects are hypoketotic
hypoglycemia, and skeletal- and cardio-myopathy. Mouse models are useful to study
the pathologic mechanisms and potential therapeutic approaches. In this study, we
used long chain acyl-CoA dehydrogenase (LCAD) knockout (KO) mice to study
hepatic and cardiac metabolism.

Methods: Hepatic glucose metabolism in fasted LCAD KO mice and wildtype
controls was assessed by infusing stable isotopes, followed by mass isotopomer
distribution analysis. Blood, plasma and organs were collected and used for
metabolite and enzyme measurements, and gene expression analysis. Cardiac function
was evaluated using cinematographic magnetic resonance imaging. Myocardial lipid
content was assessed using localized proton magnetic resonance spectroscopy.
Cardiac energy metabolism was measured using isolated working heart perfusions.

Results: Fasted LCAD KO mice have secondary carnitine deficiency and mild
hypoketotic hypoglycemia. Carnitine administration does not prevent hypoglycemia.
Our stable isotope infusion study shows that the hypoglycemia is caused by an
increase of glucose metabolic clearance rate and a small decrease of endogenous
glucose production. Importantly, gluconeogenesis rate was not affected, despite
decreased hepatic glucose-6-phosphate levels. Plasma lactate, pyruvate and alanine
levels were decreased indicating changes in tissue pyruvate metabolism.

Left ventricular ejection fraction was not impaired in LCAD KO mice despite cardiac
hypertrophy and lipid accumulation. The cardiac hypertrophy is non progressive and
expression markers for heart failure are not increased. Moreover in ex vivo working
heart perfusions, LCAD KO hearts functioned normally during 30 minutes of low
workload, but also during a 30 minute period of increased workload and pacing.
Remarkably, palmitate oxidation was increased in LCAD KO hearts, with a parallel
decrease in glucose oxidation rates.

Conclusions: Liver and heart can compensate for a significant defect in FAO as
demonstrated in the LCAD KO. Although whole body glucose use is increased in this
mouse model, LCAD KO hearts respond by increasing FAO rate. Failure of these
compensatory mechanisms may be crucial in the pathogenesis of FAO defects.