Review Article

Narrative review of metabolomics in cardiovascular disease

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Abstract: Cardiovascular diseases are accompanied by disorders in the cardiac metabolism. Furthermore, comorbidities often associated with cardiovascular disease can alter systemic and myocardial metabolism contributing to worsening of cardiac performance and health status. Biomarkers such as natriuretic peptides or troponins already support diagnosis, prognosis and treatment of patients with cardiovascular diseases and are represented in international guidelines. However, as cardiovascular diseases affect various pathophysiological pathways, a single biomarker approach cannot be regarded as ideal to reveal optimal clinical application. Emerging metabolomics technology allows the measurement of hundreds of metabolites in biological fluids or biopsies and thus to characterize each patient by its own metabolic fingerprint, improving our understanding of complex diseases, significantly altering the management of cardiovascular diseases and possibly personalizing medicine. This review outlines current knowledge, perspectives as well as limitations of metabolomics for diagnosis, prognosis and treatment of cardiovascular diseases such as heart failure, atherosclerosis, ischemic and non-ischemic cardiomyopathy. Furthermore, an ongoing research project tackling current inconsistencies as well as clinical applications of metabolomics will be discussed. Taken together, the application of metabolomics will enable us to gain more insights into pathophysiological interactions of metabolites and disease states as well as improving therapies of patients with cardiovascular diseases in the future.

Keywords: Metabolomics; ischemic heart disease; atherosclerosis; heart failure

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Introduction

It is not unpredictable that disorders in the cardiac energy metabolism are major contributors to many cardiovascular disease as the heart is the most metabolically demanding organ in the body (1). Furthermore, conditions often associated with cardiovascular disease pathogenesis can change cardiac function and myocardial metabolism. Alterations in substrate metabolism resulting from onset of cardiovascular disease can contribute to characteristic changes in the patient's metabolic profile (2,3).

Thanks to new "omics" tools (genomics, transcriptomics, proteomics and metabolomics) we now have a much broader understanding of pathophysiological molecular, cellular

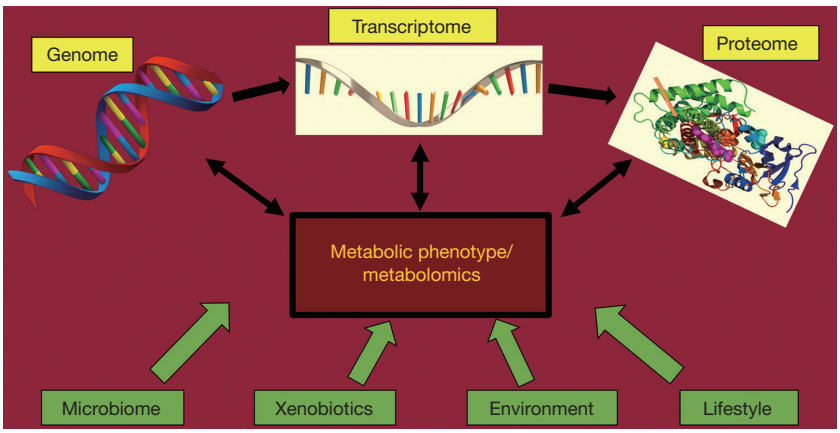

Figure 1 A metabolomics-centric view of the metabolic pathways. Genetic variations lead to changes in gene expression (transcriptome) which affect protein variations (proteome). The metabolic phenotype is influenced by many factors. In turn, variations in metabolism can modify genomic, transcriptomic and proteomic outputs.

and functional alterations that take place in cardiovascular diseases (4). Modern metabolomics technologies represent a tool to measure a plethora of metabolites in biological samples including blood plasma, urine and tissues. These snapshots might serve as prognostic and diagnostic tools to identify early specific changes during onset and progression of cardiovascular disease (5) (*Figure 1*). Therefore, metabolomics are representing an important tool to provide further insights into the pathophysiology of cardiovascular diseases and advance clinicians' understanding of pathogenesis of cardiovascular disease.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jtd-21-22).

Metabolomic analytic techniques

Currently, two techniques dominate metabolomic studies: nuclear magnetic resonance (NMR) and mass spectrometry (MS) (6). Both techniques are able to identify and quantify different metabolites in an automated manner. Due to the complexity of the human metabolome, none of the available techniques is able to provide an overview of the complete metabolome in biological samples due to the chemical diversity as well as very broad concentration range of different metabolites and metabolite classes (7-9). Therefore, often more than one analytical technique is applied. NMR delivers detailed information about the structure allowing identification of the molecules. MS-based platforms coupled to liquid or gas chromatography (GC) separation systems yield better sensitivity, but molecules must be ionized to be detected via MS and the selected separation methods play a huge role which molecules can be analyzed (7,10,11). Detailed reviews with focus on technical features of metabolomic platforms have previously been published (12).

Nuclear magnetic resonance

NMR was the first analytical platform and is highly selective for the respective metabolite and non-destructive with minimal sample preparation (11,13-15). The basis of this technique is to identify the metabolites by chemical shifts in resonance frequency. Advantages of NMR are robust, reproducible results with minimal sample preparation at low costs (16). Multiple spectral libraries provide detailed information about the metabolite structure for identification, especially using multidimensional NMR including 1D, fast 2D or ultrafast schemes (17-19). Furthermore, no chemical derivatization is needed for NMR analysis reducing sample preparation, duration and analytic variability (15,20).

Proton NMR (H-NMR), as most popular NMR techniques, displays fast acquisition times with high sensitivity of protons to NMR and abundance of protons in organic molecules (21). H-nuclei exhibit a small range in chemical shift. Therefore, NMR can be used as 2-dimensional NMR to detect and avoid co-resonances of metabolites with similar chemical shifts (22).

In contrast, C-atoms have a wider chemical shift, thus

C-NMR delives detailed positional information about stable isotope compounds (23).

However, the sensitivity of NMR assays is poorer compared to MS which relates to the strength of the magnet (5). Via NMR, quantification of only around 100 of the most abundant metabolites is possible while low abundant compounds cannot be determined in complex sample matrices (24,25). Furthermore, much larger amounts of starting material are needed for analyses via NMR, in comparison to MS. This is especially crucial in studies using mice, where only small amounts of tissue or biofluids are available or for studies with human tissue material of low availability. In the last years, most metabolomic studies used NMR as a stand-alone technique, however a complimentary approach with MS is becoming increasingly popular, as it improves sensitivity and metabolome coverage (26-28).

Mass spectrometry

MS identifies metabolites on basis of their mass/charge ratio. Mass spectrometers consist of three basic components: The ionization source, the mass analyser and the ion detector (29). Prior to infusion into the MS source, often separation of metabolites within processed biological samples is applied using liquid chromatography (LC) or GC (30). This chromatographical separation increases selectivity and confidence in compound identification while it decreases potential ion suppression effects in the mass spectrometer due to fewer co-eluting compounds reaching the mass detector at a given time (30).

GC based MS requires volatile metabolites and gas-phase chemistry. However, because most metabolites are not naturally volatile, they must be derivatized artificially, which requires a variety of preparations (31). Thus, unstable and easily degradable metabolites such as α-keto acids, acyl-CoAs and acylcarnitines are not optimally suitable for GC-MS. Until now, for most GC-based targeted metabolomic studies, quadrupole GC-MS is used (32). Its main function is to select ions for more accurate analyses, since mass selectivity and mass range is limited by various parameters. Using a time of flight (TOF) analyser, mass accuracy and range can be improved (33). A TOF MS analyser is able to identify a mass/charge ratio value based on the time taken by a pulse of ions to traverse a known distance (34). Because even well-prepared samples might exhibit identification problems with large molecules due to similar mass/charge ratio, GC-MS is often combined with tandem MS (MS/MS) (35-37). Via tandem MS, greater certainty in the identification of large ions is provided due to specific fragment ions and fragment patterns (34). Combination of GC-Q-TOF and tandem MS systems offers high separation capability and good mass accuracy, which is ideal for non-targeted metabolomic profiling (38). However, limited metabolite coverage and restricted usability for labile compounds are still a problem, even for the latest systems.

LC is a separation technique often used for involatile and polar compounds with high molecular weight. However, also smaller metabolites can be separated using LC. LC is able to separate a wide range of metabolites, optimal for high-throughput and extensive metabolomic analyses (39). After injection into a moving stream of the mobile phase (solvent mixture), samples are transferred onto the chromatographic column containing a stationary phase of diverse chemical composition. Separation is based on the compound's affinity to mobile phase versus stationary phase (40). Therefore, different types of chromatographic columns can be used providing very diverse separation properties (41). In normal-phase chromatography, mobile phase is nonpolar and stationary phase is polar, and molecules separate according to their polarity. Reversed-phase chromatography operates vice versa and is more efficient, stable and withholds polar analytes, therefore best applied for nonpolar metabolites such as glycerolipids, phospholipids, fatty acids, acyl-carnitines and acyl-CoAs. In hydrophilic interaction chromatography the stationary phase is polar, similar to normal-phase chromatography. However, the solvent phase is highly hydrophobic enhancing the retention and separation of extremely polar analytes. Hydrophilic interaction chromatography is therefore used for nucleotides, phosphate compounds, organic acids and sugar monomers (42,43).

Heart failure

The healthy human heart is able to select its substrates for energy production depending on the substrate availability and the myocardial energy demand (44,45). Oxidative phosphorylation, oxygen consumption and ATP production is reduced during heart failure (HF) resulting in lower ATP levels compared to healthy hearts (46). Metabolism of one substrate can inhibit utilization of an alternative one. An example was previously published for the glucose-fatty acid cycle, where a higher release of fatty acids (FA) and ketone bodies lead to abnormalities in the carbohydrate metabolism (47). The failing heart gradually loses its ability to select substrates flexibly. In early stages of HF, glucose

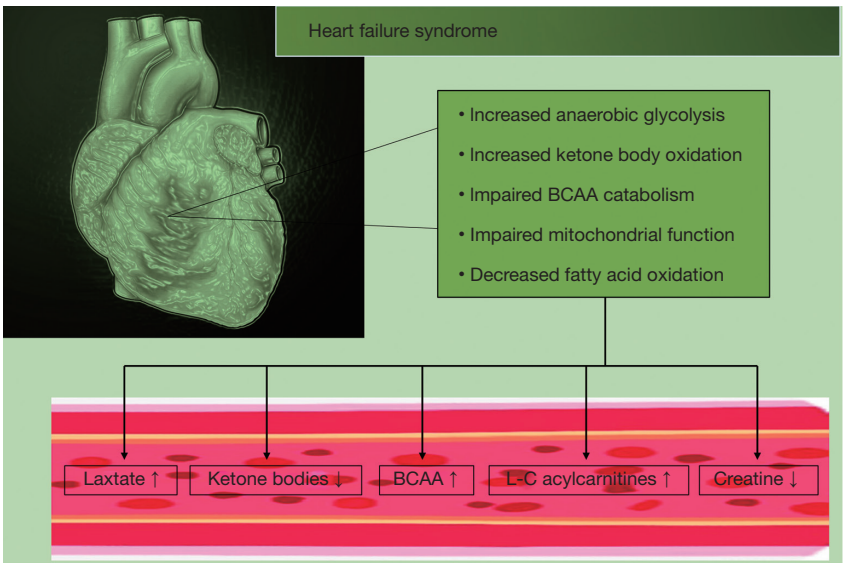

Figure 2 Heart failure is characterized by low energy state with a drop in CK activity and its substrate creatine. During heart failure the oxidative energy metabolism and the mitochondrial function is reduced, which is compensated by increased anaerobic glycolysis. Peripheral metabolomic profiles show often increased lactate, BCAA and L-C acylcarnitine levels. Furthermore, the failing heart's reliance on ketone bodies is increased to compensate the reduced fatty acid oxidation in the mitochondrion. BCAA, branch-chained amino acids; CK, creatine kinase; L-C, long-chain.

and FA metabolism is enhanced. As HF progresses, chronic hemodynamic stress leads to an increased carbohydrate metabolization instead of FA (48). End-stage HF is characterized by reduction in both substrates (49) (*Figure 2*).

Low energy state

The concept of the failing heart as an engine out of fuel is in the meantime decades old (50-52). A major reason for attention of this topic is that energy-saving treatment options for heart failure such as ACE inhibitors, angiotensin II inhibitors and beta-blockers improve prognosis of patients with heart failure (53-58). Lack of cardiac energy has a major role in heart failure (59). The human heart generates impressive amounts of ATP daily to maintain the needs of its contractile elements and ion pumps. The creatine kinase (CK) system provides an important mechanism to buffer and maintain cellular ATP levels by rapidly transferring high-energy phosphates from phosphocreatine (PCr) to adenosine diphosphate (ADP) (60,61). This reaction generates ATP 10 times faster than oxidative phosphorylation (62). During HF, studies have shown a drop in CK activity of around 20–45% (3). This is followed by a significant decrease in the PCr/ATP ratio, known as an important parameter of cardiac metabolism. This ratio correlates with New York Heart Association (NYHA) classes, systolic and diastolic function (63-65).

Together with CK, its substrate, creatine, is reduced by 50% in the failing heart (3). This is probably secondary to downregulation of the creatine transporter (responsible for myocardial uptake of this metabolite from the circulation) (*Figure 2*) (66). Nevertheless, transgenic overexpression of the creatine transporter leads to a decrease in ATP levels in myocardium of rats and reduced left ventricular function despite significant increasing myocardial creatine concentrations and PCr/ATP ratio (67). This finding emphasizes the difficulty to transfer a metabolomic finding to the pathophysiology of HF.

Energy starvation during HF results in essential ion transport abnormalities including Ca^{2+} release and uptake (68-71). Ca^{2+} is known to be crucial for the cardiac muscle contraction (72,73). Furthermore, it is essential for regulation of key Krebs cycle enzymes affecting mitochondrial metabolism all resulting in a diminished ATP production (74,75). Despite efforts and progress in this research field of cardiac energy metabolism during HF, there is still no simple answer to the question whether changes in the substrate utilization are cause or result of the

disease.

Fatty acid metabolism

To date, several abnormalities in the process of FA metabolism have been identified among HF patients. Free FA can cross the lipid bilayer (76). After entering the cytoplasm, free FA are either bound by heart-type cytoplasmatic fatty acid-binding protein (H-FABP$_c$) or are converted into acyl-CoA which can be transported into mitochondria, where acyl-CoA is oxidized generating ATP (76).

Attention has primarily focused on changes in acylcarnitine profiles, since acylcarnitines are derivatives of fatty acyl-CoAs, reflecting changes in FA oxidation rates and specific defects in the mitochondrial β-oxidation machinery (77).

Elevated levels of circulating C16 and C18:1 acylcarnitines in patients with end-stage heart failure were associated with an increased risk for mortality and rehospitalization due to HF (78). Consequently, after implantation of left ventricular assist device (LVAD) circulating long-chained (L-C) acylcarnitines decreased (78). In line with these findings, among patients with heart failure with preserved ejection fraction (HFpEF) circulating L-C acylcarnitines were increased. Even higher levels are found among patients with heart failure with reduced ejection fraction (HFrEF) (79). Bedi *et al.* found controversial results, in which acylcarnitines were reduced in myocardial tissue from end-stage HF patients at the time of heart transplantation or implantation of LVAD compared to tissue from patients with no history of HF (80). The authors recruited only non-diabetic HF patients, whereas the previously mentioned study included a large fraction of HF patients with diabetes. In obese and diabetic patients circulating acylcarnitines are often elevated, possibly explaining this discrepancy between the above-mentioned studies (*Figure 2*) (81).

Decreased myocardial acylcarnitines might represent the impaired mitochondrial function and subsequent FA oxidation (82-84), which is in line with previous findings showing a reduction of FA oxidation during more severe stages of HF (12,82,85,86). Results from studies in mice confirm these findings since both FA oxidation and protein expression are only mildly decreased in compensated HF, but markedly decreased in decompensated HF (82,87-89). So, it is plausible that many of these discrepancies in the acylcarnitine metabolism can be explained by the severity of HF, presence of underlying diabetes or obesity and the overall decline in left ventricular function (90). Future metabolomics studies need to consider these aspects and make distinct comparisons between these subgroups of HF patients.

Glucose metabolism

Glucose transport into myocytes is regulated by specific transmembrane glucose transporters (GLUTs) localized in the sarcolemma (91). Expression levels of GLUT-1 and GLUT-4 correlate positively with glucose uptake (92). Progression of HF is characterized by enhanced utilization of glucose instead of FA (93), while during end-stage HF the heart becomes unable to effectively utilize both substrates (94-97). During glycolysis, glucose is rapidly transformed into glucose-6-phosphate in the cytoplasm, oxidized to pyruvate and transported into the mitochondria producing ATP via the tricarboxylic acid (TCA) cycle (76). Several studies have reported that mitochondrial glucose oxidation is defective in the failing heart (98,99). Elevated circulating lactate levels may be the result of increased glycolysis and the inability of the failing heart to oxidize the increased pyruvate generated from glycolysis (98,99) because pyruvate dehydrogenase activity is decreased in HF (*Figure 2*) (90). In a rat model with compensated cardiac hypertrophy, cardiac glycolysis but not cardiac glucose oxidation was increased (100). In contrast, during compensated phases of cardiac hypertrophy in a rat model of left ventricular pressure overload, myocardial glucose oxidation rates were increased, while during decompensation of HF glucose oxidation declined (101). In hamsters with dilative cardiomyopathy (DCM) glucose-6-phosphate, fructose-6-phosphate, fructose-1,6-biphosphate, malate, iso-citrate and succinate in myocardial tissues were equal to control group at 4 weeks but were all reduced at 16 weeks (102). Nowadays, it is accepted that alterations in glucose utilization may vary, depending on HF pathology and HF stage (103). This hypothesis is supported by reduced levels of circulating glucose, glucose-1-phosphate, glucose-6-phosphate, lactate, citrate, succinate, succinyl-CoA and fumarate among patients with end-stage HF. After implantation of LVAD, circulating glucose and lactate levels increased in the non-failing heart (104).

Amino acid metabolism

Amino acids appear to contribute little to the overall cardiac

energy metabolism (105). In chronic HF patients, lower circulating levels of essential and nonessential amino acids were found in the plasma, compared to patients without any history of HF (106). Optimal HF treatment partially normalized circulating levels of amino acids like cysteine, glutamate, glycine and tryptophan (107). Furthermore, several amino acids such as leucine and isoleucine can be hydrolysed and can serve as a basis to generate ketone bodies, suggesting there may be a link between ketogenic amino acids and ketone bodies in HF (97,108,109). Both succinyl-CoA and ketone bodies can serve as fuel for the TCA cycle, possibly providing a beneficial effect on cardiac metabolism (80,110). In patients with DCM, circulating levels of ketogenic amino acids and their metabolites where found to be significantly elevated (111). Furthermore, circulating phenylalanine and spermidine levels were increased in patients with HF, with normalization of those amino acids after HF treatment (112). Among patients with severe HF, circulating levels of phenylalanine, tyrosine, methionine, histidine, threonine, homoserine, alanine and glutamine were reduced (104,113). Finally, angiotensin II-induced cardiac hypertrophy was associated with increased myocardial levels of ketogenic lysine and tyrosine (114). However, the exact role of altered amino acid metabolism during HF is still unclear.

Another actor in the pathophysiology of HF development display branched-chain amino acids (BCAA). The above-mentioned leucine and isoleucine plasma levels are elevated in chronic HF patients (106), irrespective of underlying obesity or dyslipidaemia. In mice, pharmacological treatment to increase cardiac BCAA catabolism resulted in delayed heart failure progression (115), suggesting that downregulation of the cardiac BCAA pathway may contribute to HF. Furthermore, BCAA may accumulate in the heart tissue, interact with insulin receptor-mediated signal transduction (116) and impair glucose processing (37). However, whether aberrant BCAA metabolism in HF patients is due to associated comorbidities such as type II diabetes and insulin resistance or a component of the metabolic signature of HF itself is still unknown. Although BCAA appear as a promising target for HF treatment there is also evidence of BCAAs increasing cardiac metabolic dysfunction. Branched-chain α-keto acids suppress respiratory complex I activity leading to reduced mitochondrial respiration and elevated superoxide production ultimately resulting in reduced cardiac function and promotion of HF in the setting of left ventricular pressure overload in a murine model (117) (*Figure 2*).

Ketone body metabolism

Ketone bodies can be degenerated into acetyl-CoA and thus have the possibility to maintain mitochondrial respiration in the heart. Under physiological conditions ketone bodies play a minor role in the cardiac energy production, but with increasing levels of circulating ketones their contribution to energy production increases (118). However, previous studies showed the altering ability of the human heart to extract certain circulating ketone bodies, depending on presence of left ventricular dysfunction (119). Among HF patients, levels of circulating β-hydroxybutyrate and acetone were significantly increased while their concentration in the cardiac tissue was reduced (120) (*Figure 2*).

On the other hand, serum concentrations of ketones like acetoacetate, α-hydroxybutyrate and β-hydroxybutyrate were lower in HFrEF patients than in patients without HF (121). Also, serum ketone levels were lower in HFrEF patients compared to HFpEF (121), potentially indicating changes in ketone metabolism depending on HF-degree. Accordingly, patients with severely reduced left ventricular function (<35%) displayed lower plasma levels of β-hydroxybutyrate than patients with less reduced left ventricular function and healthy controls (122). Furthermore, myocardial tissues from end-stage HF patients displayed higher β-hydroxybutyryl-CoA levels, representing the impaired FA oxidation. Increased expressions of downstream metabolites of ketone body oxidation and contemporaneous upregulation of key enzymes in the ketone body pathway hint towards increased reliance on ketones for energy in the failing heart, compensating the decline in myocardial fatty acid oxidation (80). For example, diabetic patients in the EMPA-REG outcome study, treated with a sodium-glucose cotransporter 2 inhibitor, showed a significant reduction for HF related rehospitalization. Ketone body elevation was discussed as one of the possible cardioprotective mechanisms by improving cardiac efficiency (123).

Atherosclerosis

The desire to identify individuals at great risk for atherosclerosis and consecutive ischemic heart disease has emerged over the last years. Large numbers of patients with clinically diagnosed coronary atherosclerosis present metabolic disorders in the myocardial energy production (9,11,124). Common tools such as positron emission tomography (PET) to illustrate those derangements are

expensive and are accompanied by considerable radiation exposure (125,126). Hence, blood based diagnostic tools for atherosclerosis and ischemic heart disease are warranted.

Recent studies showed circulating trimethylamine-N-oxide (TMAO) to be a significant predictor for atherosclerosis and increased risk for myocardial infarction (MI) and stroke (127,128). The host's gut microbiome plays a critical factor regulating the trimethylamine (TMA) production from dietary phosphatidylcholine, choline and carnitine. TMA is then released into the blood stream and converted to TMAO in the liver (129). TMAO potentially interferes with reverse cholesterol transport and thereby promotes plaque progression and increases the risk of cardiovascular events (127). TMAO might also promote platelet hyperreactivity since exogenous TMAO enhanced platelet aggregation in human platelet-rich plasma (128). Furthermore, in a mouse model of atherosclerosis, interfering with the microbiome's ability to convert dietary choline or carnitine into TMA resulted in progression of atherosclerotic lesions and reduced circulating TMAO levels (91). In conclusion, these results support the hypothesis that increased circulating levels of phosphatidylcholine or choline in combination with increased TMAO could serve as a novel biomarker for the diagnosis of coronary atherosclerosis.

Other promising biomarkers are plasma 18:2 monoglyceride, shown to be associated with higher risk, and 18:2 lysophosphatidylcholine and 28:1 sphingomyelin both shown to be associated with lower risk for future cardiovascular events (130). Increased levels of circulating arginine and decreased levels of 17:0 lysophosphatidylcholine and 18:2 lysophosphatidylcholine were associated with increased risk for MI. Predictive value of the Framingham risk score for cardiovascular disease increased significantly when combining and adding these three metabolites (131). Additionally, circulating phosphatidylcholines containing ceramide, sphingomyelin, diacylglycerol or palmitic acid were associated with increased risk of MI (132).

These lipid intermediates including ceramides and sphingomyelins are known to be accumulated in numerous tissues among obese and type 2 diabetes patients (133). Increased circulating levels of these metabolites possibly result in their increased concentration in myocardial, liver or skeletal tissue.

Finally, also circulating BCAAs (leucine/isoleucine, valine, glutamate/glutamine, proline and methionine) are shown to reflect the risk of future coronary artery disease (10,134). A cross-sectional study correlated increased BCAAs with carotid intima-media thickness (as index of subclinical atherosclerosis) (135).

Summarizing, changes in these biomarkers might identify patients at risk of atherosclerosis and enable us to apply therapies earlier.

Ischemic cardiomyopathy

Coronary artery disease (CAD), despite significant improvements, remains one of the leading causes of death worldwide (136). CAD can be divided into stable and unstable angina as well as MI. Unstable angina is characterized by a critical coronary stenosis, but without following myocardial cell damage. During non-ST-segment-elevation myocardial infarction (NSTEMI), this cell damage is present. ST-segment elevation myocardial infarction (STEMI) is characterized by an acute plaque rupture with following activation of plasmatic coagulation and formation of an occluding thrombus (137). During ischemic periods, oxygen and nutrition supply to the affected myocardium are markedly decreased, resulting in significant changes in the myocardial intermediary energy metabolism. Ischemic periods are characterized by a reduction in overall oxidative metabolism. To compensate this, glycolysis rates are increased. The increase in myocardial glycolysis is directly proportional to the severity and duration of ischemia (138).

Fatty acid metabolism

In the ischemic myocardium, FA oxidation rates are decreased in proportion to reduced oxygen supply, because β-oxidation of FA is dependent in oxygen for energy production (139). This was confirmed via paired collection of blood from arterial and coronary sinus blood before cardiac surgery, showing significant reduction of plasma FA in patients with CAD compared to those without CAD (140). The same experimental design showed increases in short-chain (S-C) dicarboxylacylcarnitines in CAD patients, predicting the risk for future cardiovascular events (126). Among patients with CAD but without heart failure, circulating medium-chain (M-S) and L-C acylcarnitines predicted subsequent cardiovascular events, independent from established predictors (141). However, their source and pathophysiology during CAD progression are unknown. One possible explanation might be the

participation of peroxisomes in this process. Normally, L-C dicarboxylic acids are mostly oxidized in the mitochondria, while during CAD progression peroxisomal oxidation of L-C acylcarnitines could be a compensatory mechanism to metabolize straight medium- and long-chain fatty acids (142). In STEMI patients, several plasma FA were found to be increased. Among those are palmitic acid, stearic acid, linoleic acid and oleic acid, suggesting ischemia-induced alternations in cardiac energy metabolism (143). Elevated FA like eicosatertraenoic acid and eicosatrienoic acid during MI might reflect ongoing inflammation (144). The β-oxidation machinery of unsaturated FA like linoleic acid seems to be hampered during MI, contributing to myocardial ischemia (145,146). Accordingly, S-C acylcarnitines were elevated and aspartic acid was reduced in patients with evident ischemia (147,148). Additionally, in patients with MI, higher levels of sphingolipid pathway, sphingomyelin and ceramide were found, compared to healthy patients and patients with angina (132). These results are supported by findings in which sphinganine, an intermediate of sphingoid base biosynthesis, is upregulated during acute MI (144,145). Sphingolipids and their derivates are components of cellular membranes and play an important role in vascular maturation, pathophysiology during atherosclerosis and wound healing (149). In MI, sphingolipid metabolism seems to be compromised, also resulting in increased cardiovascular diseases and obesity (150-152). Glycerophospholipids are precursors of lipid mediators and seem to be reduced during MI, namely phosphatidylserine, linoleamidoglycerophosphate choline, Lyso-PC (C18:2), Lyso-PC (C16:0), and Lyso-PC (C18:1) (145). Phosphatidylcholines can be further hydrolyzed and oxidized to prostaglandins, thromboxane and prostacyclin by cyclooxygenases and cyctochrome P450. These are all well known for their critical role during inflammation, immune response and blood pressure control (153). In summary, there is strong evidence for an altered lipid metabolism during ischemia.

Glucose metabolism

During ischemia, glucose oxidation rates are depressed, accompanied by increased glycolytic rates due to stimulated glycogenolysis (126,154). Myocardial lactate concentrations rise with the severity of the ischemic period (155).

In patients with acute ischemia due to CAD or alcohol septal ablation, increased circulating lactate levels reflect enhanced myocardial anaerobic glycolytic metabolism (119,156). Interestingly, this effect is also present in patients undergoing coronary angioplasty due to stable angina. Ischemia for at least 1 minute, due to balloon inflation, resulted in increased circulating lactate levels 10 minutes later (157).

Lower oxygen levels during ischemia inhibit aerobic oxidation and fewer metabolites enter the TCA cycle leading to lower production of its intermediates such as fumarate and succinate (158-160). Reperfusion-induced production of reactive oxygen species (ROS) seems to be regulated through tissue succinate levels (161). A mouse model simulating ischemia-reperfusion injury could show that succinate accumulates in ischemic heart tissue and succinate oxidation is a key actor for mitochondrial ROS accumulation and injury (161).

Amino acid metabolism

The healthy heart's need for amino acids as ATP source is minimal as shown in isolated rat hearts where under laboratory conditions leucine oxidations contributes to 3–5% of overall cardiac oxygen consumption (162). This is supported by the finding that infusion of phenylalanine is primarily used for anabolic purposes (105). Nevertheless, it has been proposed that especially during ischemia amino acid metabolism may be important. Comparison between arteriovenous differences between CAD patients and healthy controls showed that there is a net myocardial release of alanine and uptake of glutamate in ischemic heart disease (163). Among all amino acids, glutamate might play the most important role during ischemia. Due to ischemia, cardiomyocytes' higher levels of glutamic oxaloacetic transaminase will be released into the serum, preventing the transamination of glutamate into α-ketoglutaric acid, leading to net increase of glutamate in the ischemic tissue (164). Additionally, higher glutamate levels were shown to be associated with ongoing myocardial ischemia (165). Glutamate is able to activate ROS production, leading to inflammatory and cytotoxic cardiomyocyte death (166).

Circulating amino acids among patients who underwent coronary angiography for suspected CAD have to be shown to predict both prevalent and subsequent cardiovascular risk (167). Serum BCAA levels were elevated in sex- and age-matched CAD patients versus healthy controls, independent of other "classic" risk factors such as diabetes, hypertension and hyperlipidemia (134). N-phenylacetyl-L-glutamine was upregulated in acute MI patients compared to patients with unstable angina, suggesting a perturbed

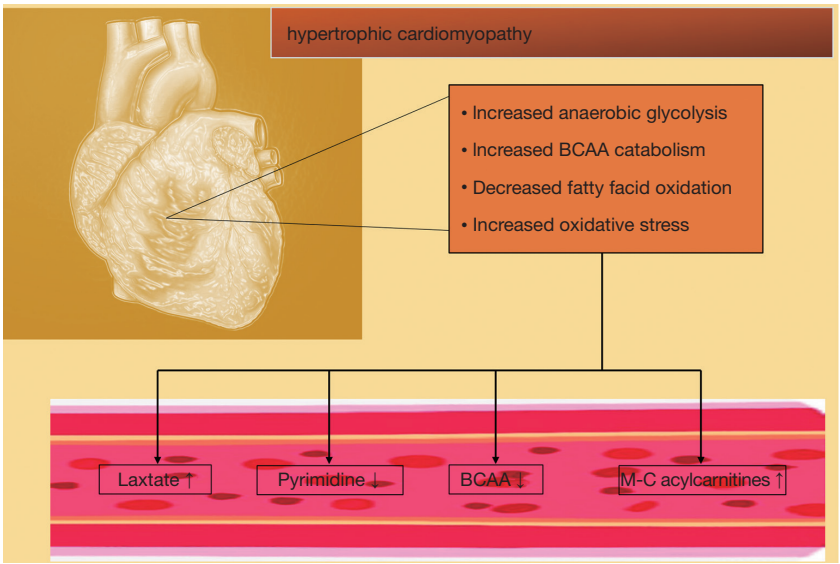

Figure 3 Hypertrophic cardiomyopathy is characterized by increased glycolysis uncoupled from glucose oxidation and accompanied by lower rates of medium-chain fatty acid oxidation. Hence, circulating metabolomic profiles often yield increases in lactate and M-C acylcarnitines. Furthermore, BCAA and oxidative stress metabolites are reduced in the circulation. BCAA, branch-chained amino acids; M-C, medium-chain.

phenylalanine metabolism during transition from unstable angina to acute MI (168). Furthermore, tryptophan-arginine-leucine were also increased among acute MI patients suggesting activated amino acid biosynthesis as an indicator for acute MI (156).

To date, myocardial amino acid uptake seems to be of little relevance to the ischemic heart compared to other substrates (169). However, in ischemic myocardium, several amino acids like leucin, alanine and isoleucine are elevated, while others like lysine and tyrosine are degraded, compared to non-infarcted myocardium (160). This might be related to the pathophysiological mechanisms of MI. However, our knowledge about the role of amino acid and protein metabolism during the progression of ischemic heart disease remains poorly understood.

Non-ischemic cardiomyopathies

Hypertrophic cardiomyopathy (HCM) and DCM reflecting major non-ischemic cardiomyopathies are both highly prevalent monogenic diseases yet showing remarkable clinical heterogeneity (170-172). Both are characterized by disproportionate cardiac chamber growth and adjustment of ventricular wall thickness, resulting in myocyte cell apoptosis and hypertrophy, fibrosis, as well as impaired cardiac metabolism (173,174).

Earlier studies identified increased glycolysis as a metabolomic hallmark of pathological HCM (96,175). Furthermore, increased glycolysis is uncoupled from glucose oxidation and accompanied by lower rates of medium-chain fatty acid oxidation (176). In non-pathological HCM in contrast to pathological HCM, glucose oxidation and long-chain fatty acid oxidation is increased (177). In mice with transverse aortic constriction, simulating HCM, cardiac levels of fatty acids, lysolipids, acylcarnitines and purines were upregulated in a time-dependent manner, whereas ascorbate, heme and pyrimidines were downregulated (37). Furthermore, BCAA and metabolites associated with oxidative stress and metabolic remodelling are elevated in pressure-overloaded hearts (37). Since the decompensated heart forfeits its ability to perform oxidative phosphorylation for ATP generation, there is presumably a decrease of the glucose and fatty acid flux into the TCA cycle (178). This is supported by findings of normal acylcarnitine and lactate levels in compensated HCM (179) (*Figure 3*). Nevertheless, these findings provide further evidence that the myocardial metabolic profile could reflect stage and aetiology of HF.

A global metabolomic analysis of DCM-simulated hamsters via δ-sarcoglycan deficiency revealed a compromised TCA cycle and glycolysis. Furthermore, DCM

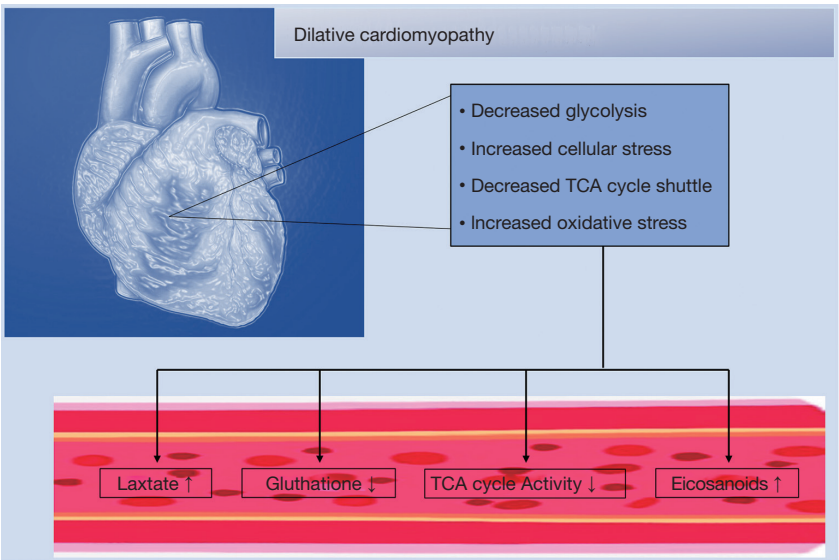

Figure 4 A hallmark of dilative cardiomyopathy is a compromised TCA cycle activity and glycolysis resulting in decreased peripheral lactate levels along with metabolites associated with oxidative stress like glutathione. Furthermore, elevated eicosanoids suggest cellular stress with consecutive activation of protective pathways with increased sphingomyelin levels. TCA, tricarboxylic acid.

hamsters suffered from altered membrane phospholipid homeostasis, glutathione biosynthesis, urea cycle and CK pathways leading to cardiac contractile dysfunction (102). Especially the decrease in glutathione and the compensatory increase in ophthalmate suggested that increased oxidative stress might play a role in DCM pathogenesis. Increasing levels of eicosanoids, ceramides and sphingomyelin suggest cellular stress and consecutive activation of protective pathways (102) (*Figure 4*).

Cardiac energy supply is normally dependent on fatty acids. Whether this change is a cause or a consequence of cardiac hypertrophy is still unclear. A study with mice, deficient in long-chain acyl-CoA synthetase 1 in the myocardium, revealed a switch from FA to glucose as mitochondrial fuel preference. This switch led to mechanistic target of rapamycin (mTOR)-dependent alterations in the cardiac metabolism, several genes involved in glycolysis as well as changed glutathione-related pathways and compensation by mTOR (180). Interestingly, for nutrient signalling, inhibition of autophagy and myocyte growth mTOR signalling has been reported as a central player (181).

In one study, comparing tissue DCM patients versus healthy controls decreased glycolysis, TCA cycle and malate-aspartate shuttle activities were observed (*Figure 4*). However, only in ischemic DCM patients an increase in ketone body oxidation and inflammatory markers was seen (182). These studies clearly indicate that a more systematic analysis of temporal changes in the cardiac metabolome among patients with ischemic and dilative cardiomyopathies is needed to reveal precise, disease-specific signatures, and possibly filter out individuals with high risk of SCD.

Current research projects

From the perspective of translational to clinical research, prior studies evaluating metabolomics profiles in patient cohorts with cardiovascular diseases were limited in different aspects: small sample size (183-185), too much pre-specified cohorts (183), inconsistent or even unclear inclusion criteria for patient selection and control groups, usually not based on international guideline-recommendations (186), and lack of predefined prognostic endpoints as demanded by these guidelines (187-189).

For example, DeFilippis *et al.* developed criteria for differentiating of thrombotic and non-thrombotic myocardial infarction (184). Other studies divided patients in normal coronary arteries, non-obstructive coronary arteries, stable angina, non-stable angina as well as acute myocardial infarction, irrespective of the international universal definitions of myocardial infarction (144). Therefore, clearly

predefined patient cohorts based on disease consensus documents are needed when investigating targeted metabolomic approaches in patients with cardiovascular diseases (190,191). To translate differential diagnostic finding by identifying significant metabolomics clusters, hard clinical endpoints in terms of prognosis, such as all-cause and cardiovascular mortality or heart failure related rehopsitalization need to assessed (144,191,192).

Therefore, we recently investigated in pragmatic research project to counterbalance these inconsistencies of metabolomics studies. The "Metabolomics and Microbiomic in Cardiovascular Diseases" (MEMORIA) study evaluates guideline-conform patient cohorts including mid-term and long-term follow-up periods (from 6 to 24 months) [https://clinicaltrials.gov/ct2/show/NCT04146701]. Cardiovascular disease cohorts will include a total of 800 patients with acute heart failure, acute myocardial infarction, such as non-ST and ST segment elevation myocardial infarction, chronic heart failure due to progressive non-ischemic and ischemic cardiomyopathies and the impact of implanted cardioverter defibrillator (ICD), well as sepsis or septic shock. Prognostic endpoints are all-cause and cardiovascular mortality, heart-failure related rehospitalization, stroke, recurrent myocardial infarction, ventricular tachyarrhythmias, quality of life. MEMORIA aims to close the gap between preliminary to clinically relevant research of targeted metabolomics in cardiovascular diseases.

Conclusions and future implications

New -omics platforms such as metabolomics provide great opportunities to gain further insights into cardiovascular disease risk and pathogenesis. Because most patients with cardiovascular diseases additionally suffer from associated comorbidities like chronic kidney disease, obesity or diabetes, metabolomics, in particular, has improved the understanding of the molecular principals of these conditions. Furthermore, metabolomics provide a functional integration of upstream genetic, transcriptomic and proteomic variations in combination with environmental factors, thus reflecting molecular processes more proximal to the respective disease state. Because clinically confounding factors like diet, age, sex and drug effects influence results and conclusions, application of metabolomic profiling of large population-based epidemiological cohorts has allowed statistical adjustment for potential confounders for future analyses (9,193). In parallel, advances in computational analyses have to continue to provide an integration of various-omics data sets to gain a more comprehensive view of molecular mechanisms of cardiovascular disease. Summarizing, metabolomics constitutes a further step towards a personalized medicine enabling us to predict, detect and understand a multitude of cardiovascular disease states.

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