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Review

Comparative Metabolomics in Single Ventricle Patients after Fontan Palliation: A Strong Case for a Targeted Metabolic Therapy

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Abstract: Most studies on single ventricle (SV) circulation take a physiological or anatomical approach. Although there is a tight coupling between cardiac contractility and metabolism, the metabolic perspective on this patient population is very recent. Early findings point to major metabolic disturbances, with both impaired glucose and fatty acid oxidation in the cardiomyocytes. Additionally, Fontan patients have systemic metabolic derangements such as abnormal glucose metabolism and hypocholesterolemia. Our literature review compares the metabolism of patients with a SV circulation after Fontan palliation with that of patients with a healthy biventricular (BV) heart, or different subtypes of a failing BV heart, by Pubmed review of the literature on cardiac metabolism, Fontan failure, heart failure (HF), ketosis, metabolism published in English from 1939 to 2023. Early evidence demonstrates that SV circulation is not only a hemodynamic burden requiring staged palliation, but also a metabolic issue with alterations similar to what is known for HF in a BV circulation. Alterations of fatty acid and glucose oxidation were found, resulting in metabolic instability and impaired energy production. As reported for patients with BV HF, stimulating ketone oxidation may be an effective treatment strategy for HF in these patients. Few but promising clinical trials have been conducted thus far to evaluate therapeutic ketosis with HF using a variety of instruments, including ketogenic diet, ketone esters, and sodium-glucose co-transporter-2 (SGLT2) inhibitors. An initial trial on a small cohort demonstrated favorable outcomes for Fontan patients treated with SGLT2 inhibitors. Therapeutic ketosis is worth considering in the treatment of Fontan patients, as ketones positively affect not only the myocardial energy metabolism, but also the global Fontan physiopathology. Induced ketosis seems promising as a concerted therapeutic strategy.

Keywords: biventricular; heart failure; nutrition; Fontan; ketones; ketogenic therapy; metabolism; single ventricle

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1. Introduction

Children with complex congenital heart disease (CHD) and single ventricle (SV) physiology typically undergo several-step surgical palliation with the aim of a total cavopulmonary connection. In this so-called Fontan circulation, the subpulmonary pump is missing. Instead, the vena cavae are anastomosed directly to the pulmonary arteries, causing elevated systemic venous pressure and chronically decreased cardiac output [1–4].

Even if the outcome of SV patients is steadily improving, particularly their largest subgroup—i.e., SV patients with aortic atresia and a hypoplastic left heart (HLHS, 40% of cases [5]) and a morphologically right ventricle (RV) serving as the subsystemic

ventricle—performs worse than patients with a morphologically left ventricle (LV) [5–14], particularly with respect to atrioventricular valve failure, impaired ventricular function and/or failure of the Fontan circulation with upstream issues such as liver cirrhosis or protein-losing enteropathy [15–17]. Ventricular dysfunction is currently considered to be inevitable for SV patients [18]. In addition to these complications, Fontan patients reveal alterations in their pulmonary, hematologic, immunologic, endocrinologic and metabolic systems [1,19].

Pharmacological interventions for both patients with a failing biventricular (BV) and patients with a failing SV heart currently target either hemodynamics or the neurohormonal axis, with conflicting evidence regarding the clinical benefit [20–24]. A more recent axis actively targeted in BV HF therapy is the metabolic axis [25–36]. Maintaining ketone metabolism is reported to have a protective effect in hypertrophic and failing BV hearts [37–41]. Keeping in mind the metabolic alterations in the Fontan patient [42,43], metabolism may be a promising therapeutic target also in Fontan patients with a failing SV or Fontan circulatory failure.

Reviewing the literature, we compare the energy metabolism in patients with healthy, or with a failing BV heart with that reported in SV patients after Fontan palliation. Focusing on lipid and ketone metabolism, and focusing on the role of therapeutic ketosis in BV HF, a potential role of metabolism-targeted therapy in Fontan patients will be discussed.

2. Cardiac Energy Metabolism

The heart is a biomechanical pump with complex hemodynamics. Ninety percent of the cellular adenosine triphosphate (ATP) is used to sustain the contraction-relaxation of the cardiac muscle [44]. Mitochondria make up one-third of the cardiac myocyte volume [45]. In the whole human body, cardiomyocytes exhibit the highest content in mitochondria, consistent with the fact that the heart is the organ with the highest energy consumption [46]. Thus, it is not surprising that an altered energy state could contribute to HF. The energy starvation model has been proposed as the basis of progressive HF [47–50], taking into account alterations of the three different stages of ATP production: perturbed substrate consumption; altered oxidative phosphorylation; and reduced energy transfer to ATP-consuming reactions. ATP production is controlled and regulated by a very complex set of transcriptions of metabolically relevant proteins (receptors, regulators, transporters, enzymes) that can be quantified through analysis of metabolites.

2.1. Energy Metabolism in the Healthy Heart

The "omnivore heart" and its diverse substrate consumption. Cardiomyocytes have the capacity to oxidize fatty acids, carbohydrates, amino acids, ketones, and lactate [51]. The substrate preferences are changing with development. The fetus lives in a hypoxic environment, what was called 'Everest in utero' [52], and depends on his mother's metabolism. Glucose is the dominant substrate used for ATP production, with a very low level of fatty acids and high level of lactate [53,54]. Change of available substrates, increasing oxygen level and improved cardiac workload drive metabolic maturation. Originally, it was thought that within the first week postnatally, glucose use in the heart drops significantly with fatty acid oxidation rising [55], reaching an adult metabolic pattern. Recent studies hypothesize that transition to fatty acid oxidation may start earlier, from the late gestational period [56]. Due to the surge of oxidative capacity—one third of cardiac myocytes' volume being mitochondria—60–90% of the energy used for mechanical performance originates from mitochondrial fatty acid oxidation, with the remainder originating from glucose, lactate, and ketone bodies [57,58] (Table 1).

Table 1. State of the heart and metabolic state.

	Metabolic State					
	Substrate Consumption			**ETC**	**CK**	**Therapeutic Ketosis**
	Fatty acids	*Glucose*	*Ketone bodies*			
Healthy heart	60–70% [57,58]	Remaining [57,58]	Remaining [57,58]	balanced		
HfrEF	Early HF: no change [48,59,60] Late HF: ↓ [48,59,60]	Early HF: ↑ [48,59,60] Late HF: ↓ [60–66]	Progressing HF: ↑ [35,65,67–75]	Loss of electrons [76] Accumulation of ROS [76]	early HF: ↓ [48,77–79]	CO +40% [80] EF +8% [80]
BV-HF	↓ [81]	↑ [82–85]	Progressing HF: ↑ [69,86–88]	Loss of electrons [89,90] Accumulation of ROS [91,92]	↓ [89,93]	CO +27% [87] PVR—18% [87]
SV-HF	↓ [94]	↓ [95]	?	Loss of electrons [96] Accumulation of ROS [76,97,98]	?	?

BV, biventricular; CK, creatine kinase energy shuttle; CO, cardiac output; EF, ejection fraction; ETC, electron transport chain; HF, heart failure; PVR, pulmonary vascular resistance; ROS, reactive oxygen species; SV, single ventricle; ↑, increase; ↓, decrease. Note the similar findings for BV HF and SV HF with regards to substrate consumption (fatty acids, glucose, ketone bodies). Thus, therapeutic ketosis is worth considering in the treatment of Fontan patients.

Biosynthesis of ketone bodies is connected to various metabolic pathways such as beta-oxidation, Krebs cycle, sterol biosynthesis, glucose metabolism, and mitochondrial electron transport chain [36,99,100]. Among all organs, the heart tissue exhibits the highest levels of ketolytic enzyme activity, reflecting its ability to use ketone bodies [101]. Nonetheless, under physiological conditions, ketone bodies are not contributing significantly to cardiac metabolism [102], glucose and fatty acids being the predominant substrates [61,62].

Substrate utilization is meticulously regulated, which is mandatory due to the relatively small amount of stored ATP relative to the rates of myocytal ATP consumption [49]. One of the control mechanisms is the glucose-fatty-acid-cycle. Numerous parallel mechanisms regulating the substrate utilization in cardiomyocytes were discovered, such as glucose transporter (Glut) 1, Glut 4, or peroxisome proliferator activated receptors (PPAR) [59,103].

From fuel to ATP: oxidative phosphorylation. Oxidative phosphorylation begins with the oxidation of substrates, such as fatty acids and glucose, which are converted into acetyl-coenzyme A (CoA) through pyruvate or beta-oxidation. Acetyl-CoA is fed into the Krebs cycle. Under normal conditions, mitochondrial oxidative phosphorylation matches 90–95% of the myocardial ATP demand with glycolysis filling the gap [61].

From ATP to contractile work: creatine phosphate reserve of ATP. The creatine kinase (CK) energy shuttle plays a crucial role in maintaining energy balance in cells with high and fluctuating energy demands, such as cardiomyocytes: It comprises the conversion of creatine to phosphocreatine (and back), which serves as a rapid and reversible energy storage system. This pathway enables the efficient transfer of energy from the mitochondria, where ATP is produced by oxidative phosphorylation, to the cytosol, where it is consumed during contraction.

Regulation of metabolism through gene expression. Control and regulation of cardiac metabolism are complex and include overexpression or deletion of metabolically relevant proteins, such as receptors, regulators, transporters, or enzymes.

Peroxisome proliferator activated receptors. PPAR are a family of nuclear receptor proteins that play a crucial role in regulating the expression of genes involved in lipid and glucose metabolism, inflammation, and cellular differentiation. PPAR is an abundantly

expressed key regulator of cardiac substrate switching [104–107], including fatty acid oxidation, ketogenesis, and triglyceride synthesis, by upregulation of genes involved in fatty acid metabolism. Activation of PPAR upregulates genes of fatty acid oxidation (fatty acid transport protein/cluster of differentiation 36, malonyl-CoA decarboxylase, carnitine acyltransferase (CPT)-1, medium and long chain acyl-CoA dehydrogenases) [102]. PPAR was downregulated by hypoxia in rats' hearts [108].

Adenosine monophosphate-activated protein kinase pathway, GLUT and CPT. The adenosine monophosphate-activated protein kinase (AMPK) pathway is a critical cellular signaling pathway that plays a crucial role in regulating energy homeostasis in cells. The activation of the AMPK pathway leads to the phosphorylation of numerous downstream targets involved in metabolism, transcription, and protein synthesis. Through this pathway, CPT1, medium-chain acyl-CoA dehydrogenase, cluster of differentiation 36, and fatty acid transport protein 1 are decreased in HF [61]. Inhibition of CPT1 directly inhibits fatty acid oxidation by malonyl-CoA—a phenomenon called reverse Randle effect [105].

Histone acetylation/deacetylation. Acetylation is a protein post-translational modification controlling expression and transcription of genes, regulating embryonic development, postnatal fatty acid oxidation maturation, and heart hypertrophy. It enables the cell to quickly and effectively react to cellular stress [109]. Histone acetylation regulates the electrostatic connections between DNA and histones as well as between adjacent nucleosomes within a nucleosomal fiber, which controls transcription [110]. Histone acetylationtransferases (HAT), also known as lysine acetyltransferases, which relax chromatin structure, and histone deacetylases (HDAC) which reverse the HAT process, reduce transcriptional activity and are the main regulators of HAT [111]. HDAC can be divided into two types based on their architectures and patterns of expression [112]. All tissues express class I HDAC. Class II histone deacetylases interact with the MEF2 transcription factor to control fetal cardiac and stress-responsive genes [113,114]. Activity of GLUT1, GLUT4, PDK2, muscle-glycogen synthase, mCPT-1, MCAD, and ACC is higher in the non-failing adult human heart than in the fetal heart. In the failing human heart, those metabolic genes' activities decrease to the same levels as in the fetal heart [60].

2.2. Energy Metabolism in Biventricular Patients with Congestive Heart Failure

Disturbed substrate consumption. Once the heart has reached its metabolic adulthood, the main substrates used for ATP production are fatty acids (60–70%), followed by pyruvate (glucose/lactate), ketone bodies, and amino acids. In early stages of HF, myocardial fatty acid utilization may be unchanged or augmented. In advanced stages, the myocytes switch from fatty acid to glucose oxidation, returning to a fetal pattern of energy substrate metabolism [48,59,60] (Table 1). Furthermore, myocytes may become insulin-resistant, leading to a decline in glucose/pyruvate utilization (metabolic inflexibility) [60–66]. Even though glucose uptake is increased, it does not always translate into increased glucose oxidation. Through overexpression of Glut1, the uptake increases glycolysis. Per glucose molecule, glycolysis produces two molecules of ATP compared to 31 molecules of ATP by oxidation. Thus, the energy deficit is not compensated for by substrate switch [115,116].

As described by Ritterhof et al. there is an upregulation of glucose uptake and glycolysis with either no change or even a decrease in glucose oxidation, resulting in uncoupling of substrate uptake and oxidation [59]. Ultimately, this uncoupling reduces cardiac energy availability, the affected heart exhibiting up to 30% less ATP than the healthy one [46,117].

Myocardial ketone body oxidation is increased in HF. Recent studies show this metabolic shift as a key metabolic adaptation in the failing human heart, indicating the potential of ketone bodies as an alternative fuel for HF with reduced and preserved ejection fraction (EF) [35,65,67–75]. An increased ketone body oxidation is also seen in RV failure like in pulmonary arterial hypertension (PAH) [118].

Reduced energy production. In the failing BV heart, electron transport chain activity is altered (Table 1). Alterations in mitochondrial number, structure and function, in part due to

accumulation of reactive oxidative species (ROS) harming mitochondrial deoxyribonucleic acid, may be causes of altered electron transport chain activity [97,119].

Increase in reactive oxidative species. Oxidative stress is involved in the development and progression of cardiac remodeling in HF [76]. ROS impair the electrophysiology of the contractile function by denaturing proteins involved in contractility (including L-type calcium channels, sodium channels, potassium channels, and sodium-calcium exchangers [120]) and trigger hypertrophy through modifications in the extracellular matrix [121].

Insufficient energy transfer to ATP-consuming reactions. CK energy transfer shuttle works by transferring high-energy phosphate groups from creatine phosphate to ADP to produce ATP. It was the initial mechanism of energy starvation discovered in HF, with creatine deficiency [47]: In HF, the CK system is compromised due to a variety of factors, including decreased levels of CK enzymes and alterations in the composition of the mitochondrial membrane (Table 1). As a result, ATP levels in the heart decrease. Phosphocreatine and total creatine levels decrease by up to 30–70% in an early stage of HF [48,77–79]. Consequence is the inability to deliver ATP on increased workload [122]. Reduced CK flux is a significant predictor of HF outcome [117]. Acting on reduced CK flux and on its enzymes is considered a potential HF treatment target [117,123].

Epigenetic and transcriptional changes: reactivation of fetal gene expression in the failing BV heart. The activation of fetal cardiac genes which encode proteins involved in contraction, calcium management, and metabolism, is associated with pathological heart hypertrophy. A deterioration in heart function is associated with such reprogramming. Conversely, improvement in cardiac function is associated with normalization of cardiac gene expression in the failing heart [124]. The maturation of fatty acid oxidation was delayed according to a clinical investigation based on RV myocardial biopsies from patients with CHD. Key metabolic enzyme hyperacetylation was prevented by secondary hypertrophy [125]. Lysine acetylation is involved in regulating cardiometabolic diseases. Nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-3 (SIRT3) expression was downregulated in failing hearts from patients with obesity and metabolic syndrome, which led to cyclophilin D hyperacetylation, hyperacetylation, mitochondrial permeability transition pore opening, and cardiac dysfunction [126]. In pressure overload-induced cardiac hypertrophy, histone acetylation is related to inflammation, collagen deposition, and cardiac contractile function [127]. Histone deacetylase inhibition was found to reduce cardiac hypertrophy and fibrosis in spontaneously hypertensive rats by increasing 3-acetylation on the promoters of MR target genes and suppressing gene expression [128]. The HDAC inhibitor valproic acid was shown to improve the development of atrial remodeling and postpone the onset of atrial fibrillation in mice by 4 to 8 weeks [129]. Another HDAC inhibitor, suberoylanilide hydroxamic acid, was discovered to prevent cardiac arrhythmias in dystrophic mice, including QT interval prolongation [130]. Both class I and class II HDAC are inhibited by the HDAC inhibitors that prevent LV hypertrophy.

Metabolomics as a bridge between gene and metabolism. Metabolomics is more and more used to analyze metabolites and intermediates in cardiology [131], as well as pediatric cardiology [132,133]. Interpretation can be complex.

Ketolytic metabolism was described as being increased in HF [134]. In atrial fibrillation, elevated blood levels of acylcarnitine were found and discussed as reflective of defective mitochondrial beta-oxidation [135,136].

2.3. Right Ventricular Failure: The Case of Pulmonary Arterial Hypertension

In fetal circulation, the right ventricle (RV) is responsible for up to 60% of the cardiac output [137]. Thickness and contractility are likely to be similar between LV and RV at this stage [138]. However, there are deep metabolic and electrophysiological differences between LV and RV, such as differences in systolic Ca^{2+} [139]. The molecular structure of the RV is quite different from that of the LV [140,141]. Metabolic pathways and gene transcription mechanisms in the state of pressure-overload are different in LV and RV [142]. Dysfunction of the RV is accompanied by a release of ROS, combined with chronic nitric

oxide deficiency [143]. Additionally, in RV hypertrophy specific mitochondrial remodeling was described [144].

RV failure shares with LV failure the perturbation in substrate consumption. Glucose homeostasis as well as fatty acid metabolism are impaired [82–84,145–148]. Acylcarnitine levels are disrupted in RV failure and have been associated with insulin resistance and adverse outcome [149–152].

Untypical substrate consumption. PAH is a disease resulting in RV failure. Initially regarded an isolated disease of the pulmonary circulation, evidence is accumulating that PAH is to be considered from the metabolic perspective [153,154].

Abnormal glucose oxidation. Abnormal glucose metabolism is observed in patients with PAH, even without manifest diabetes mellitus [82–84] (Table 1). In Pugh et al. [82], 56% of patients with PAH had an Hb1ac level of over 6.0%, and 15% of patients of over 6.5%—this being undiagnosed DM, reminding of findings in Fontan patients of Ohuchi et al. [155]. Insulin resistance worsened pulmonary phenotype in the West study, implying a possible causal role in PAH [83,85].

Altered fatty acid oxidation. Parallel to abnormal glucose metabolism and insulin resistance, alterations of fatty acid oxidation were found in PAH [81]. In plasma, circulating free fatty acids and acylcarnitines are significantly elevated in a similar pattern as found in Fontan patients [43]. In an animal model, altered carnitine function was tied to decreased mitochondrial function and altered nitric oxide signaling [156].

Increased ketogenesis. An increased conversion of fatty acids into ketones (ketogenesis) was found to correlate with better clinical health in PAH [118]. This is consistent with the adaptively increased uptake of ketones in HF [69]. Aarhus university is conducting a clinical trial on ketones for PAH patients [86]. There are some rationales behind such an approach. In a previous study, they found a 40% increase in cardiac output under treatment with beta-hydroxybutyrate (BHB) infusion, with an increase in RV function as well as a decrease in pulmonary vascular resistance by 20%. Their published results focus on the hemodynamic effects with an average increase in cardiac output by 27%, and a decrease in pulmonary vascular resistance by 18%, irrespective of the cause of right-sided HF (10 patients with PAH, 10 patients with chronic thromboembolic pulmonary hypertension), and at average a blood ketones level of 3.3 mmol/L [87].

While our article was submitted, a non-reviewed article from the Lillehei heart institute (Minnesota university) describes that compensatory ketosis is absent in RV failure, in contrast to LV failure. The therapeutic stimulation of ketolytic activity is improving RV function, suppresses NLRP3 inflammasome activation and blunts myocardial fibrosis [88]. Those authors hypothesized an RV-liver-axis behind this specific RV dysregulation.

Oxidative stress. The electron transport chain in PAH shows pronounced alterations [89,90]. Proteomics studies in PAH identified an increased ROS production that might be related to a loss of antioxidant response [91,92].

Decreased creatine kinase shuttle. Alterations in CK were found in diastolic dysfunction in an animal model with RV HF [93,157].

Alterations in signaling pathways. Histone deacetylase inhibitors are acting differently in LV, or RV hypertrophy [158,159]. Due to the complex pathogenesis of PAH, more than a single epigenetic modulation to reverse PAH might be required [160].

Metabolomics findings. In right-sided HF, metabolomics analysis found specifically elevated blood levels of L-carnitine, acetyl-L-carnitine and long-chain acylcarnitine. Alteration of beta-oxidation of fatty acids increases the concentration of acyl-CoA, thus increasing acylcarnitine levels. The conclusion is that an increased level of acylcarnitine may reflect significant inhibition of the mitochondrial fatty acid beta-oxidation in PAH [161].

2.4. Energy Metabolism and the Single Ventricle after Fontan Palliation

Altered substrate consumption—glucose oxidation. Pyruvate metabolism might be altered in SV patients, especially in those with HF. One metabolomics study found elevated levels of circulating pyruvate in this group of patients, which might indicate an alteration of

pyruvate metabolism and glucose oxidation [95] (Table 1). Noteworthy is that the authors consider pyruvate therapy.

Altered substrate consumption—fatty acid oxidation. From biopsies collected during cardiac surgery, it was discovered that cardiac metabolic maturation happened in HLHS (dominant RV) through an increase in AMPK and PPAR-gamma coactivator 1 alpha, and that control of fatty acid oxidation is not impaired in the hearts of HLHS children [162]. This suggests beta-oxidation to work properly. Thus, SV HF might follow a metabolic pattern similar to that of BV HF, exhibiting the reverse Randle effect [105].

Surprisingly, in a very recent metabolomics study functional analysis of the mitochondrial CPT system demonstrated significantly decreased activity of the mitochondrial CPT transporters, suggesting that the diminished myocardial acylcarnitine is related to an overall decreased capacity of the failing SV to oxidize long-chain fatty acids, resulting in a diminished rate of cardiac ATP production [94]. Those findings suggest that due to the decreased enzymatic activity of CPT1/CPT2, beta-oxidation is altered in univentricular hearts which would explain the higher acylcarnitine levels found in Fontan patients compared to healthy controls [43].

Another recent metabolomics study suggests differences in 2-oxoglutarate, isocitric acid, malic acid, and cis-aconitic acid that could reflect alterations of the Krebs cycle [163]. The authors suggest Krebs cycle activation might be necessary to increase cardiac output to counteract hypoxia in Fontan patients. Nevertheless, this interesting finding would require further research, as the study compares metabolomics of various single ventricle architecture to different malformations with inhomogeneous presence or grade of pressure or volume burden such as tetralogy of Fallot or ventricular septum defects. Moreover, the number of patients included is low (n = 14), and the study includes patients with severe atrioventricular valve regurgitation or a history of protein-losing enteropathy.

Induced ketolysis in single ventricle physiology—early reports on the use of Sodium-glucose co-transporter-2 inhibitors. The decreased activity of CPT2 in SV patients without HF, and CPT1/CPT2 in SV patients with HF [94], as well as elevated circulating level of carnitine [95] might indicate metabolic perturbations. Pires da Silva et al. consider pyruvate therapy [95,164]. This is part of an approach to compensate for the decreased activity of CPT1/CPT2 by therapeutic use of cardiac anaplerosis [165]. An alternative approach is to make use of therapeutic ketosis or induced cardiac ketolysis. One means to stimulate ketone metabolism is the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors as studied in BV HF [166–171], an approach supported by a case report (Fontan circulation, 5 patients), where rehospitalization rate was reduced without acute adverse effects [172]. Although based on a very limited patient number, objective data such as increases in systemic oxygen saturation, serum albumin level, and estimated glomerular filtration rate, as well as a decrease in plasma NT-proBNP-level are promising, as NT-proBNP > 100 pg/mL has a 91% sensitivity for significant ventricular dilation, and one of 82% for ejection fraction <50% [173], and is predictive of adverse outcome [174].

While SGLT2 inhibitors' mechanism still is not completely understood, one of the main hypotheses is that SGLT2 inhibitors are increasing circulating ketone levels [168]. The improvement of parameters seen in the first use of SGLT2 inhibitors on Fontan patients match the effects of ketone bodies on hypoxia [175] and glomerular filtration rate [176], as reported in non-Fontan studies.

Inflammation and oxidative stress. In HLHS patients, disorders of cellular respiration are suspected to be present [96]. In an animal model, untypically elevated mitochondrial respiratory capacity was discovered, different from the reduced respiratory capacity typically seen in BV LV HF [96,177]. The cause of this elevation is controversial. Based on the Ohia mouse model, Xu et al., hypothesized a genetic mutation [96]. Other investigators suggested an alteration in the cardiac metabolic maturation [178]. We hypothesize that the unphysiological ventricle switch with its mechanical load changes may trigger metabolic alterations. Irrespective of the cause, such a mechanism is able to trigger an elevation of ROS, known to be one mechanism leading to cardiac hypertrophy [76,97,98]. A recent

Proteomics study on young children with an SV lesion (prior to Fontan palliation) showed decreased inflammatory cytokines and increased vascular tone modulators compared to healthy controls before stage 2 palliation, and an increase in these analytes shortly after stage 2 palliation [179]. Interestingly, tissue inhibitor of metalloproteinases-1 or and matrix metalloproteinase 7 levels were associated with greater morbidity, suggesting an important role for regulation of extracellular matrix production.

Systemic metabolic changes. Abnormalities in Fontan patients' glucose and lipid metabolism as well as in the neurohumoral axis have been reported, and this even in 'stable' Fontan patients with good exercise capacity and without signs of imminent Fontan failure [19,180–185], in part revealing similarities to findings in the BV patient with LV or RV failure. Interestingly, metabolomics studies found that even Fontan patients with good ventricular function and without signs of a Fontan failure exhibited similar lipid metabolic pattern as the BV patient with HF, particularly with respect to alterations in serum cholesterol, lipoprotein, phospholipid, and acylcarnitine concentrations [43]. Moreover, there are first reports on alterations in amino acid pathways, with some key analytes showing altered serum levels (asparagine, histidine, taurine, threonine; amino acid-derived analytes such as dimethylarginine, methionine-sulfoxide or glutamic acid), hinting at inflammation, oxidative stress and endothelial dysfunction, altered cell energy metabolism, and elevated myocardial turnover [42], similar to those found in BV patients with congestive HF.

3. Induced Ketosis in Patients with a Failing Biventricular Heart

Initially being an intuition in biochemistry [51], evidence accumulates on the therapeutic role of targeting mitochondrial oxidative metabolism [186], and especially ketone metabolism for the BV LV HF [32]. In the development of HF, cardiac alterations of metabolic processes contribute to a reduction of ATP availability, causing a decline in myocyte contractile function. In advanced HF, ketone metabolism is increased; its nature is discussed to be adaptive [29,102,187]. Nevertheless, therapeutic elevation of ketone bodies may have positive results, not only for cardiometabolic health in general but also systemic health in patients with HF in particular [188]. To date, research in this field is conducted on both LV and RV HF.

Ketones as a substrate for the failing heart. Early experimental studies showed that BHB is not only a fuel, but a super fuel for the heart [189–194]. Twenty-five percent increased contractility and decreased oxygen consumption were found at 5 mM blood level of ketone bodies [191]. It was discovered that in the healthy heart, ketones do not increase cardiac efficiency. However, ketone fuels are capable of increasing ATP production when the main cardiac fuels—fatty acids and glucose—are deficient [195]. Clinical applications are currently in development, for congestive and acute HF [188,196,197].

Ketones and oxidative stress. Oxidative stress is involved in the progression of congestive HF, showing a positive correlation between elevated oxidative stress and myocardial dysfunction [76,121,198,199]. BHB is an endogenous specific inhibitor of class I HDAC. In an experimental study, elevated levels of BHB inhibited HDAC, correlating with changes in transcription including those of the genes encoding oxidative stress resistance factors, conferring substantial protection against oxidative stress with decreased ROS production [200]. Oxidation of ketone bodies contributes to free radical homeostasis [40]. Reduced oxidative stress was also observed in mice using a ketogenic diet [201].

Ketones and inflammation. Inflammation is associated with cardiac remodeling and HF [202–204]. NLRP3 inflammasome is a new therapeutic target in the treatment of HF [205]. BHB is inhibiting NLRP3 inflammasome [206]. In ketogenic-diet-fed mice, BHB serum levels increased to 0.75–1 mM, and inhibited activation of NLRP3 inflammasome. Overexpression of D-beta-hydroxybutyrate dehydrogenase I enhanced antioxidant enzyme expression and attenuated peroxide-induced apoptosis [39]. In neurons, ketone bodies were shown to decrease mitochondrial production of ROS without affecting the endogenous antioxidant glutathione [207]. Consistently, a low-carbohydrate diet reduced inflamma-

tion [208]. High-fat diet elevating BHB was able to reduce inflammation and mitigate HF with preserved EF.

Ketones and mitochondrial respiratory complex activity. In an experimental model, ketogenic diet normalized complex I and improved complex II-III activities in rats [209]. This was discussed as originating from providing an alternative substrate as well as through the ketone-mediated downregulated oxidative stress.

Ketones, myocardial contractility, and ventricular ejection fraction. Infusion of 3-hydroxybutyrate to patients with HF with reduced EF increased the EF by 8% [80]. At the same time, cardiac output increased by 40%, with a concomitant increase in RV function and decrease of pulmonary vascular resistance by 20% each.

Ketones, myocardial remodeling, and prevention of cardiac hypertrophy. Inefficient myocardial fuel consumption can cause pathological hypertrophy [210–213]. Class I HDAC have been found responsible in the development of pathological cardiac hypertrophy and HF [124,214]. HDAC inhibition was found to be a therapeutic target for cardiac remodeling [215]. Overexpression of BBH dehydrogenase 1 has a protective role regarding resilience to pressure overload-induced cardiac remodeling [39]. In an experimental model, BHB infusion increased histone acetylation in the heart, inhibiting HDAC [200]. In preclinical model HF, elevation of BHB through ketone esters reduced pathologic remodeling [216]. Chronic elevation of BHB in dogs decreased adverse remodeling [38]. In a similar way, strict dietary carbohydrate restriction, causing elevation of ketone levels and decreasing mammalian target of rapamycin expression, suppressed hypertrophy in experimental studies [217,218]. This phenomenon was discussed to have clinical implications. In patients with HF with reduced EF, acute infusions of BHB improved contractility [80].

Ketones, endothelial function, and vascular resistance. Keeping pulmonary vascular resistance low is necessary in Fontan circulation [219,220]. In BV patients with HF, endothelial dysfunction, induced by oxidative stress, and elevated vascular resistance contribute to the development of HF and are associated with an increased mortality [221,222]. Mechanisms involved are complex, including oxidative stress, inflammation, and alteration of nitric oxide metabolism. The ketone body BHB presented as a potent vasodilator both in experimental models and human trials [223]. Under BHB infusion, myocardial blood flow increased and induced vasodilation [80,224]. BHB infusion increased blood flow in the renal system [170]. Ketone ester reduced risk of aortic dissection [225].

Antiarrhythmic potential of ketones. Ketone oxidation, membrane excitability, and arrhythmogenesis are interrelated. BHB contributed to a 24% improvement in cardiac efficiency, mitochondrial function and the stabilization of cellular membrane potential, enhancing the antiarrhythmic potential of the myocardial cell [36].

Ketones and oxygen consumption. Ketone oxidation spares oxygen consumption and is neuroprotective through two mechanisms, oxygenation improvement and decreased blood carbon dioxide [226,227]. Compared to fatty acid oxidation, ketones produce more ATP per molecule of oxygen [228,229].

Ketones in RV failure. Nutritional ketosis improved PAH through reversal of the metabolic syndrome [230]. In a similar way, use of the SGLT2 inhibitor empagliflozin prevented the progression of PAH [231]. A clinical trial is currently conducted on the use of an OHB infusion in patients with idiopathic PAH [86] (Table 1).

4. Impact of Ketones Apart from That on the Cardiovascular System Relevant to Fontan Circulation

The Fontan circulation with its elevated central venous pressure and limited cardiac output has consequences on all organ systems [19,232]. Ketone bodies are organ-protective. In the following, we aim to estimate to which extent Fontan circulation pathophysiology benefits from this protection (Figure 1).

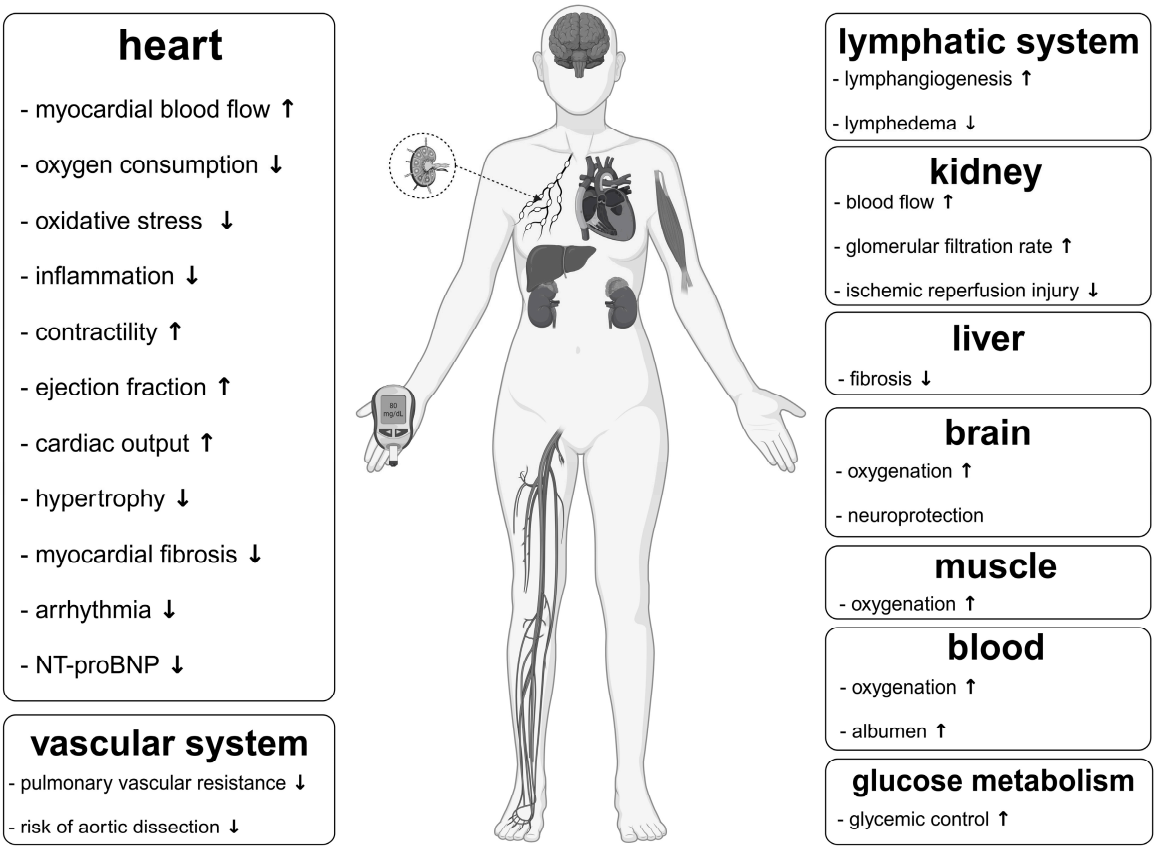

Figure 1. Proven or assumed benefit of ketone bodies on various organ systems. NT-proBNP, N-terminal pro-B-type natriuretic peptide. ↑, increase; ↓, decrease. Created with BioRender.com.

Hepatoprotection. Deficiencies in hepatic ketogenesis are associated with non-alcoholic fatty liver disease and fibrosis [233]. Therapeutic ketosis was explored in the treatment of non-alcoholic fatty liver disease, with effective improvement and reduction of fibrosis [234–237].

Renoprotection. Numerous studies show detrimental effects of the Fontan circulation on the kidneys [238–242]. Renal ketogenesis requires further exploration. Nevertheless, renal ketogenesis is reported to be a mechanism protecting against renal ischemia-reperfusion injury [243,244].

Neuroprotection. Mild hypoxia is a common feature of the Fontan circulation [245], and ketones could be a therapeutic strategy to counteract the effects of this hypoxia. For certain anatomical variants of a SV, optimizing oxygen consumption might be critical considering altered coronary perfusion. A ketogenic diet improved the cerebral oxygen level in hypoxia after an epileptic event [175]—the assumed mechanism being altered substrate consumption, reduced glycolysis, and accumulation of lactate [246]. Exogenous ketones increased blood and muscle oxygenation in hypoxia [247].

Lymphangiogenesis. Evidence is appearing on the role of ketogenesis on the lymphangiogenesis after corneal injury and myocardial infarction in the BV patient [248]. The mechanism is also on trial for alleviating lymphedema [249,250]. Whether ketone bodies might play a therapeutic role in abnormal lymphatic flow in Fontan circulation requires further research.

Abnormal glucose patterns. Abnormal glucose metabolism is one of the underdiagnosed complications of Fontan circulation [155,180]. Alteration of insulin sensitivity is hypothesized to be a factor of Fontan-associated liver disease, which affects a high percentage of Fontan patients [251,252]. Having in mind that ketogenic diet and carbohydrate restriction are established therapies to treat insulin resistance and to improve glycemic control [253],

facing the abnormal glucose metabolism inherent to Fontan, the therapeutic potential of ketogenic diet and carbohydrate restriction might be worth considering.

5. Rationale of a Targeted Metabolic Therapy in Fontan Patients

Current approaches to HF in Fontan patients are widely based on treatment regimens for BV HF. Their application varies among centers, and polymedication is common, often with the potential of complex drug interaction [22,23]. Apart from the therapeutic potential of ketone bodies in BV HF that should apply to SV patients, there are features unique to Fontan circulation that—based on the effects on similar complications—might benefit from therapeutic ketosis.

Therapeutic modulation of the ketone pathway. SGLT2 inhibitors are considered to positively address HF through an increase in cardiac ketone oxidation [168]. The first trial of SGLT2 inhibitors on Fontan patients is promising [172]. Though the trial size was limited, the benefits seen in the study support therapeutic ketosis in HF. SGLT2 inhibitor use is currently supported by FDA only for patients over 18 years old [254]. Other means to achieve therapeutic ketosis including ketogenic diet, medium chain triglycerides supplementation, or application of ketone esters (Figure 2).

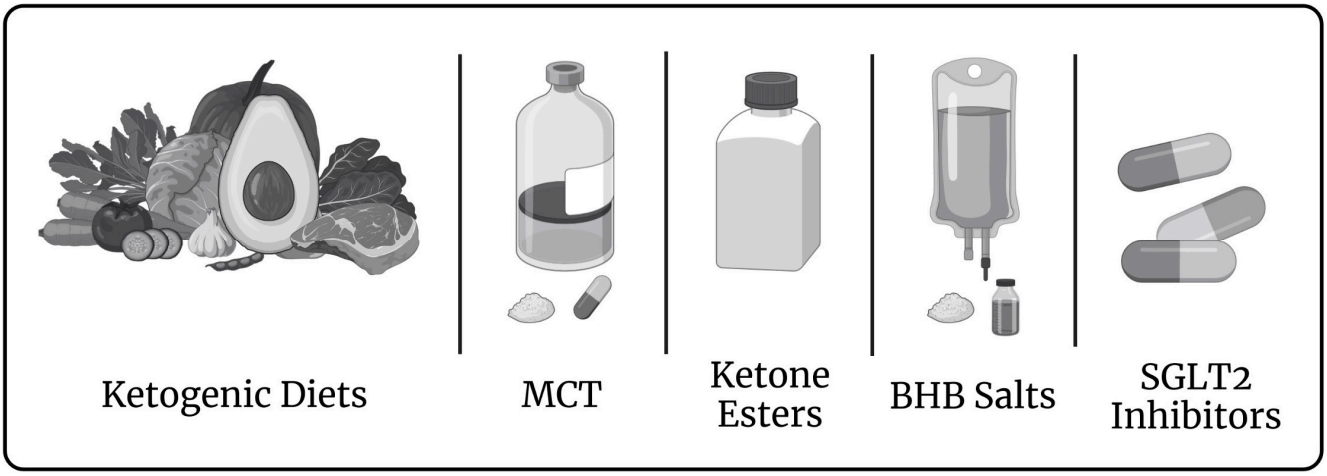

Figure 2. Means to achieve therapeutic ketosis. MCT, medium chain triglycerides; BHB, beta-hydroxybutyrate; SGLT2, sodium-glucose co-transporter 2. Created with BioRender.com.

A strong case for therapeutic ketosis in Fontan patients. Therapeutic ketosis has been in use already for 100 years in pediatric neurology [255]. Numerous reviews judge it a safe dietary therapy with minor adverse effects to be monitored [256,257]. It is a sustainable therapy [258], and it is used from toddler age to adult age [259]. The therapy has spread from pediatric neurology to other fields, such as certain inherited metabolic disorders [260], adults' BV congestive LV HF [216–218], intensive care management [261], or oncology [262]. Due to the unique nature of SV patients and the potential of interactions with their polymedication commonly present, induction of ketosis should only be undertaken under close medical control.

Additional candidate mechanisms for metabolism-targeted therapy for Fontan patients. Cardiac anaplerosis might be able to replete tricarboxylic acid intermediates and alleviate the substrate consumption alterations [165]. Among other regimens, there is pyruvate therapy [164], application of glutamine [263] (PAH patients showed an increased anaplerosis under glutamine [264]), or branched-chain amino acids [265] and odd-chain fatty acids [266,267]. Octanoate is modulating metabolic acetyl-CoA histone acetylation, promoting cardiac repair after myocardial infarction [268]. It is currently applied to Fontan patients with lymphatic complications such as protein-losing enteropathy (supplementation of the low-fat diet with medium chain triglycerides) [269]. It is unclear how octanoate could

bypass CPTI/CPTII transporter and act as a fuel in the mitochondria in the cardiomyocyte, the results being controversial [270,271].

6. Limitations

SV malformation is a rare disease. Most studies on cardiac and systemic metabolism of Fontan patients were conducted on a limited number of patients. The etiology of all SV malformations might not be identical, and metabolism as well as gene transcription might vary. Furthermore, metabolomics results should be treated with caution as interpretation can be complex. Large-scale (multicenter) studies are necessary to further explore the metabolic impairment of the SV heart and the ketones' therapeutic potential in the respective patients.

7. Methods

Our literature review compares the metabolism of patients with an SV circulation after Fontan palliation with that of patients with a healthy BV heart, or different subtypes of a failing BV heart, by Pubmed review of the literature on cardiac metabolism, Fontan failure, heart failure, ketosis, metabolism, published in English from 1939 to 2023.

8. Conclusions

Evidence is growing that SV circulation after Fontan palliation not only is a hemodynamically challenging state, but also raises a metabolic issue with its alterations of fatty acid oxidation as well as glucose oxidation, similar to those reported in the failing BV heart, generating metabolic instability and disturbed energy production that *per se* may become a cause of circulatory failure. Evidence accumulates that stimulating ketone oxidation as a targeted metabolic therapy might be a therapeutic strategy to address HF in BV patients. Therapeutic ketosis may be worth considering also in the treatment of Fontan patients, as ketones positively affect not only the myocardial energy metabolism, but also the global Fontan pathophysiology. Induced ketosis seems promising as a therapeutic strategy for chronic ventricular failure and low-grade inflammation, as well as diseased liver, kidney, and intestines. Ketone esters, 1,3 butadeniol, or octanoate might provide a third fuel to the SV heart, and a well-formulated ketogenic diet taking into account the micronutritional status inherent to Fontan patients may have an integrative, concerted effect on the several complications of Fontan circulation.

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References

1. Rychik, J.; Atz, A.M.; Celermajer, D.S.; Deal, B.J.; Gatzoulis, M.A.; Gewillig, M.H.; Hsia, T.-Y.; Hsu, D.T.; Kovacs, A.H.; McCrindle, B.W.; et al. Evaluation and Management of the Child and Adult with Fontan Circulation: A Scientific Statement from the American Heart Association. *Circulation* **2019**, *140*, e234–e284. [CrossRef]
2. Fontan, F.; Baudet, E. Surgical Repair of Tricuspid Atresia. *Thorax* **1971**, *26*, 240–248. [CrossRef]
3. Kreutzer, G.; Galíndez, E.; Bono, H.; De Palma, C.; Laura, J.P. An Operation for the Correction of Tricuspid Atresia. *J. Thorac. Cardiovasc. Surg.* **1973**, *66*, 613–621. [CrossRef] [PubMed]

4. Gewillig, M.; Brown, S.C. The Fontan Circulation after 45 Years: Update in Physiology. *Heart* **2016**, *102*, 1081–1086. [CrossRef] [PubMed]
5. Alsoufi, B.; Gillespie, S.; Kim, D.; Shashidharan, S.; Kanter, K.; Maher, K.; Kogon, B. The Impact of Dominant Ventricle Morphology on Palliation Outcomes of Single Ventricle Anomalies. *Ann. Thorac. Surg.* **2016**, *102*, 593–601. [CrossRef]
6. Kutty, S.; Jacobs, M.L.; Thompson, W.R.; Danford, D.A. Fontan Circulation of the Next Generation: Why It's Necessary, What It Might Look Like. *J. Am. Heart Assoc.* **2020**, *9*, e013691. [CrossRef] [PubMed]
7. Rychik, J. Path Taken in a Fontan Circulation: Room for Optimism in the Face of Uncertainty. *Heart* **2021**, *107*, 521–522. [CrossRef]
8. Zhu, A.; Meza, J.M.; Prabhu, N.K.; McCrary, A.W.; Allareddy, V.; Turek, J.W.; Andersen, N.D. Survival After Intervention for Single-Ventricle Heart Disease Over 15 Years at a Single Institution. *Ann. Thorac. Surg.* **2022**, *114*, 2303–2312. [CrossRef]
9. Lewis, M.; Rosenbaum, M. The Miracle Baby Grows Up: Hypoplastic Left Heart Syndrome in the Adult. *Curr. Cardiol. Rep.* **2017**, *19*, 74. [CrossRef]
10. Julsrud, P.R.; Weigel, T.J.; Van Son, J.A.; Edwards, W.D.; Mair, D.D.; Driscoll, D.J.; Danielson, G.K.; Puga, F.J.; Offord, K.P. Influence of Ventricular Morphology on Outcome after the Fontan Procedure. *Am. J. Cardiol.* **2000**, *86*, 319–323. [CrossRef]
11. McGuirk, S. The Impact of Ventricular Morphology on Midterm Outcome Following Completion Total Cavopulmonary Connection. *Eur. J. Cardiothorac. Surg.* **2003**, *24*, 37–46. [CrossRef] [PubMed]
12. Anderson, P.A.W.; Sleeper, L.A.; Mahony, L.; Colan, S.D.; Atz, A.M.; Breitbart, R.E.; Gersony, W.M.; Gallagher, D.; Geva, T.; Margossian, R.; et al. Contemporary Outcomes after the Fontan Procedure. *J. Am. Coll. Cardiol.* **2008**, *52*, 85–98. [CrossRef]
13. Backer, C.L. The Functionally Univentricular Heart. *J. Am. Coll. Cardiol.* **2012**, *59*, 1186–1187. [CrossRef] [PubMed]
14. d'Udekem, Y.; Xu, M.Y.; Galati, J.C.; Lu, S.; Iyengar, A.J.; Konstantinov, I.E.; Wheaton, G.R.; Ramsay, J.M.; Grigg, L.E.; Millar, J.; et al. Predictors of Survival After Single-Ventricle Palliation. *J. Am. Coll. Cardiol.* **2012**, *59*, 1178–1185. [CrossRef]
15. King, G.; Buratto, E.; Daley, M.; Iyengar, A.; Alphonso, N.; Grigg, L.; Cordina, R.; d'Udekem, Y.; Konstantinov, I.E. Impact of Aortic Atresia After Fontan Operation in Patients With Hypoplastic Left Heart Syndrome. *Ann. Thorac. Surg.* **2022**, *116*, 95–102. [CrossRef]
16. Iyengar, A.J.; Winlaw, D.S.; Galati, J.C.; Wheaton, G.R.; Gentles, T.L.; Grigg, L.E.; Justo, R.N.; Radford, D.J.; Weintraub, R.G.; Bullock, A.; et al. The Extracardiac Conduit Fontan Procedure in Australia and New Zealand: Hypoplastic Left Heart Syndrome Predicts Worse Early and Late Outcomes. *Eur. J. Cardiothorac. Surg.* **2014**, *46*, 465–473. [CrossRef]
17. Book, W.M.; Gerardin, J.; Saraf, A.; Marie Valente, A.; Rodriguez, F. Clinical Phenotypes of Fontan Failure: Implications for Management: Fontan Phenotypes. *Congenit. Heart Dis.* **2016**, *11*, 296–308. [CrossRef]
18. Sable, C.; Foster, E.; Uzark, K.; Bjornsen, K.; Canobbio, M.M.; Connolly, H.M.; Graham, T.P.; Gurvitz, M.Z.; Kovacs, A.; Meadows, A.K.; et al. Best Practices in Managing Transition to Adulthood for Adolescents with Congenital Heart Disease: The Transition Process and Medical and Psychosocial Issues: A Scientific Statement from the American Heart Association. *Circulation* **2011**, *123*, 1454–1485. [CrossRef]
19. Michel, M.; Zlamy, M.; Entenmann, A.; Pichler, K.; Scholl-Bürgi, S.; Karall, D.; Geiger, R.; Salvador, C.; Niederwanger, C.; Ohuchi, H. Impact of the Fontan Operation on Organ Systems. *Cardiovasc. Hematol. Disord. Drug Targets* **2019**, *19*, 205–214. [CrossRef]
20. Harteveld, L.M.; Blom, N.A.; Terol Espinosa de Los Monteros, C.; Kuipers, I.M.; Rammeloo, L.A.J.; Hazekamp, M.G.; van Dijk, J.G.; ten Harkel, A.D.J. 3-Month Enalapril Treatment in Pediatric Fontan Patients with Moderate to Good Systolic Ventricular Function. *Am. J. Cardiol.* **2022**, *163*, 98–103. [CrossRef] [PubMed]
21. Shaddy, R.E.; Boucek, M.M.; Hsu, D.T.; Boucek, R.J.; Canter, C.E.; Mahony, L.; Ross, R.D.; Pahl, E.; Blume, E.D.; Dodd, D.A.; et al. Carvedilol for Children and Adolescents With Heart Failure: A Randomized Controlled Trial. *JAMA* **2007**, *298*, 1171. [CrossRef] [PubMed]
22. Schranz, D.; Voelkel, N.F. "Nihilism" of Chronic Heart Failure Therapy in Children and Why Effective Therapy Is Withheld. *Eur. J. Pediatr.* **2016**, *175*, 445–455. [CrossRef] [PubMed]
23. Anderson, P.A.W.; Breitbart, R.E.; McCrindle, B.W.; Sleeper, L.A.; Atz, A.M.; Hsu, D.T.; Lu, M.; Margossian, R.; Williams, R.V. The Fontan Patient: Inconsistencies in Medication Therapy Across Seven Pediatric Heart Network Centers. *Pediatr. Cardiol.* **2010**, *31*, 1219–1228. [CrossRef] [PubMed]
24. Ghanayem, N.S.; Berger, S.; Tweddell, J.S. Medical Management of the Failing Fontan. *Pediatr. Cardiol.* **2007**, *28*, 465–471. [CrossRef] [PubMed]
25. Taegtmeyer, H. Metabolism—The Lost Child of Cardiology. *J. Am. Coll. Cardiol.* **2000**, *36*, 1386–1388. [CrossRef]
26. Taegtmeyer, H. Cardiac Metabolism as a Target for the Treatment of Heart Failure. *Circulation* **2004**, *110*, 894–896. [CrossRef]
27. Ashrafian, H.; Frenneaux, M.P.; Opie, L.H. Metabolic Mechanisms in Heart Failure. *Circulation* **2007**, *116*, 434–448. [CrossRef]
28. Kimball, T.H.; Vondriska, T.M. Metabolism, Epigenetics, and Causal Inference in Heart Failure. *Trends Endocrinol. Metab.* **2020**, *31*, 181–191. [CrossRef]
29. Selvaraj, S.; Kelly, D.P.; Margulies, K.B. Implications of Altered Ketone Metabolism and Therapeutic Ketosis in Heart Failure. *Circulation* **2020**, *141*, 1800–1812. [CrossRef]
30. Taegtmeyer, H. Energy Metabolism of the Heart: From Basic Concepts to Clinical Applications Applications. *Curr. Probl. Cardiol.* **1994**, *19*, 61–86. [CrossRef]
31. Christensen, K.H. Treatment with the Ketone Body 3-Hydroxybutyrate in Patients with Acute Heart Failure. 2022. Available online: https://clinicaltrials.gov/ct2/show/NCT04442555 (accessed on 20 July 2022).

32. Yurista, S.R.; Chong, C.-R.; Badimon, J.J.; Kelly, D.P.; de Boer, R.A.; Westenbrink, B.D. Therapeutic Potential of Ketone Bodies for Patients with Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2021**, *77*, 1660–1669. [CrossRef] [PubMed]
33. Takahara, S.; Soni, S.; Phaterpekar, K.; Kim, T.T.; Maayah, Z.H.; Levasseur, J.L.; Silver, H.L.; Freed, D.H.; Ferdaoussi, M.; Dyck, J.R.B. Chronic Exogenous Ketone Supplementation Blunts the Decline of Cardiac Function in the Failing Heart. *ESC Heart Fail.* **2021**, *8*, 5606–5612. [CrossRef] [PubMed]
34. Takahara, S.; Soni, S.; Maayah, Z.H.; Ferdaoussi, M.; Dyck, J.R.B. Ketone Therapy for Heart Failure: Current Evidence for Clinical Use. *Cardiovasc. Res.* **2022**, *118*, 977–987. [CrossRef]
35. Monzo, L.; Sedlacek, K.; Hromanikova, K.; Tomanova, L.; Borlaug, B.A.; Jabor, A.; Kautzner, J.; Melenovsky, V. Myocardial Ketone Body Utilization in Patients with Heart Failure: The Impact of Oral Ketone Ester. *Metabolism* **2021**, *115*, 154452. [CrossRef] [PubMed]
36. Papazafiropoulou, A.; Georgopoulos, M.; Katsilambros, N. Ketone Bodies and the Heart. *Arch. Med. Sci. Atheroscler. Dis.* **2021**, *6*, 209–214. [CrossRef]
37. Schulze, P.C.; Wu, J.M.F. Ketone Bodies for the Starving Heart. *Nat. Metab.* **2020**, *2*, 1183–1185. [CrossRef]
38. Horton, J.L.; Davidson, M.T.; Kurishima, C.; Vega, R.B.; Powers, J.C.; Matsuura, T.R.; Petucci, C.; Lewandowski, E.D.; Crawford, P.A.; Muoio, D.M.; et al. The Failing Heart Utilizes 3-Hydroxybutyrate as a Metabolic Stress Defense. *JCI Insight* **2019**, *4*, e124079. [CrossRef]
39. Uchihashi, M.; Hoshino, A.; Okawa, Y.; Ariyoshi, M.; Kaimoto, S.; Tateishi, S.; Ono, K.; Yamanaka, R.; Hato, D.; Fushimura, Y.; et al. Cardiac-Specific Bdh1 Overexpression Ameliorates Oxidative Stress and Cardiac Remodeling in Pressure Overload–Induced Heart Failure. *Circ. Heart Fail.* **2017**, *10*, e004417. [CrossRef]
40. Schugar, R.C.; Moll, A.R.; André d'Avignon, D.; Weinheimer, C.J.; Kovacs, A.; Crawford, P.A. Cardiomyocyte-Specific Deficiency of Ketone Body Metabolism Promotes Accelerated Pathological Remodeling. *Mol. Metab.* **2014**, *3*, 754–769. [CrossRef]
41. Kolb, H.; Kempf, K.; Röhling, M.; Lenzen-Schulte, M.; Schloot, N.C.; Martin, S. Ketone Bodies: From Enemy to Friend and Guardian Angel. *BMC Med.* **2021**, *19*, 313. [CrossRef]
42. Michel, M.; Dubowy, K.-O.; Entenmann, A.; Karall, D.; Adam, M.G.; Zlamy, M.; Odri Komazec, I.; Geiger, R.; Niederwanger, C.; Salvador, C.; et al. Targeted Metabolomic Analysis of Serum Amino Acids in the Adult Fontan Patient with a Dominant Left Ventricle. *Sci. Rep.* **2020**, *10*, 8930. [CrossRef]
43. Michel, M.; Dubowy, K.-O.; Zlamy, M.; Karall, D.; Adam, M.G.; Entenmann, A.; Keller, M.A.; Koch, J.; Odri Komazec, I.; Geiger, R.; et al. Targeted Metabolomic Analysis of Serum Phospholipid and Acylcarnitine in the Adult Fontan Patient with a Dominant Left Ventricle. *Ther. Adv. Chronic Dis.* **2020**, *11*, 204062232091603. [CrossRef] [PubMed]
44. Opie, L.H. *Heart Physiology: From Cell to Circulation*, 4th ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2004.
45. Barth, E. Ultrastructural Quantitation of Mitochondria and Myofilaments in Cardiac Muscle from 10 Different Animal Species Including Man. *J. Mol. Cell. Cardiol.* **1992**, *24*, 669–681. [CrossRef] [PubMed]
46. Ingwall, J.S.; Weiss, R.G. Is the Failing Heart Energy Starved?: On Using Chemical Energy to Support Cardiac Function. *Circ. Res.* **2004**, *95*, 135–145. [CrossRef]
47. Herrmann, G.; Decherd, G. The chemical nature of heart failure. *Ann. Intern. Med.* **1939**, *12*, 1233. [CrossRef]
48. Neubauer, S. The Failing Heart—An Engine Out of Fuel. *N. Engl. J. Med.* **2007**, *356*, 1140–1151. [CrossRef]
49. Sack, M.N.; Rader, T.A.; Park, S.; Bastin, J.; McCune, S.A.; Kelly, D.P. Fatty Acid Oxidation Enzyme Gene Expression Is Downregulated in the Failing Heart. *Circulation* **1996**, *94*, 2837–2842. [CrossRef]
50. Katz, A.M. Energetics and the Failing Heart. *Hosp. Pract.* **1991**, *26*, 78–90. [CrossRef]
51. Taegtmeyer, H. Failing Heart and Starving Brain. *Circulation* **2016**, *134*, 265–266. [CrossRef] [PubMed]
52. Giussani, D.A.; Bennet, L.; Sferruzzi-Perri, A.N.; Vaughan, O.R.; Fowden, A.L. Hypoxia, fetal and neonatal physiology: 100 years on from Sir Joseph Barcroft. *J. Physiol.* **2016**, *594*, 1105–1111. [CrossRef]
53. Girard, J.; Ferre, P.; Pegorier, J.P.; Duee, P.H. Adaptations of Glucose and Fatty Acid Metabolism during Perinatal Period and Suckling-Weaning Transition. *Physiol. Rev.* **1992**, *72*, 507–562. [CrossRef]
54. Ascuitto, R.J.; Ross-Ascuitto, N.T. Substrate Metabolism in the Developing Heart. *Semin. Perinatol.* **1996**, *20*, 542–563. [CrossRef]
55. Itoi, T.; Lopaschuk, G.D. The Contribution of Glycolysis, Glucose Oxidation, Lactate Oxidation, and Fatty Acid Oxidation to ATP Production in Isolated Biventricular Working Hearts from 2-Week-Old Rabbits. *Pediatr. Res.* **1993**, *34*, 735–741. [CrossRef]
56. Dimasi, C.G.; Darby, J.R.T.; Morrison, J.L. A change of heart: Understanding the mechanisms regulating cardiac proliferation and metabolism before and after birth. *J. Physiol.* **2023**, *601*, 1319–1341. [CrossRef] [PubMed]
57. Stanley, W.C.; Recchia, F.A.; Lopaschuk, G.D. Myocardial Substrate Metabolism in the Normal and Failing Heart. *Physiol. Rev.* **2005**, *85*, 1093–1129. [CrossRef]
58. Lopaschuk, G.D.; Jaswal, J.S. Energy Metabolic Phenotype of the Cardiomyocyte During Development, Differentiation, and Postnatal Maturation. *J. Cardiovasc. Pharmacol.* **2010**, *56*, 130–140. [CrossRef] [PubMed]
59. Ritterhoff, J.; Tian, R. Metabolism in Cardiomyopathy: Every Substrate Matters. *Cardiovasc. Res.* **2017**, *113*, 411–421. [CrossRef]
60. Taegtmeyer, H.; Sen, S.; Vela, D. Return to the Fetal Gene Program: A Suggested Metabolic Link to Gene Expression in the Heart. *Ann. N. Y. Acad. Sci.* **2010**, *1188*, 191–198. [CrossRef]
61. Lopaschuk, G.D.; Karwi, Q.G.; Tian, R.; Wende, A.R.; Abel, E.D. Cardiac Energy Metabolism in Heart Failure. *Circ. Res.* **2021**, *128*, 1487–1513. [CrossRef]

62. Karwi, Q.G.; Uddin, G.M.; Ho, K.L.; Lopaschuk, G.D. Loss of Metabolic Flexibility in the Failing Heart. *Front. Cardiovasc. Med.* **2018**, *5*, 68. [CrossRef] [PubMed]
63. Shah, A.; Shannon, R.P. Insulin Resistance in Dilated Cardiomyopathy. *Rev. Cardiovasc. Med.* **2003**, *4*, S50–S57. [PubMed]
64. Nikolaidis, L. The Development of Myocardial Insulin Resistance in Conscious Dogs with Advanced Dilated Cardiomyopathy. *Cardiovasc. Res.* **2004**, *61*, 297–306. [CrossRef] [PubMed]
65. Taegtmeyer, H.; Golfman, L.; Sharma, S.; Razeghi, P.; Arsdall, M. Linking Gene Expression to Function: Metabolic Flexibility in the Normal and Diseased Heart. *Ann. N. Y. Acad. Sci.* **2004**, *1015*, 202–213. [CrossRef]
66. Schulze, P.C.; Drosatos, K.; Goldberg, I.J. Lipid Use and Misuse by the Heart. *Circ. Res.* **2016**, *118*, 1736–1751. [CrossRef]
67. Kolwicz, S.C.; Airhart, S.; Tian, R. Ketones Step to the Plate: A Game Changer for Metabolic Remodeling in Heart Failure? *Circulation* **2016**, *133*, 689–691. [CrossRef] [PubMed]
68. Bedi, K.C.; Snyder, N.W.; Brandimarto, J.; Aziz, M.; Mesaros, C.; Worth, A.J.; Wang, L.L.; Javaheri, A.; Blair, I.A.; Margulies, K.B.; et al. Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure. *Circulation* **2016**, *133*, 706–716. [CrossRef]
69. Aubert, G.; Martin, O.J.; Horton, J.L.; Lai, L.; Vega, R.B.; Leone, T.C.; Koves, T.; Gardell, S.J.; Krüger, M.; Hoppel, C.L.; et al. The Failing Heart Relies on Ketone Bodies as a Fuel. *Circulation* **2016**, *133*, 698–705. [CrossRef]
70. Huynh, K. Ketone Bodies as Fuel in Heart Failure. *Nat. Rev. Cardiol.* **2016**, *13*, 123. [CrossRef]
71. Manolis, A.S.; Manolis, T.A.; Manolis, A.A. Ketone Bodies and Cardiovascular Disease: An Alternate Fuel Source to the Rescue. *Int. J. Mol. Sci.* **2023**, *24*, 3534. [CrossRef]
72. Voros, G.; Ector, J.; Garweg, C.; Droogne, W.; Van Cleemput, J.; Peersman, N.; Vermeersch, P.; Janssens, S. Increased Cardiac Uptake of Ketone Bodies and Free Fatty Acids in Human Heart Failure and Hypertrophic Left Ventricular Remodeling. *Circ. Heart Fail.* **2018**, *11*, e004953. [CrossRef]
73. Nakamura, M.; Sadoshima, J. Ketone Body Can Be a Fuel Substrate for Failing Heart. *Cardiovasc. Res.* **2019**, *115*, 1567–1569. [CrossRef]
74. Liao, S.; Tang, Y.; Yue, X.; Gao, R.; Yao, W.; Zhou, Y.; Zhang, H. β-Hydroxybutyrate Mitigated Heart Failure with Preserved Ejection Fraction by Increasing Treg Cells via Nox2/GSK-3β. *J. Inflamm. Res.* **2021**, *14*, 4697–4706. [CrossRef]
75. Deng, Y.; Xie, M.; Li, Q.; Xu, X.; Ou, W.; Zhang, Y.; Xiao, H.; Yu, H.; Zheng, Y.; Liang, Y.; et al. Targeting Mitochondria-Inflammation Circuit by β-Hydroxybutyrate Mitigates HFpEF. *Circ. Res.* **2021**, *128*, 232–245. [CrossRef] [PubMed]
76. Tsutsui, H.; Kinugawa, S.; Matsushima, S. Oxidative Stress and Heart Failure. *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *301*, H2181–H2190. [CrossRef]
77. Beer, M.; Seyfarth, T.; Sandstede, J.; Landschütz, W.; Lipke, C.; Köstler, H.; von Kienlin, M.; Harre, K.; Hahn, D.; Neubauer, S. Absolute Concentrations of High-Energy Phosphate Metabolites in Normal, Hypertrophied, and Failing Human Myocardium Measured Noninvasively with 31P-SLOOP Magnetic Resonance Spectroscopy. *J. Am. Coll. Cardiol.* **2002**, *40*, 1267–1274. [CrossRef] [PubMed]
78. Weiss, R.G.; Gerstenblith, G.; Bottomley, P.A. ATP Flux through Creatine Kinase in the Normal, Stressed, and Failing Human Heart. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 808–813. [CrossRef]
79. Smith, C.S.; Bottomley, P.A.; Schulman, S.P.; Gerstenblith, G.; Weiss, R.G. Altered Creatine Kinase Adenosine Triphosphate Kinetics in Failing Hypertrophied Human Myocardium. *Circulation* **2006**, *114*, 1151–1158. [CrossRef]
80. Nielsen, R.; Møller, N.; Gormsen, L.C.; Tolbod, L.P.; Hansson, N.H.; Sorensen, J.; Harms, H.J.; Frøkiær, J.; Eiskjaer, H.; Jespersen, N.R.; et al. Cardiovascular Effects of Treatment with the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. *Circulation* **2019**, *139*, 2129–2141. [CrossRef]
81. Brittain, E.L.; Talati, M.; Fessel, J.P.; Zhu, H.; Penner, N.; Calcutt, M.W.; West, J.D.; Funke, M.; Lewis, G.D.; Gerszten, R.E.; et al. Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension. *Circulation* **2016**, *133*, 1936–1944. [CrossRef] [PubMed]
82. Pugh, M.E.; Robbins, I.M.; Rice, T.W.; West, J.; Newman, J.H.; Hemnes, A.R. Unrecognized Glucose Intolerance Is Common in Pulmonary Arterial Hypertension. *J. Heart Lung Transplant.* **2011**, *30*, 904–911. [CrossRef]
83. West, J.; Niswender, K.D.; Johnson, J.A.; Pugh, M.E.; Gleaves, L.; Fessel, J.P.; Hemnes, A.R. A Potential Role for Insulin Resistance in Experimental Pulmonary Hypertension. *Eur. Respir. J.* **2013**, *41*, 861–871. [CrossRef]
84. Zamanian, R.T.; Hansmann, G.; Snook, S.; Lilienfeld, D.; Rappaport, K.M.; Reaven, G.M.; Rabinovitch, M.; Doyle, R.L. Insulin Resistance in Pulmonary Arterial Hypertension. *Eur. Respir. J.* **2008**, *33*, 318–324. [CrossRef]
85. Zare, E.; Kafshbani, P.; Chenaghlou, M.; Noori, M.; Ghaemmaghami, Z.; Amin, A.; Taghavi, S.; Naderi, N. Prognostic Significance of Insulin Resistance in Pulmonary Hypertension. *ESC Heart Fail.* **2022**, *9*, 318–326. [CrossRef]
86. University of Aarhus. Ketones for Pulmonary Hypertension—Effects on Hemodynamics (KEPAH). 2021. Available online: https://clinicaltrials.gov/ct2/show/NCT04615754 (accessed on 22 March 2023).
87. Nielsen, R.; Christensen, K.H.; Gopalasingam, N.; Berg-Hansen, K.; Seefeldt, J.; Homilius, C.; Boedtkjer, E.; Andersen, M.J.; Wiggers, H.; Møller, N.; et al. Hemodynamic Effects of Ketone Bodies in Patients with Pulmonary Hypertension. *J. Am. Heart Assoc.* **2023**, *12*, e028232. [CrossRef]
88. Blake, M.; Puchalska, P.; Kazmirczak, F.; Thenappan, T.; Crawford, P.A.; Prins, K.W. Ketone Bodies in Right Ventricular Failure: A Unique Therapeutic Opportunity. *bioRxiv* **2023**. [CrossRef]

89. McCullough, D.J.; Kue, N.; Mancini, T.; Vang, A.; Clements, R.T.; Choudhary, G. Endurance Exercise Training in Pulmonary Hypertension Increases Skeletal Muscle Electron Transport Chain Supercomplex Assembly. *Pulm. Circ.* **2020**, *10*, 1–11. [CrossRef]
90. Cawthon, D.; Beers, K.; Bottje, W.G. Electron Transport Chain Defect and Inefficient Respiration May Underlie Pulmonary Hypertension Syndrome (Ascites)-Associated Mitochondrial Dysfunction in Broilers. *Poult. Sci.* **2001**, *80*, 474–484. [CrossRef]
91. Xu, W.; Comhair, S.A.A.; Chen, R.; Hu, B.; Hou, Y.; Zhou, Y.; Mavrakis, L.A.; Janocha, A.J.; Li, L.; Zhang, D.; et al. Integrative Proteomics and Phosphoproteomics in Pulmonary Arterial Hypertension. *Sci. Rep.* **2019**, *9*, 18623. [CrossRef]
92. Huertas, A.; Tu, L.; Humbert, M.; Guignabert, C. Chronic Inflammation within the Vascular Wall in Pulmonary Arterial Hypertension: More than a Spectator. *Cardiovasc. Res.* **2020**, *116*, 885–893. [CrossRef]
93. Fowler, E.D.; Hauton, D.; Boyle, J.; Egginton, S.; Steele, D.S.; White, E. Energy Metabolism in the Failing Right Ventricle: Limitations of Oxygen Delivery and the Creatine Kinase System. *Int. J. Mol. Sci.* **2019**, *20*, 1805. [CrossRef]
94. Garcia, A.M.; Toni, L.S.; Miyano, C.A.; Sparagna, G.C.; Jonscher, R.; Phillips, E.K.; Karimpour-Fard, A.; Chapman, H.L.; Baybayon-Grandgeorge, A.N.; Pietra, A.E.; et al. Cardiac Transcriptome Remodeling and Impaired Bioenergetics in Single-Ventricle Congenital Heart Disease. *JACC Basic Transl. Sci.* **2023**, *8*, 258–279. [CrossRef]
95. Pires da Silva, J.; Pietra, A.E.; Baybayon-Grandgeorge, A.N.; Garcia, A.M. Serum Metabolic Profiling Identifies Key Differences between Patients with Single-Ventricle Heart Disease and Healthy Controls. *Int. J. Transl. Med.* **2022**, *2*, 78–96. [CrossRef]
96. Xu, X.; Lin, J.-H.I.; Bais, A.S.; Reynolds, M.J.; Tan, T.; Gabriel, G.C.; Kondos, Z.; Liu, X.; Shiva, S.S.; Lo, C.W. Mitochondrial Respiration Defects in Single-Ventricle Congenital Heart Disease. *Front. Cardiovasc. Med.* **2021**, *8*, 734388. [CrossRef]
97. Ide, T.; Tsutsui, H.; Hayashidani, S.; Kang, D.; Suematsu, N.; Nakamura, K.; Utsumi, H.; Hamasaki, N.; Takeshita, A. Mitochondrial DNA Damage and Dysfunction Associated with Oxidative Stress in Failing Hearts After Myocardial Infarction. *Circ. Res.* **2001**, *88*, 529–535. [CrossRef]
98. Tsutsui, H. Mitochondrial Oxidative Stress and Heart Failure. *Intern. Med.* **2006**, *45*, 809–813. [CrossRef]
99. Randle, P.J.; Garland, P.B.; Hales, C.N.; Newsholme, E.A. The glucose fatty-acid cycle its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* **1963**, *281*, 785–789. [CrossRef]
100. Koeslag, J.H.; Noakes, T.D.; Sloan, A.W. Post-Exercise Ketosis. *J. Physiol.* **1980**, *301*, 79–90. [CrossRef]
101. Robinson, A.M.; Williamson, D.H. Physiological Roles of Ketone Bodies as Substrates and Signals in Mammalian Tissues. *Physiol. Rev.* **1980**, *60*, 143–187. [CrossRef]
102. Lopaschuk, G.D.; Karwi, Q.G.; Ho, K.L.; Pherwani, S.; Ketema, E.B. Ketone Metabolism in the Failing Heart. *Biochim. Biophys. Acta BBA Mol. Cell Biol. Lipids* **2020**, *1865*, 158813. [CrossRef]
103. Hue, L.; Taegtmeyer, H. The Randle Cycle Revisited: A New Head for an Old Hat. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *297*, E578–E591. [CrossRef]
104. Barger, P.M.; Kelly, D.P. PPAR Signaling in the Control of Cardiac Energy Metabolism. *Trends Cardiovasc. Med.* **2000**, *10*, 238–245. [CrossRef]
105. Taegtmeyer, H.; Wilson, C.R.; Razeghi, P.; Sharma, S. Metabolic Energetics and Genetics in the Heart. *Ann. N. Y. Acad. Sci.* **2005**, *1047*, 208–218. [CrossRef]
106. Kelly, D.P. PPARs of the Heart: Three Is a Crowd. *Circ. Res.* **2003**, *92*, 482–484. [CrossRef]
107. Lehman, J.J.; Kelly, D.P. Gene Regulatory Mechanisms Governing Energy Metabolism during Cardiac Hypertrophic Growth. *Heart Fail. Rev.* **2002**, *7*, 175–185. [CrossRef]
108. Razeghi, P.; Young, M.E.; Abbasi, S.; Taegtmeyer, H. Hypoxia in Vivo Decreases Peroxisome Proliferator-Activated Receptor α-Regulated Gene Expression in Rat Heart. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 5–10. [CrossRef]
109. Yang, M.; Zhang, Y.; Ren, J. Acetylation in Cardiovascular Diseases: Molecular Mechanisms and Clinical Implications. *Biochim. Biophys. Acta BBA Mol. Basis Dis.* **2020**, *1866*, 165836. [CrossRef]
110. Shogren-Knaak, M.; Ishii, H.; Sun, J.-M.; Pazin, M.J.; Davie, J.R.; Peterson, C.L. Histone H4-K16 Acetylation Controls Chromatin Structure and Protein Interactions. *Science* **2006**, *311*, 844–847. [CrossRef]
111. Peleg, S.; Feller, C.; Ladurner, A.G.; Imhof, A. The Metabolic Impact on Histone Acetylation and Transcription in Ageing. *Trends Biochem. Sci.* **2016**, *41*, 700–711. [CrossRef]
112. Verdin, E.; Dequiedt, F.; Kasler, H.G. Class II Histone Deacetylases: Versatile Regulators. *Trends Genet.* **2003**, *19*, 286–293. [CrossRef]
113. McKinsey, T.A.; Olson, E.N. Cardiac Histone Acetylation—Therapeutic Opportunities Abound. *Trends Genet.* **2004**, *20*, 206–213. [CrossRef]
114. Backs, J.; Olson, E.N. Control of Cardiac Growth by Histone Acetylation/Deacetylation. *Circ. Res.* **2006**, *98*, 15–24. [CrossRef]
115. Allard, M.F.; Schonekess, B.O.; Henning, S.L.; English, D.R.; Lopaschuk, G.D. Contribution of Oxidative Metabolism and Glycolysis to ATP Production in Hypertrophied Hearts. *Am. J. Physiol. Heart Circ. Physiol.* **1994**, *267*, H742–H750. [CrossRef]
116. Diakos, N.A.; Navankasattusas, S.; Abel, E.D.; Rutter, J.; McCreath, L.; Ferrin, P.; McKellar, S.H.; Miller, D.V.; Park, S.Y.; Richardson, R.S.; et al. Evidence of Glycolysis Up-Regulation and Pyruvate Mitochondrial Oxidation Mismatch During Mechanical Unloading of the Failing Human Heart. *JACC Basic Transl. Sci.* **2016**, *1*, 432–444. [CrossRef]
117. Bottomley, P.A.; Panjrath, G.S.; Lai, S.; Hirsch, G.A.; Wu, K.; Najjar, S.S.; Steinberg, A.; Gerstenblith, G.; Weiss, R.G. Metabolic Rates of ATP Transfer Through Creatine Kinase (CK Flux) Predict Clinical Heart Failure Events and Death. *Sci. Transl. Med.* **2013**, *5*, 215re3. [CrossRef]

118. Mey, J.T.; Hari, A.; Axelrod, C.L.; Fealy, C.E.; Erickson, M.L.; Kirwan, J.P.; Dweik, R.A.; Heresi, G.A. Lipids and Ketones Dominate Metabolism at the Expense of Glucose Control in Pulmonary Arterial Hypertension: A Hyperglycaemic Clamp and Metabolomics Study. *Eur. Respir. J.* **2020**, *55*, 1901700. [CrossRef]
119. Zhou, B.; Tian, R. Mitochondrial Dysfunction in Pathophysiology of Heart Failure. *J. Clin. Investig.* **2018**, *128*, 3716–3726. [CrossRef]
120. Takimoto, E.; Kass, D.A. Role of Oxidative Stress in Cardiac Hypertrophy and Remodeling. *Hypertension* **2007**, *49*, 241–248. [CrossRef]
121. van der Pol, A.; van Gilst, W.H.; Voors, A.A.; van der Meer, P. Treating Oxidative Stress in Heart Failure: Past, Present and Future. *Eur. J. Heart Fail.* **2019**, *21*, 425–435. [CrossRef]
122. Nascimben, L.; Ingwall, J.S.; Pauletto, P.; Friedrich, J.; Gwathmey, J.K.; Saks, V.; Pessina, A.C.; Allen, P.D. Creatine Kinase System in Failing and Nonfailing Human Myocardium. *Circulation* **1996**, *94*, 1894–1901. [CrossRef]
123. Keceli, G.; Gupta, A.; Sourdon, J.; Gabr, R.; Schär, M.; Dey, S.; Tocchetti, C.G.; Stuber, A.; Agrimi, J.; Zhang, Y.; et al. Mitochondrial Creatine Kinase Attenuates Pathologic Remodeling in Heart Failure. *Circ. Res.* **2022**, *130*, 741–759. [CrossRef]
124. Olson, E.N.; Backs, J.; McKinsey, T.A. Control of Cardiac Hypertrophy and Heart Failure by Histone Acetylation/Deacetylation. In *Novartis Foundation Symposia*; Bock, G., Goode, J., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 2008; pp. 3–19. [CrossRef]
125. Fukushima, A.; Zhang, L.; Huqi, A.; Lam, V.H.; Rawat, S.; Altamimi, T.; Wagg, C.S.; Dhaliwal, K.K.; Hornberger, L.K.; Kantor, P.F.; et al. Acetylation Contributes to Hypertrophy-Caused Maturational Delay of Cardiac Energy Metabolism. *JCI Insight* **2018**, *3*, e99239. [CrossRef]
126. Castillo, E.C.; Morales, J.A.; Chapoy-Villanueva, H.; Silva-Platas, C.; Treviño-Saldaña, N.; Guerrero-Beltrán, C.E.; Bernal-Ramírez, J.; Torres-Quintanilla, A.; García, N.; Youker, K.; et al. Mitochondrial Hyperacetylation in the Failing Hearts of Obese Patients Mediated Partly by a Reduction in SIRT3: The Involvement of the Mitochondrial Permeability Transition Pore. *Cell Physiol. Biochem.* **2019**, *53*, 465–479. [CrossRef] [PubMed]
127. Ooi, J.Y.Y.; Tuano, N.K.; Rafehi, H.; Gao, X.-M.; Ziemann, M.; Du, X.-J.; El-Osta, A. HDAC Inhibition Attenuates Cardiac Hypertrophy by Acetylation and Deacetylation of Target Genes. *Epigenetics* **2015**, *10*, 418–430. [CrossRef] [PubMed]
128. Kang, S.-H.; Seok, Y.M.; Song, M.; Lee, H.-A.; Kurz, T.; Kim, I. Histone Deacetylase Inhibition Attenuates Cardiac Hypertrophy and Fibrosis through Acetylation of Mineralocorticoid Receptor in Spontaneously Hypertensive Rats. *Mol. Pharmacol.* **2015**, *87*, 782–791. [CrossRef] [PubMed]
129. Scholz, B.; Schulte, J.S.; Hamer, S.; Himmler, K.; Pluteanu, F.; Seidl, M.D.; Stein, J.; Wardelmann, E.; Hammer, E.; Völker, U.; et al. HDAC (Histone Deacetylase) Inhibitor Valproic Acid Attenuates Atrial Remodeling and Delays the Onset of Atrial Fibrillation in Mice. *Circ. Arrhythm. Electrophysiol.* **2019**, *12*, e007071. [CrossRef]
130. Colussi, C.; Berni, R.; Rosati, J.; Straino, S.; Vitale, S.; Spallotta, F.; Baruffi, S.; Bocchi, L.; Delucchi, F.; Rossi, S.; et al. The Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid Reduces Cardiac Arrhythmias in Dystrophic Mice. *Cardiovasc. Res.* **2010**, *87*, 73–82. [CrossRef]
131. Müller, J.; Bertsch, T.; Volke, J.; Schmid, A.; Klingbeil, R.; Metodiev, Y.; Karaca, B.; Kim, S.-H.; Lindner, S.; Schupp, T.; et al. Narrative Review of Metabolomics in Cardiovascular Disease. *J. Thorac. Dis.* **2021**, *13*, 2532–2550. [CrossRef]
132. Bassareo, P.P.; McMahon, C.J. Metabolomics: A New Tool in Our Understanding of Congenital Heart Disease. *Children* **2022**, *9*, 1803. [CrossRef]
133. Michel, M.; Laser, K.T.; Dubowy, K.-O.; Scholl-Bürgi, S.; Michel, E. Metabolomics and Random Forests in Patients with Complex Congenital Heart Disease. *Front. Cardiovasc. Med.* **2022**, *9*, 994068. [CrossRef]
134. Murashige, D.; Jang, C.; Neinast, M.; Edwards, J.J.; Cowan, A.; Hyman, M.C.; Rabinowitz, J.D.; Frankel, D.S.; Arany, Z. Comprehensive Quantification of Fuel Use by the Failing and Nonfailing Human Heart. *Science* **2020**, *370*, 364–368. [CrossRef]
135. Smith, E.; Fernandez, C.; Melander, O.; Ottosson, F. Altered Acylcarnitine Metabolism Is Associated With an Increased Risk of Atrial Fibrillation. *J. Am. Heart Assoc.* **2020**, *9*, e016737. [CrossRef]
136. Ruiz, M.; Labarthe, F.; Fortier, A.; Bouchard, B.; Thompson Legault, J.; Bolduc, V.; Rigal, O.; Chen, J.; Ducharme, A.; Crawford, P.A.; et al. Circulating Acylcarnitine Profile in Human Heart Failure: A Surrogate of Fatty Acid Metabolic Dysregulation in Mitochondria and Beyond. *Am. J. Physiol. Heart Circ. Physiol.* **2017**, *313*, H768–H781. [CrossRef] [PubMed]
137. Penny, D.J.; Redington, A.N. Function of the Left and Right Ventricles and the Interactions Between Them. *Pediatr. Crit. Care Med.* **2016**, *17*, S112–S118. [CrossRef] [PubMed]
138. Sanz, J.; Sánchez-Quintana, D.; Bossone, E.; Bogaard, H.J.; Naeije, R. Anatomy, Function, and Dysfunction of the Right Ventricle. *J. Am. Coll. Cardiol.* **2019**, *73*, 1463–1482. [CrossRef] [PubMed]
139. Kondo, R.P.; Dederko, D.A.; Teutsch, C.; Chrast, J.; Catalucci, D.; Chien, K.R.; Giles, W.R. Comparison of Contraction and Calcium Handling between Right and Left Ventricular Myocytes from Adult Mouse Heart: A Role for Repolarization Waveform: Interventricular Heterogeneity of Cardiac Myocyte Contractions. *J. Physiol.* **2006**, *571*, 131–146. [CrossRef]
140. Sedmera, D. Form Follows Function: Developmental and Physiological View on Ventricular Myocardial Architecture. *Eur. J. Cardiothorac. Surg.* **2005**, *28*, 526–528. [CrossRef]
141. Garcia, A.M.; Beatty, J.-T.; Nakano, S.J. Heart Failure in Single Right Ventricle Congenital Heart Disease: Physiological and Molecular Considerations. *Am. J. Physiol. Heart Circ. Physiol.* **2020**, *318*, H947–H965. [CrossRef] [PubMed]

142. Friehs, I.; Cowan, D.B.; Choi, Y.-H.; Black, K.M.; Barnett, R.; Bhasin, M.K.; Daly, C.; Dillon, S.J.; Libermann, T.A.; McGowan, F.X.; et al. Pressure-Overload Hypertrophy of the Developing Heart Reveals Activation of Divergent Gene and Protein Pathways in the Left and Right Ventricular Myocardium. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *304*, H697–H708. [CrossRef]
143. Schreckenberg, R.; Rebelo, M.; Deten, A.; Weber, M.; Rohrbach, S.; Pipicz, M.; Csonka, C.; Ferdinandy, P.; Schulz, R.; Schlüter, K.-D. Specific Mechanisms Underlying Right Heart Failure: The Missing Upregulation of Superoxide Dismutase-2 and Its Decisive Role in Antioxidative Defense. *Antioxid. Redox Signal.* **2015**, *23*, 1220–1232. [CrossRef]
144. Nagendran, J.; Gurtu, V.; Fu, D.Z.; Dyck, J.R.B.; Haromy, A.; Ross, D.B.; Rebeyka, I.M.; Michelakis, E.D. A Dynamic and Chamber-Specific Mitochondrial Remodeling in Right Ventricular Hypertrophy Can Be Therapeutically Targeted. *J. Thorac. Cardiovasc. Surg.* **2008**, *136*, 168–178.e3. [CrossRef] [PubMed]
145. Bokhari, S.; Raina, A.; Berman Rosenweig, E.; Schulze, P.C.; Bokhari, J.; Einstein, A.J.; Barst, R.J.; Johnson, L.L. PET Imaging May Provide a Novel Biomarker and Understanding of Right Ventricular Dysfunction in Patients With Idiopathic Pulmonary Arterial Hypertension. *Circ. Cardiovasc. Imaging* **2011**, *4*, 641–647. [CrossRef] [PubMed]
146. Gomez-Arroyo, J.; Mizuno, S.; Szczepanek, K.; Van Tassell, B.; Natarajan, R.; dos Remedios, C.G.; Drake, J.I.; Farkas, L.; Kraskauskas, D.; Wijesinghe, D.S.; et al. Metabolic Gene Remodeling and Mitochondrial Dysfunction in Failing Right Ventricular Hypertrophy Secondary to Pulmonary Arterial Hypertension. *Circ. Heart Fail.* **2013**, *6*, 136–144. [CrossRef] [PubMed]
147. Piao, L.; Marsboom, G.; Archer, S.L. Mitochondrial Metabolic Adaptation in Right Ventricular Hypertrophy and Failure. *J. Mol. Med.* **2010**, *88*, 1011–1020. [CrossRef]
148. Fessel, J.P.; Hamid, R.; Wittmann, B.M.; Robinson, L.J.; Blackwell, T.; Tada, Y.; Tanabe, N.; Tatsumi, K.; Hemnes, A.R.; West, J.D. Metabolomic Analysis of Bone Morphogenetic Protein Receptor Type 2 Mutations in Human Pulmonary Endothelium Reveals Widespread Metabolic Reprogramming. *Pulm. Circ.* **2012**, *2*, 201–213. [CrossRef] [PubMed]
149. Schooneman, M.G.; Vaz, F.M.; Houten, S.M.; Soeters, M.R. Acylcarnitines. *Diabetes* **2013**, *62*, 1–8. [CrossRef] [PubMed]
150. Kalim, S.; Clish, C.B.; Wenger, J.; Elmariah, S.; Yeh, R.W.; Deferio, J.J.; Pierce, K.; Deik, A.; Gerszten, R.E.; Thadhani, R.; et al. A Plasma Long-Chain Acylcarnitine Predicts Cardiovascular Mortality in Incident Dialysis Patients. *J. Am. Heart Assoc.* **2013**, *2*, e000542. [CrossRef]
151. Aitken-Buck, H.M.; Krause, J.; Zeller, T.; Jones, P.P.; Lamberts, R.R. Long-Chain Acylcarnitines and Cardiac Excitation-Contraction Coupling: Links to Arrhythmias. *Front. Physiol.* **2020**, *11*, 577856. [CrossRef]
152. Brunner, N.W.; Skhiri, M.; Fortenko, O.; Hsi, A.; Haddad, F.; Khazeni, N.; Zamanian, R.T. Impact of Insulin Resistance on Ventricular Function in Pulmonary Arterial Hypertension. *J. Heart Lung Transplant.* **2014**, *33*, 721–726. [CrossRef]
153. Assad, T.R.; Hemnes, A.R. Metabolic Dysfunction in Pulmonary Arterial Hypertension. *Curr. Hypertens. Rep.* **2015**, *17*, 20. [CrossRef]
154. Graham, B.B.; Kumar, R.; Mickael, C.; Sanders, L.; Gebreab, L.; Huber, K.M.; Perez, M.; Smith-Jones, P.; Serkova, N.J.; Tuder, R.M. Severe Pulmonary Hypertension Is Associated with Altered Right Ventricle Metabolic Substrate Uptake. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2015**, *309*, L435–L440. [CrossRef]
155. Ohuchi, H.; Negishi, J.; Hayama, Y.; Miike, H.; Suzuki, D.; Nakajima, K.; Konagai, N.; Iwasa, T.; Sakaguchi, H.; Kurosaki, K.; et al. Abnormal Glucose Metabolism in Patients with Fontan Circulation: Unique Characteristics and Associations with Fontan Pathophysiology. *Am. Heart J.* **2019**, *216*, 125–135. [CrossRef]
156. Sharma, S.; Sud, N.; Wiseman, D.A.; Carter, A.L.; Kumar, S.; Hou, Y.; Rau, T.; Wilham, J.; Harmon, C.; Oishi, P.; et al. Altered Carnitine Homeostasis Is Associated with Decreased Mitochondrial Function and Altered Nitric Oxide Signaling in Lambs with Pulmonary Hypertension. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2008**, *294*, L46–L56. [CrossRef]
157. Fowler, E.D.; Benoist, D.; Drinkhill, M.J.; Stones, R.; Helmes, M.; Wüst, R.C.I.; Stienen, G.J.M.; Steele, D.S.; White, E. Decreased Creatine Kinase Is Linked to Diastolic Dysfunction in Rats with Right Heart Failure Induced by Pulmonary Artery Hypertension. *J. Mol. Cell. Cardiol.* **2015**, *86*, 1–8. [CrossRef]
158. Bernal-Ramirez, J.; Díaz-Vesga, M.C.; Talamilla, M.; Méndez, A.; Quiroga, C.; Garza-Cervantes, J.A.; Lázaro-Alfaro, A.; Jerjes-Sanchez, C.; Henríquez, M.; García-Rivas, G.; et al. Exploring Functional Differences between the Right and Left Ventricles to Better Understand Right Ventricular Dysfunction. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 9993060. [CrossRef]
159. Bogaard, H.J.; Mizuno, S.; Hussaini, A.A.A.; Toldo, S.; Abbate, A.; Kraskauskas, D.; Kasper, M.; Natarajan, R.; Voelkel, N.F. Suppression of Histone Deacetylases Worsens Right Ventricular Dysfunction after Pulmonary Artery Banding in Rats. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 1402–1410. [CrossRef]
160. Chelladurai, P.; Boucherat, O.; Stenmark, K.; Kracht, M.; Seeger, W.; Bauer, U.; Bonnet, S.; Pullamsetti, S.S. Targeting Histone Acetylation in Pulmonary Hypertension and Right Ventricular Hypertrophy. *Br. J. Pharmacol.* **2021**, *178*, 54–71. [CrossRef]
161. Chen, C.; Luo, F.; Wu, P.; Huang, Y.; Das, A.; Chen, S.; Chen, J.; Hu, X.; Li, F.; Fang, Z.; et al. Metabolomics Reveals Metabolite Changes of Patients with Pulmonary Arterial Hypertension in China. *J. Cell. Mol. Med.* **2020**, *24*, 2484–2496. [CrossRef]
162. Rawat, S.; Fukushima, A.; Zhang, L.; Hugi, A.; Lam, V.; Altamimi, T.; Wagg, C.; Petinelli, R.; Dhaliwal, K.; Hornberger, L.; et al. Control of cardiac fatty acid metabolism in infants with hypoplastic left heart syndrome. *J. Mol. Cell. Cardiol.* **2018**, *124*, 91–92. [CrossRef]
163. Motoki, N.; Motoki, H.; Utsumi, M.; Yamazaki, S.; Obinata, H.; Takei, K.; Yasukochi, S. Identification of metabolomic profile related to adult Fontan pathophysiology. *Int. J. Cardiol. Heart Vasc.* **2021**, *37*, 100921. [CrossRef]

164. Li, M.; Zhou, S.; Chen, C.; Ma, L.; Luo, D.; Tian, X.; Dong, X.; Zhou, Y.; Yang, Y.; Cui, Y. Therapeutic Potential of Pyruvate Therapy for Patients with Mitochondrial Diseases: A Systematic Review. *Ther. Adv. Endocrinol. Metab.* **2020**, *11*, 204201882093824. [CrossRef]
165. Des Rosiers, C.; Labarthe, F.; Lloyd, S.G.; Chatham, J.C. Cardiac Anaplerosis in Health and Disease: Food for Thought. *Cardiovasc. Res.* **2011**, *90*, 210–219. [CrossRef]
166. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bělohlávek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef]
167. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef]
168. Lopaschuk, G.D.; Verma, S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors. *JACC Basic Transl. Sci.* **2020**, *5*, 632–644. [CrossRef]
169. Maejima, Y. SGLT2 Inhibitors Play a Salutary Role in Heart Failure via Modulation of the Mitochondrial Function. *Front. Cardiovasc. Med.* **2020**, *6*, 186. [CrossRef]
170. Pietschner, R.; Kolwelter, J.; Bosch, A.; Striepe, K.; Jung, S.; Kannenkeril, D.; Ott, C.; Schiffer, M.; Achenbach, S.; Schmieder, R.E. Effect of Empagliflozin on Ketone Bodies in Patients with Stable Chronic Heart Failure. *Cardiovasc. Diabetol.* **2021**, *20*, 219. [CrossRef]
171. Takada, S.; Sabe, H.; Kinugawa, S. Treatments for Skeletal Muscle Abnormalities in Heart Failure: Sodium-Glucose Transporter 2 and Ketone Bodies. *Am. J. Physiol. Heart Circ. Physiol.* **2022**, *322*, H117–H128. [CrossRef]
172. Muneuchi, J.; Sugitani, Y.; Kobayashi, M.; Ezaki, H.; Yamada, H.; Watanabe, M. Feasibility and Safety of Sodium Glucose Cotransporter-2 Inhibitors in Adults with Heart Failure after the Fontan Procedure. *Case Rep. Cardiol.* **2022**, *2022*, 5243594. [CrossRef]
173. Ghelani, S.J.; Opotowsky, A.R.; Harrild, D.M.; Powell, A.J.; Azcue, N.; Ahmad, S.; Clair, N.S.; Bradwin, G.; Rathod, R.H. Characterization of Circulating and Urinary Biomarkers in the Fontan Circulation and Their Correlation with Cardiac Imaging. *Am. J. Cardiol.* **2022**, *162*, 177–183. [CrossRef]
174. van den Bosch, E.; Bossers, S.S.M.; Kamphuis, V.P.; Boersma, E.; Roos-Hesselink, J.W.; Breur, J.M.P.J.; Ten Harkel, A.D.J.; Kapusta, L.; Bartelds, B.; Roest, A.A.W.; et al. Associations Between Blood Biomarkers, Cardiac Function, and Adverse Outcome in a Young Fontan Cohort. *J. Am. Heart Assoc.* **2021**, *10*, e015022. [CrossRef]
175. Gom, R.C.; Bhatt, D.; Villa, B.R.; George, A.G.; Lohman, A.W.; Mychasiuk, R.; Rho, J.M.; Teskey, G.C. The Ketogenic Diet Raises Brain Oxygen Levels, Attenuates Postictal Hypoxia, and Protects against Learning Impairments. *Neurobiol. Dis.* **2021**, *154*, 105335. [CrossRef]
176. Trevisan, R.; Nosadini, R.; Fioretto, P.; Avogaro, A.; Duner, E.; Jori, E.; Valerio, A.; Doria, A.; Crepaldi, G. Ketone Bodies Increase Glomerular Filtration Rate in Normal Man and in Patients with Type 1 (Insulin-Dependent) Diabetes Mellitus. *Diabetologia* **1987**, *30*, 214–221. [CrossRef]
177. Zhou, B.; Wang, D.D.-H.; Qiu, Y.; Airhart, S.; Liu, Y.; Stempien-Otero, A.; O'Brien, K.D.; Tian, R. Boosting NAD Level Suppresses Inflammatory Activation of PBMCs in Heart Failure. *J. Clin. Investig.* **2020**, *130*, 6054–6063. [CrossRef]
178. Lopaschuk, G.D.; Persad, K.L. Failure to Launch. *JACC Basic Transl. Sci.* **2023**, *8*, 280–282. [CrossRef]
179. Frank, B.S.; Khailova, L.; Silveira, L.; Mitchell, M.B.; Morgan, G.J.; Hsieh, E.W.Y.; DiMaria, M.V.; Twite, M.; Klawitter, J.; Davidson, J.A. Proteomic profiling identifies key differences between inter-stage infants with single ventricle heart disease and healthy controls. *Transl. Res.* **2021**, *229*, 24–37. [CrossRef]
180. Ohuchi, H.; Miyamoto, Y.; Yamamoto, M.; Ishihara, H.; Takata, H.; Miyazaki, A.; Yamada, O.; Yagihara, T. High Prevalence of Abnormal Glucose Metabolism in Young Adult Patients with Complex Congenital Heart Disease. *Am. Heart J.* **2009**, *158*, 30–39. [CrossRef]
181. Whiteside, W.; Tan, M.; Ostlund, R.E.; Yu, S.; Ma, L.; Rocchini, A. Altered Cholesterol Metabolism and Hypocholesterolemia in Patients with Single Ventricle Following Fontan Palliation. *J. Pediatr.* **2016**, *171*, 73–77. [CrossRef]
182. Whiteside, W.; Tan, M.; Yu, S.; Rocchini, A. Low Total, Low-Density Lipoprotein, High-Density Lipoprotein, and Non–High-Density Lipoprotein Cholesterol Levels in Patients with Complex Congenital Heart Disease after Fontan Palliation. *J. Pediatr.* **2013**, *162*, 1199–1204. [CrossRef]
183. Lubert, A.M.; Alsaied, T.; Palermo, J.J.; Anwar, N.; Urbina, E.M.; Brown, N.M.; Alexander, C.; Almeneisi, H.; Wu, F.; Leventhal, A.R.; et al. Fontan-Associated Dyslipidemia. *J. Am. Heart Assoc.* **2021**, *10*, e019578. [CrossRef]
184. Zyblewski, S.C.; Argraves, W.S.; Graham, E.M.; Slate, E.H.; Atz, A.M.; Bradley, S.M.; McQuinn, T.C.; Wilkerson, B.A.; Wing, S.B.; Argraves, K.M. Reduction in postoperative high-density lipoprotein cholesterol levels in children undergoing the Fontan operation. *Pediatr. Cardiol.* **2012**, *33*, 1154–1159. [CrossRef]
185. Saraf, A.; De Staercke, C.; Everitt, I.; Haouzi, A.; Ko, Y.A.; Jennings, S.; Kim, J.H.; Rodriguez, F.H.; Kalogeropoulos, A.P.; Quyyumi, A.; et al. Biomarker profile in stable Fontan patients. *Int. J. Cardiol.* **2020**, *305*, 56–62. [CrossRef]
186. Fillmore, N.; Lopaschuk, G.D. Targeting Mitochondrial Oxidative Metabolism as an Approach to Treat Heart Failure. *Biochim. Biophys. Acta BBA Mol. Cell Res.* **2013**, *1833*, 857–865. [CrossRef]
187. Karwi, Q.G.; Biswas, D.; Pulinilkunnil, T.; Lopaschuk, G.D. Myocardial Ketones Metabolism in Heart Failure. *J. Card. Fail.* **2020**, *26*, 998–1005. [CrossRef]

188. Lopaschuk, G.D.; Dyck, J.R.B. Ketones and the Cardiovascular System. *Nat. Cardiovasc. Res.* **2023**, *2*, 425–437. [CrossRef]
189. Kashiwaya, Y.; Sato, K.; Tsuchiya, N.; Thomas, S.; Fell, D.A.; Veech, R.L.; Passonneau, J.V. Control of Glucose Utilization in Working Perfused Rat Heart. *J. Biol. Chem.* **1994**, *269*, 25502–25514. [CrossRef]
190. Cahill, G.F.; Veech, R.L. Ketoacids? Good Medicine? *Trans. Am. Clin. Climatol. Assoc.* **2003**, *114*, 149–163.
191. Veech, R.L.; Chance, B.; Kashiwaya, Y.; Lardy, H.A.; Cahill, G.F., Jr. Ketone Bodies, Potential Therapeutic Uses. *IUBMB Life Int. Union Biochem. Mol. Biol. Life* **2001**, *51*, 241–247. [CrossRef]
192. Veech, R.L. The Therapeutic Implications of Ketone Bodies: The Effects of Ketone Bodies in Pathological Conditions: Ketosis, Ketogenic Diet, Redox States, Insulin Resistance, and Mitochondrial Metabolism. *Prostaglandins Leukot. Essent. Fatty Acids* **2004**, *70*, 309–319. [CrossRef]
193. Sato, K.; Kashiwaya, Y.; Keon, C.A.; Tsuchiya, N.; King, M.T.; Radda, G.K.; Chance, B.; Clarke, K.; Veech, R.L. Insulin, Ketone Bodies, and Mitochondrial Energy Transduction. *FASEB J.* **1995**, *9*, 651–658. [CrossRef]
194. Mudaliar, S.; Alloju, S.; Henry, R.R. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. *Diabetes Care* **2016**, *39*, 1115–1122. [CrossRef]
195. Ho, K.L.; Karwi, Q.G.; Wagg, C.; Zhang, L.; Vo, K.; Altamimi, T.; Uddin, G.M.; Ussher, J.R.; Lopaschuk, G.D. Ketones Can Become the Major Fuel Source for the Heart but Do Not Increase Cardiac Efficiency. *Cardiovasc. Res.* **2021**, *117*, 1178–1187. [CrossRef]
196. Berg-Hansen, K.; Christensen, K.H.; Gopalasingam, N.; Nielsen, R.; Eiskjær, H.; Møller, N.; Birkelund, T.; Christensen, S.; Wiggers, H. Beneficial Effects of Ketone Ester in Patients with Cardiogenic Shock: A Randomized, Controlled, Double-Blind Trial. *JACC Heart Fail.* 2023, *ahead of print*. [CrossRef]
197. Lopaschuk, G.D.; Karwi, Q.G. Jump Starting the Heart: Ketone Esters Improve Cardiac Function in Patients with Cardiogenic Shock. *JACC Heart Fail.* 2023, *in press*. [CrossRef]
198. Dubois-Deruy, E.; Peugnet, V.; Turkieh, A.; Pinet, F. Oxidative Stress in Cardiovascular Diseases. *Antioxidants* **2020**, *9*, 864. [CrossRef]
199. Grieve, D. Oxidative Stress in Heart Failure More than Just Damage. *Eur. Heart J.* **2003**, *24*, 2161–2163. [CrossRef]
200. Shimazu, T.; Hirschey, M.D.; Newman, J.; He, W.; Shirakawa, K.; Le Moan, N.; Grueter, C.A.; Lim, H.; Saunders, L.R.; Stevens, R.D.; et al. Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor. *Science* **2013**, *339*, 211–214. [CrossRef]
201. Guo, Y.; Zhang, C.; Shang, F.-F.; Luo, M.; You, Y.; Zhai, Q.; Xia, Y.; Suxin, L. Ketogenic Diet Ameliorates Cardiac Dysfunction via Balancing Mitochondrial Dynamics and Inhibiting Apoptosis in Type 2 Diabetic Mice. *Aging Dis.* **2020**, *11*, 229. [CrossRef]
202. Murphy, S.P.; Kakkar, R.; McCarthy, C.P.; Januzzi, J.L. Inflammation in Heart Failure. *J. Am. Coll. Cardiol.* **2020**, *75*, 1324–1340. [CrossRef]
203. Shirazi, L.F.; Bissett, J.; Romeo, F.; Mehta, J.L. Role of Inflammation in Heart Failure. *Curr. Atheroscler. Rep.* **2017**, *19*, 27. [CrossRef]
204. Adamo, L.; Rocha-Resende, C.; Prabhu, S.D.; Mann, D.L. Reappraising the Role of Inflammation in Heart Failure. *Nat. Rev. Cardiol.* **2020**, *17*, 269–285. [CrossRef]
205. Suetomi, T.; Willeford, A.; Brand, C.S.; Cho, Y.; Ross, R.S.; Miyamoto, S.; Brown, J.H. Inflammation and NLRP3 Inflammasome Activation Initiated in Response to Pressure Overload by Ca^{2+}/Calmodulin-Dependent Protein Kinase II δ Signaling in Cardiomyocytes Are Essential for Adverse Cardiac Remodeling. *Circulation* **2018**, *138*, 2530–2544. [CrossRef]
206. Youm, Y.-H.; Nguyen, K.Y.; Grant, R.W.; Goldberg, E.L.; Bodogai, M.; Kim, D.; D'Agostino, D.; Planavsky, N.; Lupfer, C.; Kanneganti, T.D.; et al. The Ketone Metabolite β-Hydroxybutyrate Blocks NLRP3 Inflammasome–Mediated Inflammatory Disease. *Nat. Med.* **2015**, *21*, 263–269. [CrossRef]
207. Maalouf, M.; Sullivan, P.G.; Davis, L.; Kim, D.Y.; Rho, J.M. Ketones Inhibit Mitochondrial Production of Reactive Oxygen Species Production Following Glutamate Excitotoxicity by Increasing NADH Oxidation. *Neuroscience* **2007**, *145*, 256–264. [CrossRef]
208. Forsythe, C.E.; Phinney, S.D.; Fernandez, M.L.; Quann, E.E.; Wood, R.J.; Bibus, D.M.; Kraemer, W.J.; Feinman, R.D.; Volek, J.S. Comparison of Low Fat and Low Carbohydrate Diets on Circulating Fatty Acid Composition and Markers of Inflammation. *Lipids* **2008**, *43*, 65–77. [CrossRef]
209. Greco, T.; Glenn, T.C.; Hovda, D.A.; Prins, M.L. Ketogenic Diet Decreases Oxidative Stress and Improves Mitochondrial Respiratory Complex Activity. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 1603–1613. [CrossRef]
210. Yang, D.; Liu, H.-Q.; Liu, F.-Y.; Guo, Z.; An, P.; Wang, M.-Y.; Yang, Z.; Fan, D.; Tang, Q.-Z. Mitochondria in Pathological Cardiac Hypertrophy Research and Therapy. *Front. Cardiovasc. Med.* **2022**, *8*, 822969. [CrossRef]
211. Abel, E.D.; Doenst, T. Mitochondrial Adaptations to Physiological vs. Pathological Cardiac Hypertrophy. *Cardiovasc. Res.* **2011**, *90*, 234–242. [CrossRef]
212. Kolwicz, S.C.; Tian, R. Glucose Metabolism and Cardiac Hypertrophy. *Cardiovasc. Res.* **2011**, *90*, 194–201. [CrossRef]
213. Lopaschuk, G.D.; Ussher, J.R.; Folmes, C.D.L.; Jaswal, J.S.; Stanley, W.C. Myocardial Fatty Acid Metabolism in Health and Disease. *Physiol. Rev.* **2010**, *90*, 207–258. [CrossRef]
214. Kee, H.J.; Kook, H. Roles and Targets of Class I and IIa Histone Deacetylases in Cardiac Hypertrophy. *J. Biomed. Biotechnol.* **2011**, *2011*, 928326. [CrossRef]
215. Hewitson, R.; Dargan, J.; Collis, D.; Green, A.; Moorjani, N.; Ohri, S.; Townsend, P.A. Heart Failure: The Pivotal Role of Histone Deacetylases. *Int. J. Biochem. Cell Biol.* **2013**, *45*, 448–453. [CrossRef]

216. Yurista, S.R.; Matsuura, T.R.; Silljé, H.H.W.; Nijholt, K.T.; McDaid, K.S.; Shewale, S.V.; Leone, T.C.; Newman, J.C.; Verdin, E.; van Veldhuisen, D.J.; et al. Ketone Ester Treatment Improves Cardiac Function and Reduces Pathologic Remodeling in Preclinical Models of Heart Failure. *Circ. Heart Fail.* **2021**, *14*, e007684. [CrossRef]
217. Nakamura, M.; Odanovic, N.; Nakada, Y.; Dohi, S.; Zhai, P.; Ivessa, A.; Yang, Z.; Abdellatif, M.; Sadoshima, J. Dietary Carbohydrates Restriction Inhibits the Development of Cardiac Hypertrophy and Heart Failure. *Cardiovasc. Res.* **2021**, *117*, 2365–2376. [CrossRef]
218. Okere, I.C.; Young, M.E.; McElfresh, T.A.; Chess, D.J.; Sharov, V.G.; Sabbah, H.N.; Hoit, B.D.; Ernsberger, P.; Chandler, M.P.; Stanley, W.C. Low Carbohydrate/High-Fat Diet Attenuates Cardiac Hypertrophy, Remodeling, and Altered Gene Expression in Hypertension. *Hypertension* **2006**, *48*, 1116–1123. [CrossRef]
219. Egbe, A.C.; Connolly, H.M.; Miranda, W.R.; Ammash, N.M.; Hagler, D.J.; Veldtman, G.R.; Borlaug, B.A. Hemodynamics of Fontan Failure: The Role of Pulmonary Vascular Disease. *Circ. Heart Fail.* **2017**, *10*, e004515. [CrossRef]
220. Castaldi, B.; Bordin, G.; Padalino, M.; Cuppini, E.; Vida, V.; Milanesi, O. Hemodynamic Impact of Pulmonary Vasodilators on Single Ventricle Physiology. *Cardiovasc. Ther.* **2018**, *36*, e12314. [CrossRef]
221. Zuchi, C.; Tritto, I.; Carluccio, E.; Mattei, C.; Cattadori, G.; Ambrosio, G. Role of Endothelial Dysfunction in Heart Failure. *Heart Fail. Rev.* **2020**, *25*, 21–30. [CrossRef]
222. Giannitsi, S.; Maria, B.; Bechlioulis, A.; Naka, K. Endothelial Dysfunction and Heart Failure: A Review of the Existing Bibliography with Emphasis on Flow Mediated Dilation. *JRSM Cardiovasc. Dis.* **2019**, *8*, 204800401984304. [CrossRef]
223. McCarthy, C.G.; Chakraborty, S.; Singh, G.; Yeoh, B.S.; Schreckenberger, Z.J.; Singh, A.; Mell, B.; Bearss, N.R.; Yang, T.; Cheng, X.; et al. Ketone Body β-Hydroxybutyrate Is an Autophagy-Dependent Vasodilator. *JCI Insight* **2021**, *6*, e149037. [CrossRef]
224. Gormsen, L.C.; Svart, M.; Thomsen, H.H.; Søndergaard, E.; Vendelbo, M.H.; Christensen, N.; Tolbod, L.P.; Harms, H.J.; Nielsen, R.; Wiggers, H.; et al. Ketone Body Infusion With 3-Hydroxybutyrate Reduces Myocardial Glucose Uptake and Increases Blood Flow in Humans: A Positron Emission Tomography Study. *J. Am. Heart Assoc.* **2017**, *6*, e005066. [CrossRef]
225. Ibrahim, A. The Effect of Ketone on β-Aminopropionitrile-Induced Vascular Remodeling. Master's Thesis, Georgia State University, Atlanta, GA, USA, 2022. [CrossRef]
226. Coleman, K.; Phillips, J.; Sciarini, M.; Stubbs, B.; Jackson, O.; Kernagis, D. A Metabolic Intervention for Improving Human Cognitive Performance During Hypoxia. *Aerosp. Med. Hum. Perform.* **2021**, *92*, 556–562. [CrossRef]
227. Prins, P.J.; Buxton, J.D.; McClure, T.S.; D'Agostino, D.P.; Ault, D.L.; Welton, G.L.; Jones, D.W.; Atwell, A.D.; Slack, M.A.; Slack, M.L.; et al. Ketone Bodies Impact on Hypoxic CO2 Retention Protocol During Exercise. *Front. Physiol.* **2021**, *12*, 780755. [CrossRef]
228. Kashiwaya, Y.; Pawlosky, R.; Markis, W.; King, M.T.; Bergman, C.; Srivastava, S.; Murray, A.; Clarke, K.; Veech, R.L. A Ketone Ester Diet Increases Brain Malonyl-CoA and Uncoupling Proteins 4 and 5 While Decreasing Food Intake in the Normal Wistar Rat. *J. Biol. Chem.* **2010**, *285*, 25950–25956. [CrossRef]
229. Puchalska, P.; Crawford, P.A. Multi-Dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metab.* **2017**, *25*, 262–284. [CrossRef]
230. Kim, D.; Roberts, C.; McKenzie, A.; George, M.P. Nutritional Ketosis to Treat Pulmonary Hypertension Associated with Obesity and Metabolic Syndrome: A Case Report. *Pulm. Circ.* **2021**, *11*, 2045894021991426. [CrossRef]
231. Chowdhury, B.; Luu, A.Z.; Luu, V.Z.; Kabir, M.G.; Pan, Y.; Teoh, H.; Quan, A.; Sabongui, S.; Al-Omran, M.; Bhatt, D.L.; et al. The SGLT2 Inhibitor Empagliflozin Reduces Mortality and Prevents Progression in Experimental Pulmonary Hypertension. *Biochem. Biophys. Res. Commun.* **2020**, *524*, 50–56. [CrossRef]
232. Rychik, J. The Relentless Effects of the Fontan Paradox. *Semin. Thorac. Cardiovasc. Surg. Pediatr. Card. Surg. Annu.* **2016**, *19*, 37–43. [CrossRef]
233. Mooli, R.G.R.; Ramakrishnan, S.K. Emerging Role of Hepatic Ketogenesis in Fatty Liver Disease. *Front. Physiol.* **2022**, *13*, 946474. [CrossRef]
234. Liao, Y.-J.; Wang, Y.-H.; Wu, C.-Y.; Hsu, F.-Y.; Chien, C.-Y.; Lee, Y.-C. Ketogenic Diet Enhances the Cholesterol Accumulation in Liver and Augments the Severity of CCl4 and TAA-Induced Liver Fibrosis in Mice. *Int. J. Mol. Sci.* **2021**, *22*, 2934. [CrossRef]
235. Moore, M.P.; Cunningham, R.P.; Davis, R.A.H.; Deemer, S.E.; Roberts, B.M.; Plaisance, E.P.; Rector, R.S. A Dietary Ketone Ester Mitigates Histological Outcomes of NAFLD and Markers of Fibrosis in High-Fat Diet Fed Mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2021**, *320*, G564–G572. [CrossRef]
236. Luukkonen, P.K.; Dufour, S.; Lyu, K.; Zhang, X.-M.; Hakkarainen, A.; Lehtimäki, T.E.; Cline, G.W.; Petersen, K.F.; Shulman, G.I.; Yki-Järvinen, H. Effect of a Ketogenic Diet on Hepatic Steatosis and Hepatic Mitochondrial Metabolism in Nonalcoholic Fatty Liver Disease. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 7347–7354. [CrossRef]
237. Sripongpun, P.; Churuangsuk, C.; Bunchorntavakul, C. Current Evidence Concerning Effects of Ketogenic Diet and Intermittent Fasting in Patients with Nonalcoholic Fatty Liver. *J. Clin. Transl. Hepatol.* **2022**, *10*, 730–739. [CrossRef] [PubMed]
238. Khuong, J.N.; Wilson, T.G.; Grigg, L.E.; Bullock, A.; Celermajer, D.; Disney, P.; Wijesekera, V.A.; Hornung, T.; Zannino, D.; Iyengar, A.J.; et al. Fontan-Associated Nephropathy: Predictors and Outcomes. *Int. J. Cardiol.* **2020**, *306*, 73–77. [CrossRef] [PubMed]
239. Lee, D.; Levin, A.; Kiess, M.; Sexsmith, G.; Chakrabarti, S.; Barlow, A.; Human, D.; Grewal, J. Chronic Kidney Damage in the Adult Fontan Population. *Int. J. Cardiol.* **2018**, *257*, 62–66. [CrossRef] [PubMed]

240. Binotto, M.A. Renal Function and Fontan Patients: What Is the Real Impact in the Long-Term Outcomes? *Int. J. Cardiol.* **2020**, *306*, 86–87. [CrossRef]
241. Niaz, T.; Stephens, E.H.; Gleich, S.J.; Dearani, J.A.; Johnson, J.N.; Sas, D.J.; Bly, S.; Driscoll, D.J.; Cetta, F. Acute Kidney Injury and Renal Replacement Therapy After Fontan Operation. *Am. J. Cardiol.* **2021**, *161*, 84–94. [CrossRef]
242. Zafar, F.; Lubert, A.M.; Katz, D.A.; Hill, G.D.; Opotowsky, A.R.; Alten, J.A.; Goldstein, S.L.; Alsaied, T. Long-Term Kidney Function After the Fontan Operation. *J. Am. Coll. Cardiol.* **2020**, *76*, 334–341. [CrossRef]
243. Hems, D.A.; Brosnan, J.T. Effects of Ischaemia on Content of Metabolites in Rat Liver and Kidney in Vivo. *Biochem. J.* **1970**, *120*, 105–111. [CrossRef]
244. Tran, M.T.; Zsengeller, Z.K.; Berg, A.H.; Khankin, E.V.; Bhasin, M.K.; Kim, W.; Clish, C.B.; Stillman, I.E.; Karumanchi, S.A.; Rhee, E.P.; et al. PGC1α Drives NAD Biosynthesis Linking Oxidative Metabolism to Renal Protection. *Nature* **2016**, *531*, 528–532. [CrossRef]
245. Ritmeester, E.; Veger, V.A.; van der Ven, J.P.G.; van Tussenbroek, G.M.J.W.; van Capelle, C.I.; Udink ten Cate, F.E.A.; Helbing, W.A. Fontan Circulation Associated Organ Abnormalities Beyond the Heart, Lungs, Liver, and Gut: A Systematic Review. *Front. Cardiovasc. Med.* **2022**, *9*, 826096. [CrossRef]
246. Puchowicz, M.A.; Emancipator, D.S.; Xu, K.; Magness, D.L.; Ndubuizu, O.I.; Lust, W.D.; LaManna, J.C. Adaptation to Chronic Hypoxia During Diet-Induced Ketosis. In *Oxygen Transport to Tissue XXVI*; Okunieff, P., Williams, J., Chen, Y., Eds.; Advances in Experimental Medicine and Biology; Springer: New York, NY, USA, 2005; Volume 566, pp. 51–57. [CrossRef]
247. Poffé, C.; Robberechts, R.; Podlogar, T.; Kusters, M.; Debevec, T.; Hespel, P. Exogenous Ketosis Increases Blood and Muscle Oxygenation but Not Performance during Exercise in Hypoxia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2021**, *321*, R844–R857. [CrossRef]
248. García-Caballero, M.; Zecchin, A.; Souffreau, J.; Truong, A.-C.K.; Teuwen, L.-A.; Vermaelen, W.; Martín-Pérez, R.; de Zeeuw, P.; Bouché, A.; Vinckier, S.; et al. Role and Therapeutic Potential of Dietary Ketone Bodies in Lymph Vessel Growth. *Nat. Metab.* **2019**, *1*, 666–675. [CrossRef]
249. Universitaire Ziekenhuizen KU Leuven. Ketogenic Diet: A Novel Metabolic Strategy to Treat Lymphedema Patients? 2020. Available online: https://clinicaltrials.gov/ct2/show/NCT03991897 (accessed on 4 April 2023).
250. Puchalska, P.; Crawford, P.A. Ketogenic Therapies for Lymphedema? *Nat. Metab.* **2019**, *1*, 656–657. [CrossRef]
251. Dodeja, A.; Urbina, F.; Moore-Padilla, M.; Mah, M.L.; Bradley, D.; Bradley, E. Fontan-Associated Liver Disease: Is Insulin Sensitivity Important? *J. Am. Coll. Cardiol.* **2020**, *75*, 549. [CrossRef]
252. Emamaullee, J.; Zaidi, A.N.; Schiano, T.; Kahn, J.; Valentino, P.L.; Hofer, R.E.; Taner, T.; Wald, J.W.; Olthoff, K.M.; Bucuvalas, J.; et al. Fontan-Associated Liver Disease: Screening, Management, and Transplant Considerations. *Circulation* **2020**, *142*, 591–604. [CrossRef] [PubMed]
253. Goldenberg, J.Z.; Day, A.; Brinkworth, G.D.; Sato, J.; Yamada, S.; Jönsson, T.; Beardsley, J.; Johnson, J.A.; Thabane, L.; Johnston, B.C. Efficacy and Safety of Low and Very Low Carbohydrate Diets for Type 2 Diabetes Remission: Systematic Review and Meta-Analysis of Published and Unpublished Randomized Trial Data. *BMJ* **2021**, *372*, m4743. [CrossRef]
254. Tommerdahl, K.L.; Nelson, R.G.; Bjornstad, P. Dapagliflozin in young people with type 2 diabetes. *Lancet Diabetes Endocrinol.* **2022**, *10*, 303–304. [CrossRef] [PubMed]
255. Jiang, W.; Liao, J.; Zhou, D.; Mu, J. Ketogenic Diet Therapy for Epilepsy: Past 100 Years of Practice. *Acta Epileptol.* **2022**, *4*, 15. [CrossRef]
256. Suo, C.; Liao, J.; Lu, X.; Fang, K.; Hu, Y.; Chen, L.; Cao, D.; Huang, T.; Li, B.; Li, C. Efficacy and Safety of the Ketogenic Diet in Chinese Children. *Seizure* **2013**, *22*, 174–178. [CrossRef] [PubMed]
257. Wells, J.; Swaminathan, A.; Paseka, J.; Hanson, C. Efficacy and Safety of a Ketogenic Diet in Children and Adolescents with Refractory Epilepsy—A Review. *Nutrients* **2020**, *12*, 1809. [CrossRef]
258. Dressler, A.; Trimmel-Schwahofer, P. The Ketogenic Diet for Infants: How Long Can You Go? *Epilepsy Res.* **2020**, *164*, 106339. [CrossRef]
259. Mady, M.A.; Kossoff, E.H.; McGregor, A.L.; Wheless, J.W.; Pyzik, P.L.; Freeman, J.M. The Ketogenic Diet: Adolescents Can Do It, Too. *Epilepsia* **2003**, *44*, 847–851. [CrossRef] [PubMed]
260. Scholl-Bürgi, S.; Höller, A.; Pichler, K.; Michel, M.; Haberlandt, E.; Karall, D. Ketogenic Diets in Patients with Inherited Metabolic Disorders. *J. Inherit. Metab. Dis.* **2015**, *38*, 765–773. [CrossRef]
261. Lin, K.-L.; Lin, J.-J.; Wang, H.-S. Application of Ketogenic Diets for Pediatric Neurocritical Care. *Biomed. J.* **2020**, *43*, 218–225. [CrossRef]
262. Li, J.; Zhang, H.; Dai, Z. Cancer Treatment with the Ketogenic Diet: A Systematic Review and Meta-Analysis of Animal Studies. *Front. Nutr.* **2021**, *8*, 594408. [CrossRef] [PubMed]
263. Lauzier, B.; Vaillant, F.; Merlen, C.; Gélinas, R.; Bouchard, B.; Rivard, M.-E.; Labarthe, F.; Dolinsky, V.W.; Dyck, J.R.B.; Allen, B.G.; et al. Metabolic Effects of Glutamine on the Heart: Anaplerosis versus the Hexosamine Biosynthetic Pathway. *J. Mol. Cell. Cardiol.* **2013**, *55*, 92–100. [CrossRef]
264. Hernandez-Saavedra, D.; Sanders, L.; Freeman, S.; Reisz, J.A.; Lee, M.H.; Mickael, C.; Kumar, R.; Kassa, B.; Gu, S.; D' Alessandro, A.; et al. Stable Isotope Metabolomics of Pulmonary Artery Smooth Muscle and Endothelial Cells in Pulmonary Hypertension and with TGF-Beta Treatment. *Sci. Rep.* **2020**, *10*, 413. [CrossRef]

265. Sun, H.; Olson, K.C.; Gao, C.; Prosdocimo, D.A.; Zhou, M.; Wang, Z.; Jeyaraj, D.; Youn, J.-Y.; Ren, S.; Liu, Y.; et al. Catabolic Defect of Branched-Chain Amino Acids Promotes Heart Failure. *Circulation* **2016**, *133*, 2038–2049. [CrossRef]
266. Vockley, J.; Charrow, J.; Ganesh, J.; Eswara, M.; Diaz, G.A.; McCracken, E.; Conway, R.; Enns, G.M.; Starr, J.; Wang, R.; et al. Triheptanoin Treatment in Patients with Pediatric Cardiomyopathy Associated with Long Chain-Fatty Acid Oxidation Disorders. *Mol. Genet. Metab.* **2016**, *119*, 223–231. [CrossRef]
267. Zöggeler, T.; Stock, K.; Jörg-Streller, M.; Spenger, J.; Konstantopoulou, V.; Hufgard-Leitner, M.; Scholl-Bürgi, S.; Karall, D. Long-Term Experience with Triheptanoin in 12 Austrian Patients with Long-Chain Fatty Acid Oxidation Disorders. *Orphanet J. Rare Dis.* **2021**, *16*, 28. [CrossRef]
268. Lei, I.; Tian, S.; Gao, W.; Liu, L.; Guo, Y.; Tang, P.; Chen, E.; Wang, Z. Acetyl-CoA Production by Specific Metabolites Promotes Cardiac Repair after Myocardial Infarction via Histone Acetylation. *eLife* **2021**, *10*, e60311. [CrossRef] [PubMed]
269. Johnson, J.N.; Driscoll, D.J.; O'Leary, P.W. Protein-Losing Enteropathy and the Fontan Operation. *Nutr. Clin. Pract.* **2012**, *27*, 375–384. [CrossRef] [PubMed]
270. Violante, S.; IJlst, L.; te Brinke, H.; Almeida, I.T.; Wanders, R.J.A.; Ventura, F.V.; Houten, S.M. Carnitine Palmitoyltransferase 2 and Carnitine/Acylcarnitine Translocase Are Involved in the Mitochondrial Synthesis and Export of Acylcarnitines. *FASEB J.* **2013**, *27*, 2039–2044. [CrossRef] [PubMed]
271. Pereyra, A.S.; Harris, K.L.; Soepriatna, A.H.; Waterbury, Q.A.; Bharathi, S.S.; Zhang, Y.; Fisher-Wellman, K.H.; Goergen, C.J.; Goetzman, E.S.; Ellis, J.M. Octanoate Is Differentially Metabolized in Liver and Muscle and Fails to Rescue Cardiomyopathy in CPT2 Deficiency. *J. Lipid Res.* **2021**, *62*, 100069. [CrossRef] [PubMed]