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ORIGINAL ARTICLE

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Impaired coenzyme A homeostasis in cardiac dysfunction and benefits of boosting coenzyme A production with vitamin B5 and its derivatives in the management of heart failure

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Abstract

Coenzyme A (CoA) is an essential cofactor required for over a hundred metabolic reactions in the human body. This cofactor is synthesized de novo in our cells from vitamin B5, also known as pantothenic acid, a water-soluble vitamin abundantly present in vegetables and animal-based foods. Neurodegenerative disorders, cancer, and infectious diseases have been linked to defects in de novo CoA biosynthesis or reduced levels of this coenzyme. There is now accumulating evidence that CoA limitation is a critical pathomechanism in cardiac dysfunction too. In the current review, we will summarize our current knowledge on CoA and heart failure, with emphasis on two primary cardiomyopathies, phosphopantothenoylcysteine synthetase and phosphopantothenoylcysteine decarboxylase deficiency disorders biochemically characterized by a decreased level of CoA in patients' samples. Hence, we will discuss the potential benefits of CoA restoration in these diseases and, more generally, in heart failure, by vitamin B5 and its derivatives pantethine and 4′-phosphopantetheine.

KEYWORDS

4′-phosphopantetheine, coenzyme A (CoA), cardiac dysfunction, heart failure (HF), pantethine, PPCS DD, PPCDC DD, PKAN, TANGO2 DD, Type II 3-methylglutaconic aciduria, vitamin B5 (or pantothenic acid)

1 | DE NOVO BIOSYNTHESIS OF COENZYME A

Coenzyme A (CoA) is a crucial molecule involved in acetylation reactions relevant to metabolic processes, such as the citric acid cycle, fatty acid oxidation, amino acidic metabolism, ketogenesis, synthesis of neurotransmitters, and detoxification. CoA is synthesized de novo starting from vitamin B5, also referred to as pantothenic acid (Pan), through a five-step enzymatic process (Figure 1) highly conserved from prokaryotes to higher eukaryotes.[1] In the first step, Pan is phosphorylated to phosphopantothenate (PPan) by pantothenate kinase enzymes (PANK1, *606160; PANK2, *606157; PANK3, *606161). This step involves the addition of a phosphate group to the pantothenate molecule. The following enzyme in the pathway, phosphopantothenoylcysteine synthetase (PPCS, *609853), catalyzes the condensation of cysteine and the phosphorylated pantothenate, forming phosphopantothenoylcysteine (PPan-Cys). Subsequently, phosphopantothenoylcysteine decarboxylase (PPCDC, *609854) catalyzes the decarboxylation of PPan-Cys, resulting in 4′-phospho pantetheine (PPanSH). In the final step, the bi-functional enzyme CoA synthase (COASY, *609855), possessing phosphopantetheine adenylyl-transferase (PPAT) and dephospho-CoA kinase (DPCK) domains, catalyzes a reaction of adenylation of PPanSH to form dephospho-CoA (dPCoA), which is finally phosphorylated to CoA.

Higher eukaryotes obtain Pan with the intake of vegetable- and animal-based foods (Figure 2). Gut bacteria also produce Pan, but the relative contribution of the gut bacteria and the diet to the overall level of Pan in the host is unclear.[2] The gut microbiome of *Drosophila melanogaster* can produce PPanSH, a stable intermediate of CoA biosynthesis (Figure 1), in addition to Pan.[3] Whether or not the human microbiome also produces PPanSH, additionally contributing to CoA biosynthesis in the host, remains to be elucidated.

In humans, it is assumed that ingested CoA and PPanSH are converted into Pan by digestive enzymes (alkaline phosphatases, ectonucleotide pyrophosphorylases, and vanins/pantetheinases) in the intestinal lumen. From the lumen, Pan enters the intestinal enterocytes through the sodium-dependent multivitamin transporter

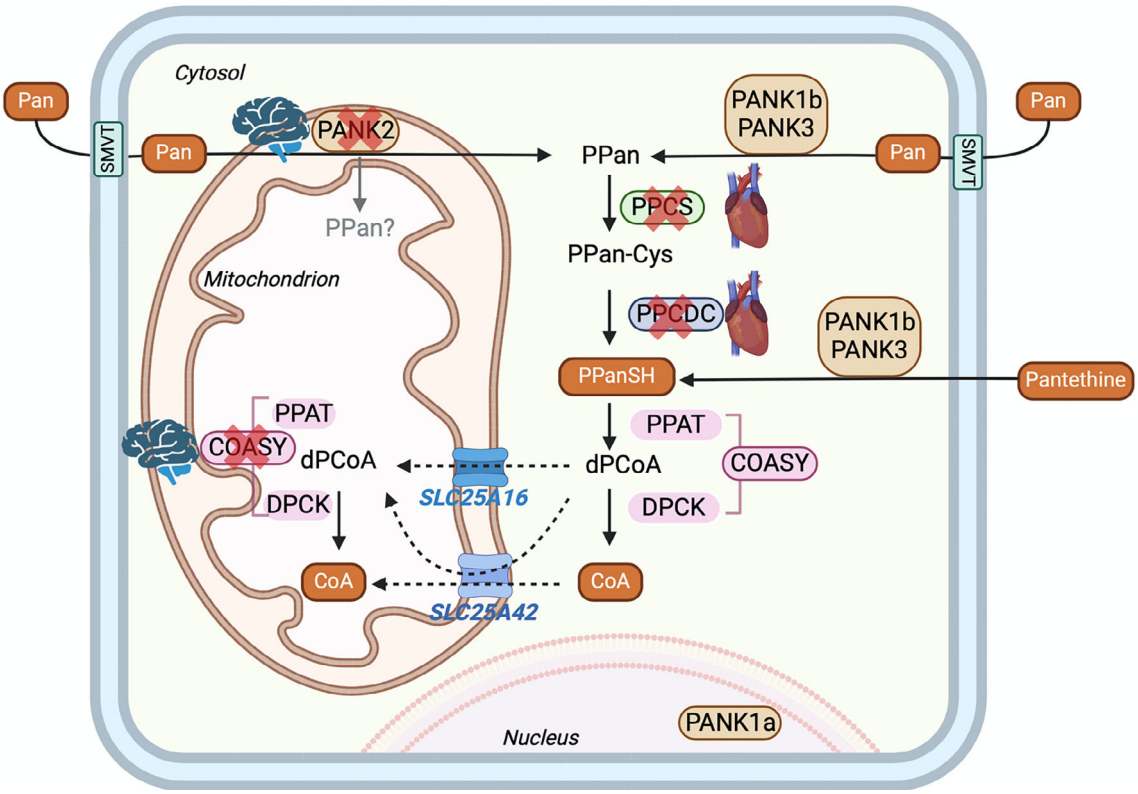

FIGURE 1 Schematic representation of the de novo CoA biosynthesis in a human cell. Red crosses indicate disease-associated enzymes. Heart and brain pictograms indicate cardiac and neurodegenerative disorders, respectively. CoA, Coenzyme A; COASY, CoA synthase; DPCK, dephospho-CoA kinase; dPCoA, dephospho-CoA; Pan, Pantothenic acid; PANK, pantothenate kinase; PPan-Cys, phosphopantothenoylcysteine; PPanSH, 4'-Phosphopantetheine; PPan, Phosphopantothenate; PPAT, phosphopantetheine adenyltransferase; PPCDC, phosphopantothenoylcysteine decarboxylase; PPCS, phosphopantothenoylcysteine synthetase; SMVT, sodium-dependent multivitamin transporter.

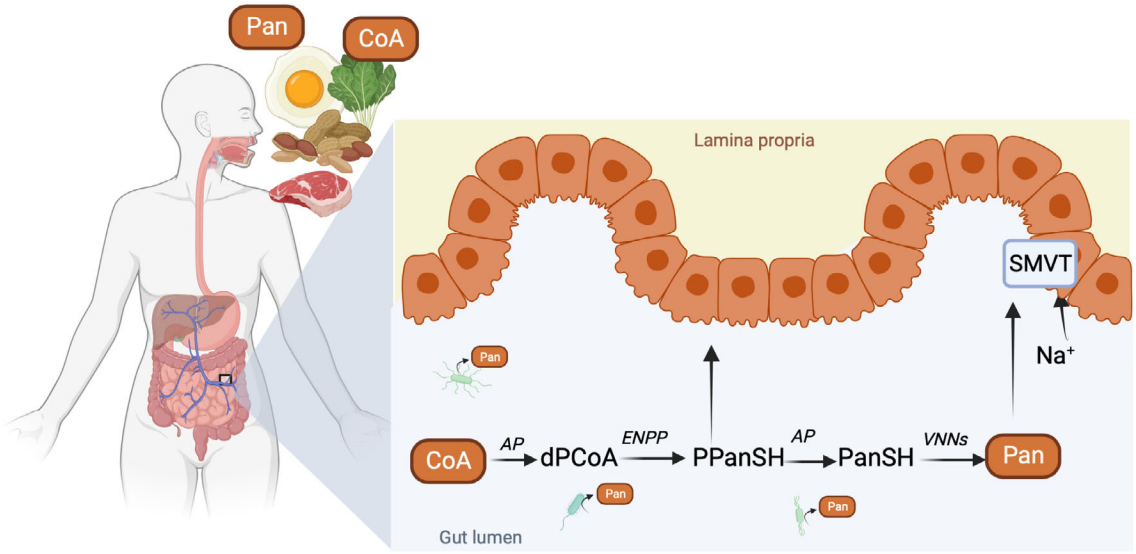

FIGURE 2 Pantothenate and coenzyme A intake in humans. AP, alkaline phosphatase; CoA, coenzyme A; dPCoA, dephospho-CoA; ENPP, ectonucleotide pyrophosphatase/phosphodiesterase; Pan, Pantothenic acid; PanSH, Pantetheine; PPanSH, 4'-Phosphopantetheine; DPCK, dephospho-CoA kinase; PPCS, phosphopantothenoylcysteine synthetase; COASY, CoA synthase; PPan-Cys, phosphopantothenoylcysteine; SMVT, sodium-dependent multivitamin transporter; VNNs, Vannins/pantetheinases.

(SMVT, *SLC5A6*, OMIM *604024) using the electrochemical gradient of sodium (Figure 2) to concentrate vitamins inside cells.[4,5] However, when the concentrations of luminal Pan are extremely high and saturate the SMVT transporter (intestinal SMVT, $k_M = 10–20\ \mu M$), diffusion is also possible. Once inside the cells, Pan is converted into CoA through the five consecutive enzymatic steps.

Since charged molecules generally do not cross membranes, it is presumed that CoA is not permeable to plasma membranes, and enterocytic enzymes degrade CoA to free Pan for its release in the bloodstream. Through the portal vein, Pan reaches the liver and, from here, the heart and all other tissues and organs, where it is taken up by SMVT and used intracellularly for the de novo biosynthesis of CoA. Alternatively, Pan diffuses passively into erythrocytes, which then transport Pan, PPan, and pantetheine (but not CoA) to the tissues.[6]

2 | TISSUES CoA HOMEOSTASIS

Based on a chromatography analysis of rat liver extracts, CoA is the Pan derivative present in the largest amount, followed by PPanSH.[7] Cardiac muscle, which depends on a high rate of substrate oxidation to meet its energy requirements, and liver, which is an active synthetic organ, have the highest CoA contents (550 nmol/g dry weight[8] and 87 to 434 nmol/g wet weight,[9,10] respectively) followed by kidney, adrenal glands, and skeletal muscle.[11]

Although the de novo biosynthesis of CoA requires Pan, fluctuations of Pan do not seem to impact CoA levels. Experiments on rats fed a Pan-deficient diet presented a reduction of Pan up to 90% in heart, kidney, gastrocnemius, and testes and 70% in liver (in blood the levels are too low to be detected), but the drastic reduction in Pan levels did not result in CoA lowering in any of these tissues. When Pan-deficient rats were subjected to fasting and alloxan-induced diabetes, myocardial and liver levels of CoA were still comparable to those of animals fed the Pan-deprived diet and standard diet. This indicates that CoA is tightly regulated at tissue level by mechanisms other than Pan concentrations, for instance, by the enzymes involved in the CoA synthetic and/or degradative pathways. However, despite CoA levels being maintained constant, rats fed a Pan-deficient diet grew slower than animals fed a standard diet.[11] Possible explanations could be that (i) the temporal window of the investigation was insufficient to detect the CoA decrease in heart and liver; (ii) CoA levels in those two tissues were kept constant at the expense of CoA levels in other tissues, or (iii) total levels of CoA remain constant, but the ratio between free CoA and acyl ester varied. For example, in perfused rat hearts receiving no exogenous substrate, 80% of the total CoA is present in the free form, whereas, in the presence of high levels of fatty acids, pyruvate, or ketone bodies, 80% of the total is present as acyl esters, principally acetyl-CoA.[12,13] The ratio of free CoA to acyl-CoA is important in determining the rate of several key metabolic reactions, including those catalyzed

by acyl-CoA synthetase,[14] pyruvate dehydrogenase,[15] and a-ketoglutarate dehydrogenase.[16]

3 | RELEVANCE OF PAN AND CoA FOR THE HEART

The abundant presence of Pan in food and the observation that tissue levels of CoA remain fairly stable even upon deprivation of Pan from the diet has led us to underestimate the consequences of CoA deficiency. In recent years, the identification of inherited disorders associated with pathogenic variants in genes directly involved in the CoA biosynthesis (*PANK2*, *PPCS*, *PPCDC*, *COASY*)[17–20] and transport (*SLC25A42*)[21,22] and the observation that various pathological conditions such as cancer,[23,24] diabetes,[25] colitis,[26] and infectious diseases[27,28] are associated with reduced levels of CoA has put the spotlight on the relevance of this cofactor in human function and dysfunction. Evidence is now accumulating that CoA limitation can represent a critical pathomechanism in cardiac dysfunction as well.

In this review, we will sum up findings about CoA and heart failure (HF), that is, clinical conditions where structural and/or functional abnormalities of the heart affect blood pumping,[55] with emphasis on more recent findings. We will omit the role of CoA alterations in other pathological conditions, as this topic has been comprehensively reviewed elsewhere.[29–31] Moreover, the complex abnormalities of the discussed cardiac diseases are possibly not caused solely by decreased CoA levels. Explanations for those complexities are discussed in detail elsewhere[18,31] and will not be addressed in this review.

Early evidence of CoA reduction in hypertrophied hearts of animal models dates back to 1983. Cats subjected to pulmonary artery (PA) banding presented a 50% decrease in total CoA in the hypertrophied right ventricle and a 25% decrease in the nonhypertrophied left ventricles. Rats subjected to aortic banding presented a 20% reduction in total CoA. Although the level of CoA was reduced in myocardial tissue in both cats and rats, Pan levels were unaltered. Carnitine and long-chain fatty acyl-carnitine levels were unchanged in both ventricles of PA-banded cats while they were reduced by 25% in hypertrophied rat hearts.[32] Reduced expression of PPCS in *Drosophila* led to impaired tissue morphogenesis during oogenesis,[33] reduced viability and cardiac dysfunction presenting with a significant increase in heart rate, heart wall shortening, and arrhythmia index and a decrease in systolic length.[18] Viability was restored by supplementing the fly food with pantethine, a dimer of PanSH.[18]

Indirect evidence speaking in favor of CoA reduction in humans came first in 1994. A young boy with a dilated cardiomyopathy secondary to type II 3-methylglutaconic aciduria, also known as Barth syndrome, was orally administered large doses of Pan (150 mg/day), ahead of any Pan and CoA measure in tissues, and recovered significantly and steadily. The ejection fraction increased from 28% to 52%, the left ventricle size normalized, the patient gained weight, and the neutrophil cell count as well as the hypocholesterolaemia and hyperuricaemia normalized.[34] Based on the positive outcome reported in,[34] three additional patients received Pan, but, despite an initial improvement of the myocardial function, the long-term treatment with Pan failed to show a sustained positive effect.[35]

Reduced levels of Pan were detected in plasma of individuals with coronary heart disease (CHD) (33.3 ng/mL on average in CHD individuals versus 36.9 ng/mL in controls). In addition to low Pan levels, CHD cases also had a higher frequency of hypertension, diabetes, plasma homocysteine levels, and hyperlipidemia.[36] Despite the evidence of Pan decrease in CHD, no clinical trial with Pan was pursued.

More recently, CoA deficiency has been hypothesized in TANGO2 deficiency disorder (DD). First described in 2016, TANGO2 DD is an autosomal recessive condition due to pathogenic biallelic variants in the *TANGO2* gene.[37,38] Clinically, it is characterized by symptoms typically beginning in late infancy, such as developmental delay, gait abnormalities, speech difficulties, and seizures. As further manifestations, life-threatening acute metabolic crises with rhabdomyolysis, hypoglycemia, secondary heart failure, and arrhythmias can occur. During a metabolic crisis 65% of individuals manifest a so-called cardiac crisis.[39] Among them, almost 75% can suffer from sudden cardiac death. The prognosis is closely dependent on echocardiogram (ECG) alterations. The most common ECG feature during metabolic crises is a marked QT interval prolongation (>500 ms) and, more rarely, intermittent Brugada type I pattern.[40,41] Life-threatening ventricular tachycardias (VTs), with Torsade de Point (TdP) being the most common, are the leading causes of mortality.[42] Unexplained sudden death during sleep not linked with metabolic crisis has also been described.[39,43]

Heart failure can appear in about 70% of patients in cardiac crisis. Typically, a systolic dysfunction can manifest quickly during a metabolic crisis. Consequently, the systolic function should be monitored echocardiographically with attention during a metabolic crisis. Both ECG alterations and systolic dysfunction can be fully restored when the crisis resolves.[42] Heart failure has been so far reported in individuals who are experiencing a cardiac crisis. Of interest is that a heart transplantation has been performed on one individual. A long-term cardiac follow-up among TANGO-deficiency patients is still lacking.[44] As a rare manifestation, supraventricular tachycardias

and AV-block can occur.[45] Acute and long-term management remains challenging and unclear, as the specific pathophysiological mechanism is still undetermined. During acute metabolic crises, the management of arrhythmias is based on restoring metabolic balance, with the aim of maintaining electrolyte and glucose levels in the normal range.[45] Isoprenaline or temporary pacing can be helpful in the presence of Brugada and long QT syndrome features. Avoiding QT-prolonging medications is also recommended and the treatment with cardioselective beta-blockers has also been proposed. The indication as secondary prevention of implantable cardioverter-defibrillator (ICD) in TANGO2 DD patients is probably not conceivable. On the other hand, the long-term management of TANGO2 DD patients is still symptomatic and preventive, including avoidance of triggers for acute metabolic crises and closed follow-up during infections, as well as a regular neurological, cardiological, and endocrinological check-up.[45,46]

Targeted therapy with daily supplementation of B-complex vitamin (at the minimum recommended daily allowance for age) has been associated with a significant reduction of metabolic crises and cardiac manifestations in TANGO2 DD patients.[42,47] Supporting evidence came from studies with a *Drosophila* TANGO2 DD model and human TANGO2 DD patient's cells in which phenotypes were rescued by supplementation of Pan.[48] Based on rescue with this CoA precursor it was hypothesized (but not yet proven) that CoA levels may be decreased in TANGO2 DD patients.

Direct evidence of CoA reduction in human cardiac diseases came first in 2018. Pathogenic variants in *PPCS*, one of the four genes directly involved in the biosynthesis of CoA (Figure 1), were identified in five individuals presenting with autosomal recessive dilated cardiomyopathy.[18]

Clinically, PPCS deficiency disorder (PPCS DD) is characterized by an early-onset cardiomyopathy (between 2 weeks to 3 years of age) with a variable degree of progression and severity. In the initial cohort from Iuso et al. (two families and five individuals in total) extracardiac features were identified in addition to severe dilated cardiomyopathy in only one individual (II.2, family A). This patient manifested with neonatal onset poor feeding, dysmorphism, muscular hypotonia, and transient creatine kinase elevation.[18]

Subsequently, Lok et al. expanded the phenotypic spectrum of PPCS DD reporting a case with dilated cardiomyopathy, recurrent rhabdomyolysis and necrotizing myopathy.[49] In particular, the patient repeatedly had normal echocardiograms till the age 22 of life, when she deteriorated suddenly and suffered a cardiac arrest requiring cardiopulmonary resuscitation and intubation. A repeat echocardiogram revealed significant biventricular dysfunction (with an ejection fraction of 20%) and a dilated cardiomyopathy. Previously, in Iuso et al., another patient (IV.8, family B) was reportedly healthy until the age of 3 years (an echocardiogram at 12 months of age was normal) when he presented in a state of cardiogenic shock following an adenovirus-associated acute febrile respiratory illness. He was intubated and mechanically ventilated. An ECG reported dilated cardiomyopathy with extremely reduced LV function (EF 6%–10%), associated with moderate mitral regurgitation and mild tricuspid regurgitation.[49] Low levels of CoA have been detected in patients' fibroblasts.[18,49]

An additional six patients from five unrelated families have been recently reported at the 2023 SSIEM Annual Symposium.[50] The newly identified patients present DCM with variable degrees of severity, accompanied by extracardiac features, and, in one case, global loss of brain with prominent sulci and ventricles.[50] Similar to reported cases, these patients also presented low levels of CoA in fibroblasts. Reduced levels of CoA were also reported in iPSC-derived cardiomyocytes from two patients.[50] The fact that defective CoA represents a consistent feature of PPCS deficiency and that DCM may evolve later in time offers the perspective of therapeutic opportunity for these patients. Pantethine supplementation in patients' fibroblasts and cardiomyocytes led to an increase in intracellular CoA; supplementation in the *Drosophila* model of the disorder improved their viability.[18] Based on the promising readouts from cellular and animal models of PPCS DD, pantethine treatment is currently undertaken by living patients.

One of the reported patients showed improved exertional dyspnea and a 12% increase in ventricular ejection fraction, while the cardiac function of his brother stabilized upon pantethine supplementation.[18] A third identified case reported no episodes of arrhythmia since commencing pantethine supplementation and the echocardiography revealed fully recovered left ventricle function, while a fourth case gained a normal-sized left ventricle with low-normal function and reported improvement in appetite and stamina (manuscript submitted[50]). Of interest is that a heart transplantation has been successfully performed in one individual and long-term follow-up is awaited.

Biallelic pathogenic variants have been identified also in other genes involved in the biosynthesis of CoA, *PPCDC*.[19] Only two patients, siblings from a non-consanguineous family, have been reported so far. PPCDC DD presents with a fatal early-onset form of dilated cardiomyopathy, lactic acidosis, and elevated long-chain acylcarnitine.

Low levels of CoA were also reported in fibroblasts of PPCDC DD patients. Additionally, fibroblasts showed loss of maximal respiratory capacity but high levels of total ATP in presence of glucose, thus suggesting an

increase in the use of the glycolytic pathway to produce energy and a mitochondrial defect associated with a reduced capacity to catabolize fatty acids. No treatment was possible as both patients died in the first year, but treatment with PanSH could have been a therapeutic approach.

4 | USE OF PAN AND ITS DERIVATIVE MOLECULES PANTETHINE AND PPanSH AS A THERAPEUTIC APPROACH IN HEART FAILURE

Studies on animal models have shown the positive effects of Pan derivatives on induced cardiac stress. For instance, dexpanthenol, an alcohol derivative of Pan, showed a protective effect on rat hearts with isoproterenol-induced cardiac damage[51] and on the cardiovascular dysfunction triggered by cecal ligation and puncture-induced sepsis.[52] This rescue mechanism could be related to preservation and improvement of the cardiac antioxidant status, as suggested in another study in rats showing a protective effect of dexpanthenol on cardiac endothelial dysfunction in streptozocin-induced type 1 diabetes,[53] or improved bioenergetic availability of the cardiac cells, which preferentially utilize fatty acids as a source of energy, requiring CoA for their activation and utilization.[54,55]

In humans, Pan supplementation has been utilized to treat secondary cardiac decompensations in type II 3-methylglutaconic aciduria, although with variable results.[34,35] To our knowledge, there are no additional reports of a sole utilization of Pan in the treatment of HF. Instead, Pan in combination with other B vitamins (at the minimum recommended daily allowance for age) has been tested in TANGO2 DD and resulted in a significant reduction of metabolic crises and cardiac manifestations in patients.[47] Despite the evidence that Pan can ameliorate HF is anecdotal, Pan could be a safe strategy to boost CoA biosynthesis, with a few exceptions. The use of Pan should be limited in case of breast cancer, as it has been shown that Pan supports MYC oncogenic metabolism and tumor progression.[56] Moreover, Pan is expected to be ineffective in case of defects in PANK, PPCS, PPCDC, and COASY, that is, enzymes that function downstream of Pan (Figure 1).

Treatments with derivatives of Pan, pantethine and PPanSH, are alternative therapeutic approaches. Both are reaction products downstream of the enzymes PPCS and PPCDC and are therefore expected to boost CoA levels in PPCS and PPCDC DDs. PANKs are promiscuous and can phosphorylate pantethine as well as Pan,. As such, PPanSH is synthesized and defects in PPCS and PPCDC can be overcome (Figure 1). Pantethine is indeed being used to treat PPCS-deficient patients, with amelioration or stabilization of the cardiac defect and general health improvement in treated patients.[50] Besides that, pantethine has already been used to treat hyperlipidemia, which is a major risk factor for cardiovascular diseases.[57] Several trials have been conducted since 1981, which were analyzed in 2005 (28 trials total).[58] This meta-review concluded that pantethine supplementation can be effective for the treatment of hyperlipidemia. In the context of this review, a perhaps more important observation is that pantethine is well-tolerated, with the frequency of adverse reactions being less than 2 per 100 subjects. These adverse reactions were only mild in severity.[58]

In contrast to pantethine, PPanSH is not a substrate of vanins/pantetheinases (Figure 2).[59] In turn, this raises the possibility of PPanSH being a more effective compound for the treatment of CoA-related cardiac diseases as it is more stable. So far PPanSH has not been used in HF, but only on patients with pantothenate kinase-associated neurodegeneration (PKAN, OMIM # 234200). There are two clinical trials ongoing with PPanSH (termed CoA-Z and 4′-PPT in the studies).[60,61] Like pantethine, this compound was also reported to be well-tolerated.[62]

5 | TRANSPORT OF PAN DERIVATIVES

Evidence is accumulating that both PPCS and PPCDC deficiencies can be rescued by pantethine or PPanSH by bypassing the defective CoA biosynthesis step associated with these deficiencies (Figure 1). Although it is not yet clear how these molecules enter cells, evidence already exists for over 70 years that this uptake does occur. This evidence can be derived from experiments performed in various organisms pointing to the evolutionary advantage of possessing these capacities to take up pantethine and/or PPanSH.

Early attempts to culture microorganisms using alternatives to pantothenate were performed by supplying pantethine (at the time also referred to as *Lactococcus bulgaricus Factor*, LBF). Here, different yeast strains as well as *Lactobacillus* strains were grown on pantothenate-free media. Interestingly, pantethine supplementation supported the growth of the *Lactobacillus* strains, but not of the yeast strains tested. An explanation for the differences between pantothenate and pantethine as growth factors was proposed to be the result of "differences in permeability or absorbability of the two compounds".[63] The possibility of using pantethine as an alternative for pantothenate became more evident after the discovery of substrate specificity of PANKs; as already stated above, some PANKs are promiscuous, meaning

that they can phosphorylate both pantothenate and pantethine.[64] This also indicates that if pantethine can be taken up, PPCS and PPCDC enzymatic activities are not essential. Later, it was shown that *Escherichia coli* can use extracellular pantetheine, but not PPanSH, as a source of CoA. Of additional interest was the discovery of the excretion of CoA precursors in the media, which suggests that *E. coli* transports these compounds out of the cell.[65] Evidence that CoA-precursors downstream of Pan can chemically complement defects in CoA biosynthesis steps was provided in a PPCS and PPCDC (CoaBC) deficient *E. coli* strain, which was able to grow on pantethine but not on pantothenate. How pantethine enters *E. coli* was not uncovered, although it was demonstrated that this rescue was independent of the pantothenate transporter PanF.[66] Pantethine has also been shown to improve the viability of a PPCS-deficient *D. melanogaster* model.[18] The recently discovered ability of the *Drosophila* microbiome to phosphorylate pantethine into PPanSH explains how pantethine can also rescue homozygous *dPANK/fbl*^{null} mutants exclusively in the presence of an intact microbiome.[3,67] That is, intact PanK activity of the microbiome compensates for PanK deficiency of the host. Both observations were with pantethine supplementation only, and not pantothenate. Together, these results demonstrate that pantethine has unique properties in comparison to pantothenate and that like pantothenate, (4′-phospho)panteth(e)ine can also be taken up by *Drosophila* cells. Although the transporter responsible for the uptake of extracellular pantothenate has been identified in many organisms,[68–70] a transporter of (4′-phospho) pantetheine has yet to be identified in any organism. Because of the amphipathic properties of pantetheine, it has been suggested that this molecule can diffuse over membranes.[71] Interestingly, PPanSH, was shown to have membrane permeable properties.[59] However, it remains possible that transporters exist for (4′-phospho)pantetheine that have yet to be identified.

In summary, there is evidence that cells possess uptake mechanisms for pantethine and PPanSH, however, the mechanisms behind these and whether specific cell types have their specific uptake mechanisms for these compounds remain unclear. Elucidating these uptake strategies will help enhance the therapeutic potential of pantethine and PPanSH for specific CoA-linked disorders, including cardiac diseases.

6 | OUTLOOK: TARGETING SHARED MOLECULAR ETIOLOGY IN HEART FAILURE

Despite different causative genetic factors and the lack of clinical overlap between PPCS DD, PPCDC DD, Type II 3-methylglutaconic aciduria, and TANGO2 DD, these disorders seem to share a common metabolic etiology, i.e., impaired CoA homeostasis with confirmed (PPCS- and PPCDC-DDs) or postulated (Type II 3-methylglutaconic aciduria TANGO2 DD) decrease of CoA. The shared molecular etiology is underpinned by the anecdotal observation that treating patients with compounds potentially boosting CoA biosynthesis, such as Pan (Type II 3-methylglutaconic aciduria, TANGO2 DD) and pantethine (PPCS DD) improve or stabilize their clinical conditions.

While conventional clinical trials are hardly conceivable for the limited number of affected individuals for each individual disorder, "basket trials," that is, trials targeting multiple rare disorders sharing molecular etiology rather than symptoms and clinical presentations,[72] could be an option for these rare disorders. In this perspective, a combined clinical trial with the neurodegenerative disorder PKAN could be conceived.

In addition to the above-mentioned rare disorders, it is likely that CoA dyshomeostasis also affects more common forms of HF, as seen in CHD. As in developed nations the number of individuals affected by HF is elevated, with an incidence of an estimated 1–20 cases per 1000 person-years and a prevalence of 1%–3% among adults,[73] it is important to identify effective treatments to reduce the economic burden on global healthcare expenditures.

If restoring energy balance in HF by boosting CoA levels ameliorates clinical outcomes, and enhances patients' quality of life and potentially duration of life, Pan, pantethine, or PPanSH could complement conventional treatments with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, and mineralocorticoid-receptor antagonists targeting mainly dysregulation in the neurohormonal system or reducing cardiac workload.

AUTHOR CONTRIBUTIONS

Arcangela Iuso drafted the initial manuscript and oversaw subsequent revisions. Arcangela Iuso and Ody CM Sibon conceived the idea for the study. Jouke J Wedman and Elisa Mastatuono provided parts of the initial text and helped draft the initial manuscript. All authors commented on drafts of the manuscript and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Ody CM Sibon is a co-inventor on two patent applications for 4′-phosphopantetheine for use in disorders exclusive and inclusive of PKAN. Ody CM Sibon is a co-inventor on a patent application for acetyl-4′-phosphopantetheine for use in PKAN and in related disorders. Ody CM Sibon serves as a non-compensated executive for the Spoonbill Foundation, a not-for-profit organization that may benefit from the results of this research.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

No ethical approval nor informed consent was needed as no new data were generated in the current review.

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