Cardiac Resynchronization Therapy Induces Adaptive Metabolic Transitions in the Metabolomic Profile of Heart Failure

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Abstract

Background—Heart failure (HF) is associated with ventricular dyssynchrony and energetic inefficiency, which can be alleviated by cardiac resynchronization therapy (CRT). The aim of this study was to determine the metabolomic signature in HF and its prognostic value for the response to CRT.

Methods—This prospective study consisted of 24 patients undergoing CRT for advanced HF and 10 control patients who underwent catheter ablation for supraventricular arrhythmia but not CRT. Blood samples were collected before and 3 months after CRT. Metabolomic profiling of plasma samples was performed using gas chromatography–mass spectrometry and nuclear magnetic resonance.

Results—The plasma metabolomic profile was altered in the HF patients, with a distinct panel of metabolites, including Krebs cycle and lipid, amino acid, and nucleotide metabolism. CRT improved the metabolic profile. The succinate/glutamate ratio, an index of Krebs cycle activity, improved from 0.58±0.13 to 2.84±0.60 (*P*<.05). The glucose/palmitate ratio, an indicator of the balance between glycolytic and fatty acid metabolism, increased from 0.96±0.05 to 1.54±0.09 (*P*<.01). Compared with the nonresponders to CRT, the responders had a distinct baseline plasma metabolomic profile, including higher isoleucine, phenylalanine, leucine, glucose, and valine levels and lower glutamate levels at baseline (*P*<.05).

Conclusion—CRT improves plasma metabolomic profile of HF patients indicating harmonization of myocardial energy substrate metabolism. CRT responders may have a favorable metabolic profile as a potential biomarker for predicting CRT outcome.

Keywords

heart failure; metabolism; cardiac resynchronization therapy

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Introduction

Heart failure (HF) is a complex clinical syndrome associated with cardiac structural, metabolic, and functional deficiency[1–4]. Cardiac remodeling in HF involves ventricular electrical and mechanical dyssynchrony, which results in metabolic heterogeneity and energy insufficiency[5–7]. Impaired myocardial substrate metabolism and phosphotransfer dynamics further contribute to HF abnormalities[5, 6, 8–11]. Cardiac resynchronization therapy (CRT) effectively treats HF by correcting cardiac dyssynchrony, resulting in improvement of HF symptoms, ventricular function, quality of life, and overall survival[12, 13]. The reduction of mechanical dyssynchrony within the left ventricle and subsequent improvement in left ventricular (LV) efficiency and oxygen consumption have been considered the main mechanistic benefits of CRT[14, 15]. Although the subcellular metabolic and energy systems are affected in HF[16, 17], little is known about the effect of CRT on myocardial substrate metabolism[18, 19].

Metabolomics analyzes a large range of metabolites from multiple metabolic pathways and increasingly demonstrates the potential to provide individualized and predictive information for disease progression and personalization of treatment[20–31]. Determining the association of metabolomic changes with HF and CRT is necessary for understanding the mechanisms of re-regularization of cardiac metabolism derived from this therapy[18]. The aim of this study was to determine 1) the metabolomic signature in HF and the therapeutic effects of CRT on the metabolomic profile and the pathways of adaptive metabolic remodeling that lead to recovery of myocardial function and 2) the panel of metabolic markers that predicts which patients will respond to CRT.

Methods

Study Patients

This single-center prospective study consisted of 24 consecutive patients who received CRT-D (defibrillation) for advanced HF at Mayo Clinic, Rochester, Minnesota, from March 1 through November 30, 2010. All patients were clinically recommended for device implantation according to current guidelines for CRT[32]. The Mayo Clinic Institutional Review Board approved this study, and all patients provided signed consent for the study. Ten age-matched control patients underwent catheter ablation for supraventricular arrhythmia with a normal left ventricular ejection fraction (LVEF) of greater than 55%.

Baseline Evaluation

All HF patients underwent a baseline evaluation before CRT, including assessment of New York Heart Association (NYHA) functional class, concomitant cardiovascular conditions (e.g., hypertension, coronary artery disease, and diabetes mellitus), electrocardiographic QRS duration and morphologic characteristics, and transthoracic echocardiography. Echocardiographic parameters included LV end-systolic and diastolic dimensions, LVEF, and pulmonary artery systolic pressure. Medication use was recorded and confirmed that patients were taking optimal medication dose for HF. Patients continued on stable medication dosage during the study.

CRT Implantation and Blood Sample Collection

All patients underwent conscious sedation throughout the procedure for CRT implantation. The right femoral artery was cannulated for continuous monitoring during the procedure in both HF and control patients. Blood samples were taken from a peripheral vein before the device was implanted. These blood samples (5 mL) were collected into EDTA tubes containing 100 μL of injected stop solution (dipyrimidole,10 μM; EHNA, 5 μM; iodotubercidin, 2 μM; AOPCP, 50 μM, in 0.9% NaCl) to reduce blood nucleotide metabolism; stored on ice; and then centrifuged at 3,200 rpm for 10 minutes at 4°C. Plasma aliquots were stored at −80°C until analyses.

Patient Follow-up

The HF patients returned for a clinical follow-up 3 months after CRT. The NYHA functional class was reassessed, and echocardiography was repeated. Peripheral venous blood samples were collected for post-CRT metabolic measurements. Metabolomic profile was successfully determined in 19 patients. Improvement in LVEF by more than 5% and reduction of NYHA ≥ 1 class were considered as CRT responders.

Metabolomic Analyses

Sample Treatment and Instrumental Conditions for GC-MS Metabolomic Analysis—For gas chromatography–mass spectrometry (GC-MS), plasma (100 μL) was extracted using a 900-μL methanol:water (8:1, v/v) mixture containing 5 μg internal standard, myristic-d$_{27}$ acid, at ambient temperature[33]. Supernatant (900 μL) was transferred and completely dried in a vacuum concentrator. Subsequently, the tubes were methoximated and derivatized and then analyzed using an Agilent 6890 GC oven with Agilent 5973 MS[34].

Sample Treatment and Instrumental Conditions for ^{1}H NMR Metabolomic Analysis—For nuclear magnetic resonance (NMR) imaging, plasma (60 μL) was diluted 140 μL with 0.2M phosphate buffer (pH 7.4):D$_2$O containing a mixture of 16 mM formate and 4 mM TSP (1:1, v/v). After filtering (0.22 μm), the samples were transferred into a 3-mm-diameter NMR tube. High-resolution ^{1}H NMR spectra were acquired at 600 MHz on a Bruker Avance III 600 spectrometer. Spectra peaks were identified according to Chenomx NMR Suite 6.1 software and data in the literature[35, 36].

Metabolomic Data Analysis—The data files from GC-MS analyses were deconvoluted using AMDIS software[37], and then SpectConnect (http://spectconnect.mit.edu/index.php) was used to list and track metabolite peaks[38]. Quality control-based signal correction and integration of data were used to minimize intra- and inter-day variations[29]. The Agilent Fiehn GC/MS Metabolomics RTL Library was used for metabolite identification. Data analysis of ^{1}H NMR spectra was done with the MestRenova (Mestrelab). The identified peaks were integrated and normalized according to an internal standard (fumarate). Analysis of the ^{1}H NMR spectra and GC-MS chromatogram permitted detection over 400 metabolite peaks, major of which are presented in Supplemental Table 1. Orthogonal partial least squares discriminant analysis (OPLS-DA) was performed using Umetrics SIMCA-P+ version 12.0. The variable importance in the projection values was calculated to identify a

panel of the most important metabolites, and regression coefficients were used to validate group separation.

Statistical Analysis

All data are expressed as mean ± standard error of the mean. The Student unpaired *t* test was used, and differences were considered statistically significant at *P*<.05. One-way analysis of variance was used to test differences among groups.

Results

Baseline Characteristics

The baseline demographic characteristics in 24 CRT patients and 10 control patients are shown in Table 1. Age and sex were not significantly different between the 2 groups. Ten HF patients (42%) had ischemic cardiomyopathy. The incidence of hypertension and diabetes was not significantly different in the 2 groups. All HF patients had NYHA class III symptoms. The mean LVEF was 23.5±6.3% in the CRT group compared with 62.9%±3.3% in the control group (*P*<.001). More patients in the CRT group received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (*P*<.001) and statins (*P*=.002) than in the control group.

Improvement in HF After CRT

At 3-month follow-up, the post-CRT group had significant improvement in HF symptoms. The severity of the NYHA class was reduced, while LV systolic function, the severity of mitral regurgitation, and elevated pulmonary artery systolic pressure were improved (Table 2). LVEF improved from 23.5%±6.3% to 32.0±8.6% (*P*<.001).

Shift in Plasma Metabolomic Profile Associated With HF

Here, using metabolomic technologies we demonstrate that the HF pre-CRT group had a significantly altered plasma metabolomic profile compared with the control group (Figure 1A). The integral metabolomic profile in the HF pre-CRT group clustered separately from the control group on the OPLS-DA score plot. The panel of most important metabolites in group discrimination is shown in Figure 1B. The full list of major metabolites detected in the HF pre- and post-CRT and control groups is presented in Supplemental Table 1. In HF pre-CRT, as markers of altered mitochondrial function, succinate was reduced and glutamate was increased. A decrease in amino and fatty acids and an increase in urate levels were apparent (Figure 1C). Metabolic pathways most affected in HF patients included amino acid and lipid metabolism and Krebs cycle, with a smaller contribution of carbohydrate metabolism, energy transfer, neurotransmitter metabolism, ammonia detoxification, and nucleotide degradation metabolism (Figure 1D).

Changes in Plasma Metabolomic Profile After CRT

Three months after CRT, the plasma metabolomic profile was significantly changed (Figure 2A). Scores of the integral metabolomic profile of each HF patient post-CRT clustered separately from the original state on the OPLS-DA plot, indicating a transition to a new

metabolic state. Moreover, changes in metabolomic profile specific to mechanical and electrical dyssynchrony can be evaluated by comparing HF pre-CRT and post-CRT (Figure 2). An integrated panel of the most important metabolites allowing post-CRT group discrimination included the branched-chain amino acid isoleucine, glutamine and glycerol-1-phosphate associated with mitochondrial oxidation, and metabolites of fatty acid and amino acid metabolism (Figure 2B). The pattern of metabolite changes indicates improved substrate metabolism after CRT (Figure 2C). Among the most improved metabolic pathways were amino acid and lipid metabolism and Krebs cycle, with a reduced contribution of substrate shuttling, energy/oxidative stress, ammonia detoxification, and myofibrillar protein turnover (Figure 2D). Several metabolites including cysteine, glutamate, glycerol-1-phosphate, glycine, malate and tryptophan restored to control values after CRT (Supplemental Table 1). This pattern is supported by changes in the succinate/glutamate ratio, an index of Krebs cycle activity[39], which improved from 0.58 ± 0.13 to 2.84 ± 0.60 ($P<.$ 05) after CRT (Figure 3A). Similarly, the citrate/glutamate ratio increased from 0.69 ± 0.12 to 2.62 ± 0.63 ($P<.001$) after CRT. The glucose/palmitate ratio, an indicator of the balance between glycolytic and fatty acid metabolism, increased from 0.96 ± 0.05 to 1.54 ± 0.09 ($P<.001$). The glutamine/glutamate ratio, an indicator of ammonia fixation, improved from 0.66 ± 0.12 to 2.71 ± 0.46 ($P<.001$) after CRT. Although HF post-CRT metabolomic profile improved significantly, it was still different from the control group (Supplemental Figure 1A). A panel of the most important metabolites in group distinction included glutamic and succinic acids, glycerol, glycerol-1-phosphate, free fatty and amino acids (Supplemental Figure 1B), reflecting Krebs cycle, lipid and amino acid metabolism.

Correlation Between Plasma Metabolites and Cardiac Performance

A panel of representative metabolites correlated with LVEF at baseline in HF pre-CRT group (Figure 3B). Plasma levels of glutamate and urate, glucose, threitol, urea, and creatinine correlated negatively, while levels of linoleate, cysteine, glycine, serine, glycerol, serotonin, threonine, and succinate correlated positively with LVEF in HF pre-CRT group. Three months after CRT plasma levels of glucose, serotonin, lactate, alanine and glycerol-1-phosphate correlated positively with LVEF (Figure 3C). Glucose levels positively correlated with delta LVEF improvement, while myristic acid negative correlation with delta LVEF (Figure 3D). Transitions in the global metabolomic matrix were compared between control, HF pre-CRT and post-CRT patient groups (Supplemental Figure 2). In the heat map, the red color indicates an increased metabolite level, and green indicates a decreased metabolite level. The HF post-CRT group had a distinct cluster of decreased metabolite levels and another cluster with increased metabolite levels. The cluster of decreased metabolites included glycerol, *N*-methylhistidine, myristic, oleic, palmic, stearic, palmitoleic, heptadecanoic, tryptophan, glycerol-1-phosphate, gluconate, 2-hydroxybutyrate (2-HB), and malate. The cluster of increased metabolites included amino acids proline, leucine, and glutamine, as well as acetate, succinate, glycolic acid, acetoacetate, 3-hydoxybutyrate (3-HB), and others (Supplemental Figure 2).

Baseline Metabolomic Profile Predicts Improvement in LVEF After CRT

Of 24 HF patients who received CRT, 10 (41%) had an improvement in LVEF by more than 5% and reduction of NYHA   1 class and were considered CRT responders. This group of

patients differed in their pre-CRT baseline plasma metabolomic profile from nonresponders in the OPLS-DA plot analysis (Figure 4A). Panel of most important metabolites allowing distinction between responders and non-responders to CRT therapy included isoleucine, phenylalanine, leucine, glutamate, acetone, phosphoric acid, glycerol, lactate, valine, glucose and other metabolites (Figure 4B). Among them were three branched-chain amino acids - isoleucine, leucine and valine, essential for protein synthesis and metabolic signaling, with lower levels in non-responders (Figure 4C). Patients who responded to CRT had higher amino acids phenylalanine, isoleucine, leucine, valine, and glucose and lower glutamate levels (Figure 4C; P<.05).

By comparing pre- and post-CRT metabolite values, responders had higher 2-hydroxypyridine, alanine, acetate, glycerol -1-P, isoleucine, N-methylhistidine, ornithine, oxalic acid, phosphoric acid, succinate and tyrosine levels 3 month after CRT (Supplemental Table 2), while levels of benzoic acid, galacturonic acid, gluconic acid, glutamic acid, and other metabolites were lower post- CRT. Non-responders had a different increased or reduced metabolites profile after CRT (Supplemental Table 2). Analyses of specific metabolic traits following CRT (Supplemental Table 3) reveal that nonresponders had significantly smaller and negative change in ornithine and higher delta in porphine levels.

Discussion

Metabolomic Signatures in HF

Systolic HF is associated with cardiac conduction abnormalities and dyssynchrony, which results in poorly coordinated contractions precipitating energy inefficiency and LV dysfunction[1, 5, 6, 13, 40]. Cardiac dyssynchrony affects many systems ranging from gene expression, ion channels, sarcomeres, mitochondrial energy metabolism and metabolic pathways[41–43]. CRT improves chamber mechano-energy efficiency, reducing morbidity and mortality of HF patients[13–15, 44]. Emerging metabolomic profiling of disease phenotypes permits comprehensive and simultaneous systematic fingerprinting of multiple metabolites and metabolic pathways[22, 24–28]. Here, metabolomic profiling indicates that HF patients have altered plasma metabolomic profiles, with a distinct panel of representative metabolites of lipid, amino acid, and nucleotide metabolism and mitochondrial Krebs cycle–associated substrates such as succinate and glutamate. Most altered in HF patients were the reduced level of succinate and the increased level of glutamate, the indicators of mitochondrial dysfunction and metabolic remodeling[45]. The lower succinate level suggests decreased concentration of Krebs cycle intermediates, which are critical for burning fats and carbohydrates[45, 46]. Diminished substrate metabolism is also indicated by changes in the succinate/glutamate and citrate/glutamate ratios, which were significantly decreased in HF. Thus, insufficient mitochondrial substrate utilization and metabolomic heterogeneity may contribute to energy deficiency in HF. The higher plasma levels of glutamate, urate, urea, and creatinine confer the alterations in Krebs cycle, amino acid changes, nucleotide degradation, and ammonia detoxification, the indicators of heart dysfunction[29, 47]. Since glutamate and succinate are on opposite ends of the correlation panel, their plasma ratio could have a diagnostic and prognostic value. Thus, the plasma metabolomic fingerprint reflects an altered energy and metabolic environment in patients with HF.

In HF, deficient substrate oxidation may cause a decrease in the ATP level and an increase in the end product of purine metabolism, such as urate levels[22]. This is a sign of an impairment of oxidative metabolism and highly correlates with measures of functional capacity and disease severity of HF[1, 5]. Therefore, urate has been suggested as a marker of HF[29, 47]. We had similar findings in our study. The decreased levels of threonine, glycine, serine, and cysteine indicate energy deficiency and mitochondrial dysfunction in HF[48]. The plasma levels of glycerol, linoleate, myristate, and cholesterol, which were reduced in HF patients, may indicate reduced lipid metabolism. Similarly others using different analytical platforms and patient groups found altered metabolomic profiles in heart failure and identified candidate disease biomarkers[19, 29, 49, 50]. Consistent with derangement in different metabolic pathways at a systemic level, as we observed in our study, HF patients had higher serum concentrations of phenylalanine, tyrosine, isoleucine, creatine, and lower serum levels of lactate, citrate and lysine[49]. In patients with heart failure significant changes in serum metabolomics profiles, especially the concentration of 3-hydroxybutyrate, acetone and succinate[19] and 2-oxoglutarate and pseudouridine,[51] was demonstrated. In another study CHF patients were characterized by higher levels of lactate, alanine, creatine, proline, isoleucine, leucine and lower levels of valine, glutamine, glutamate, choline, glycine, glucose, tyrosine and histidine[50]. More recently, metabolomic fingerprint of heart failure patients was characterized by lower levels of lactate, methionine and by higher levels of formate, phenylalanine, glucose, serine, acetate, hypoxanthine, creatine and creatinine[52]. In the study by Lin et al[53], HF metabolomic profile was characterized by higher levels of acetoacetate and urea and by lower levels of threonine, glycine, ethanol, histidine, alanine and tyrosine, consistent with our findings.

The Effects of CRT on Systemic Metabolism

Our study shows that CRT induces a significant shift in the metabolomic profile in HF patients, suggesting adaptive metabolic transitions. After CRT, an integral panel of the most important metabolites, including representatives of fatty acid (myristate, oleate, stearate, palmitate, palmitoleate, and heptadecanoate), amino acid (glutamine, glutamate, tryptophan, tyrosine, isoleucine, and *N*-methylhistidine), lipid (glycerol-1-phosphate and 2-HB), and Krebs cycle (citrate) metabolism, were improved. The improvement of substrate metabolism is indicated by changes in the succinate/glutamate and citrate/glutamate ratios; they are indicators of Krebs cycle activity, which are decreased in HF and significantly restored after CRT. Decreased levels of glutamine and malate and increased levels of citrate and alanine indicate a shift to more aerobic oxidation after CRT. A decreased glutamine/glutamate ratio in HF was also improved after CRT, indicating an improvement of ammonia fixation and detoxification. In addition, augmented levels of free fatty acids, amino acids, ketone bodies, and glycerol-1-phosphate suggest increased substrate reserve and shuttling of redox equivalents to mitochondria. Moreover, CRT also significantly increased the glucose/palmitate ratio, suggesting enhanced glycolytic metabolism. Several metabolites return to control values after CRT. However, CRT had also specific metabolic effects such as activation of substrate utilization, amino acid and energy metabolism. CRT also improves metabolomics environment which is associated with a delta change in LVEF, as a evidence of improved heart performance similar to other reports[18, 43, 52, 54]. Although post-CRT metabolomic profile improved significantly, many metabolite levels have not been restored

to the normal range, indicating existence of resynchronization independent metabolic disturbances associated with HF[49, 50, 53]. Clinically we observe that the extent of LVEF improvement is variable individually, and that only approximate 10% CRT recipients are super-responders with LVEF normalization.

We found that CRT improves mitochondrial function as manifested in increased succinate/ glutamate and citrate/glutamate ratios compared to HF group, consistent with other reports[17, 42] which found augmented ATP synthase activity and glutamate/malate and succinate oxidations in heart mitochondria. Other recent studies revealed remodeling of sarcomeric proteins, including α-actinin, in HF that was reversed after CRT[43]. Moreover, at systemic level CRT promoted oxidative metabolism in peripheral muscles because of improved heart function and circulation.[55] In summary, CRT induces pathways of adaptive metabolic transitions in the HF metabolomic profile, thus facilitating myocardial function recovery.

Metabolic Biomarker for Response to CRT

Predictive analytics is emerging area in personalized medicine[56, 57]. This study suggests a specific plasma metabolic signature for response to CRT. Responders had higher baseline levels of isoleucine, phenylalanine, leucine, glucose, and valine and lower glutamate, essential for protein synthesis and metabolic signaling[58, 59]. These metabolites may represent a better metabolic reserve and a higher potential for metabolic recovery in CRT responders. Analysis of metabolomic traits following CRT revealed that responders had higher amino acid, phosphoric acid, urea and Krebs cycle metabolite levels along with 2-hydroxypyridine, which derivatives have antioxidant properties, and oxalic acid, which may indicate higher intake and metabolism of vitamin C. Higher plasma levels of citrate, creatine and creatinine in nonresponders indicate energetic deficiency. Nonresponders had also negative change in ornithine and higher increase in porphine levels compared to responders. Ornithine is a metabolite of urea cycle and ammonia detoxification while porphine is a product of degradation of porphyrins in heme containing proteins, which have energetic significance. Other studies have demonstrated that myocardial fatty acid extraction and calculated ATP synthesis flux may serve as biomarkers in identifying nonresponders to CRT[18]. Adaptive metabolic remodeling after CRT may facilitate development of prognostic tests for identifying CRT responders in a larger patient population. This requires larger scale metabolomics studies using complementary technologies as limited scale metabolite profiling may not be sufficient to establish predictive tests[52]. Similarly to our data, other studies[52] have demonstrated a different metabolomic profile after CRT, which was also different from the fingerprint of healthy controls. The levels of serum metabolites - tyrosine, lactate, proline and alanine were significantly higher after CRT when compared to baseline[52]. However, in this study, which used only ^{1}H NMR technique, accuracy of discrimination between responders and non-responders remained low[52]. In our study we used wider range metabolomic profiling using GC-MS and ^{1}H NMR techniques.

Conclusions

Our study suggests that HF is associated with a significantly altered metabolomic profile. Elevated plasma and myocardial free fatty acids may have negative impact on glycolytic

ATP/energy transfer mechanism thus perpetuating energy imbalances and electrical instability. CRT improves the plasma metabolomic profile, including metabolic pathways of amino acid and lipid metabolism, ammonia detoxification, and Krebs cycle. A predictive panel of metabolites has been established to identify CRT responders. The results indicate that CRT facilitates synchronized metabolic signaling associated with improved substrate oxidation and overall energy metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

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CRT	cardiac resynchronization therapy
GC-MS	gas chromatography–mass spectrometry
HF	heart failure
LV	left ventricular
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
NMR	nuclear magnetic resonance
OPLS-DA	orthogonal partial least squares discriminant analysis
VIP	variable importance in the projection

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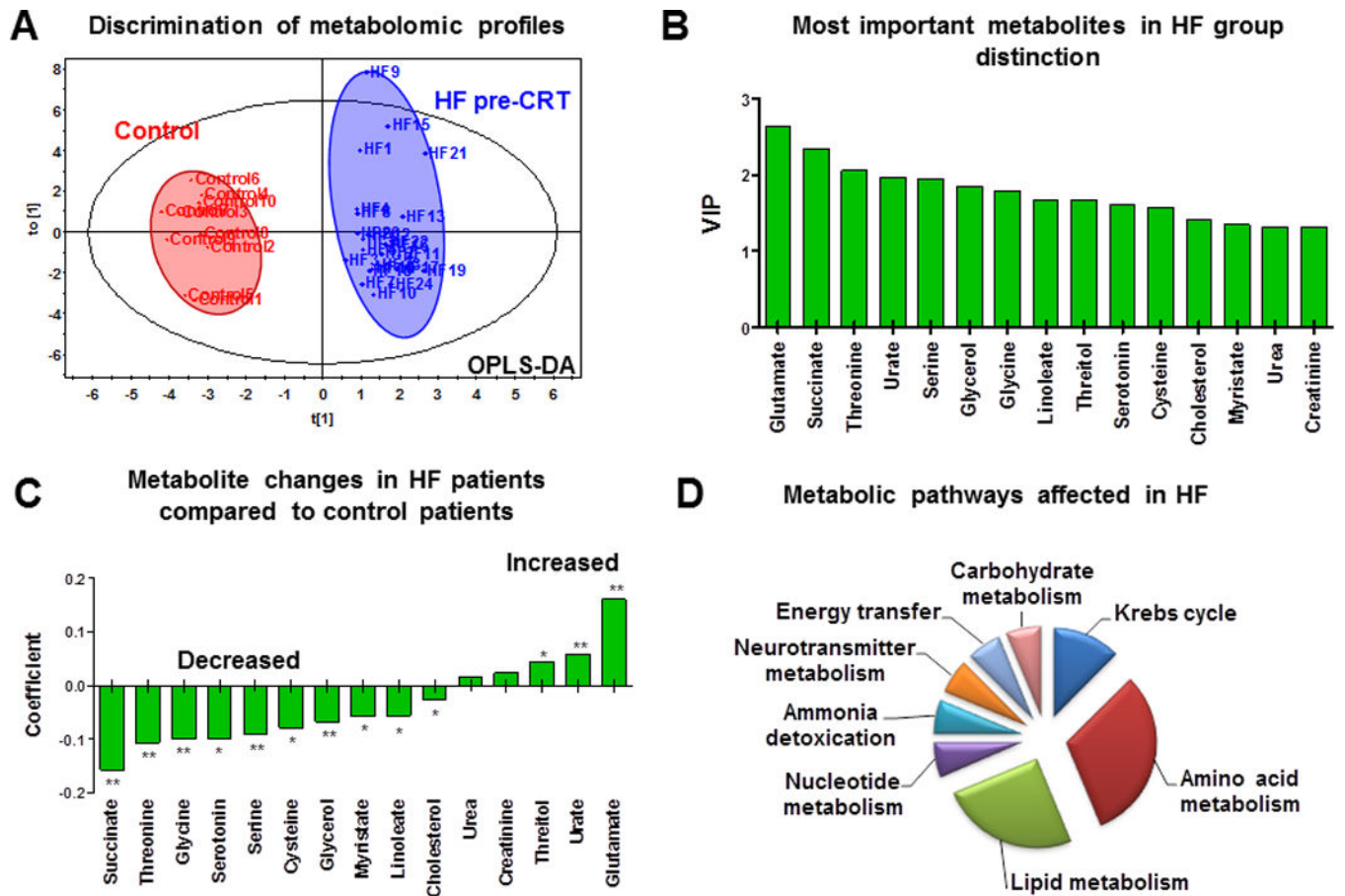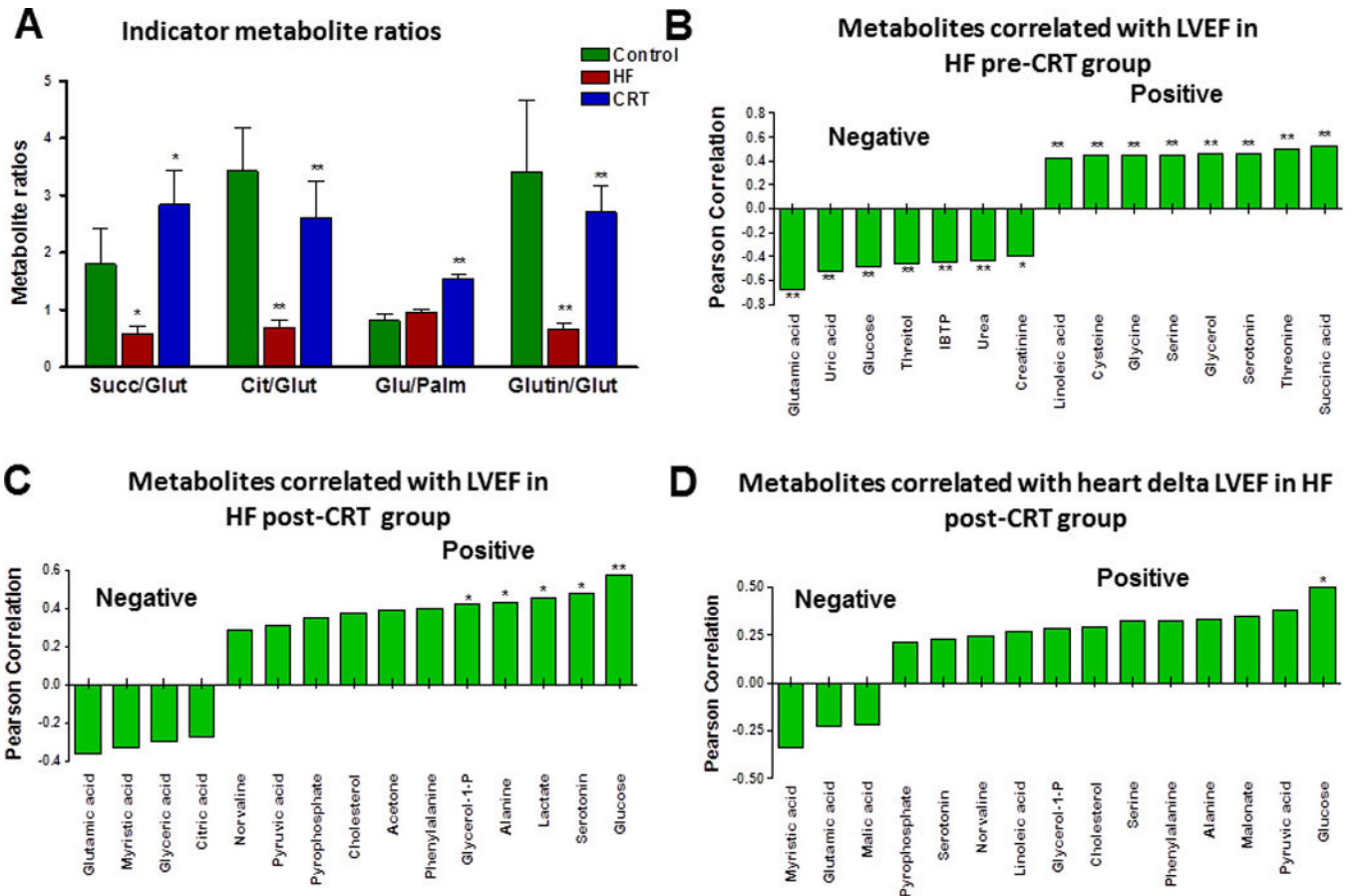
Figure 1.
Metabolomic signature of heart failure (HF). A, Changes in plasma metabolomic profile of HF patients by orthogonal partial least squares discriminant analysis (OPLS-DA). B, Most important metabolites in the metabolomic signature of HF by variable importance in the projection (VIP). C, Pattern of plasma metabolite changes in HF patients (N=24, * $P<.05$; ** $P<.001$). D, Metabolic pathways most affected in HF as deduced from an altered plasma metabolomic profile.
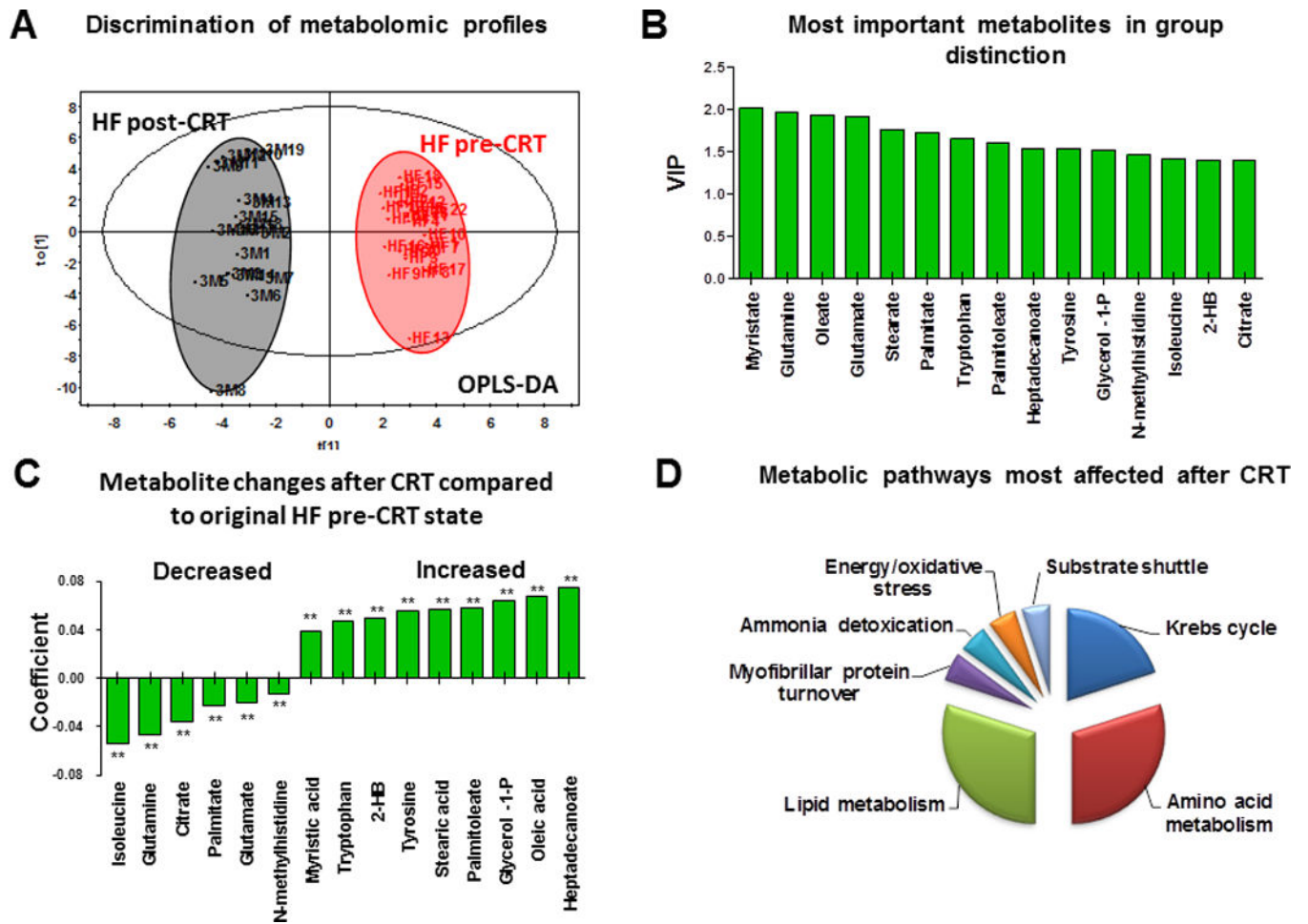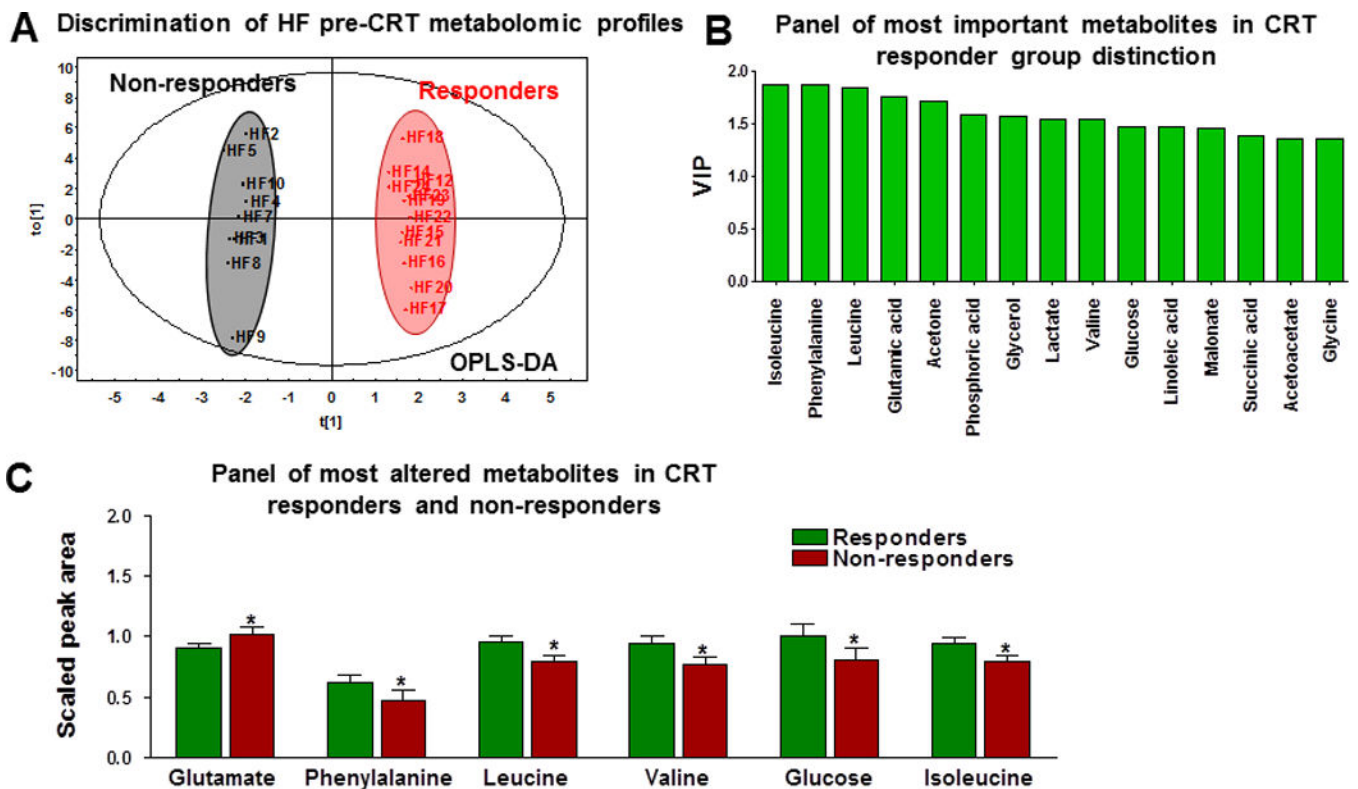
Figure 2.
Metabolomic signature of cardiac resynchronization therapy (CRT). A, Changes in plasma metabolomic profiles of patients with heart failure (HF) after CRT by orthogonal partial least squares discriminant analysis (OPLS-DA). 3M indicates 3-month follow-up. B, Most important metabolites in metabolomic signature of CRT by variable importance in the projection (VIP). C, Pattern of plasma metabolite changes in HF patients after CRT (N=19, **$P<.001$). D, Metabolic pathways most affected after CRT as deduced from an altered plasma metabolomic profile.

Figure 3.
Improvement of indicator metabolite ratios and correlations between plasma metabolites and cardiac performance (left ventricle ejection fraction [LVEF]) after cardiac resynchronization therapy (CRT). A, Changes in indicator metabolite ratios in HF pre-CRT and HF post-CRT. B, A panel of metabolites that correlate positively and negatively with LVEF in HF pre-CRT group (*P<.05; ** P<.001). C, A panel of metabolites that correlate positively and negatively with LVEF in HF post-CRT group (*P<.05; ** P<.001). D, A panel of metabolites that correlate positively and negatively with delta LVEF in HF post-CRT group (*P<.05). Cit/Glut indicates citrate/glutamate; Glu/Palm, glucose/palmitate; Glutin/Glut, glutamine/glutamate; HF, heart failure; Succ/Glut, succinate/glutamate.

Figure 4.
Metabolomic profiles of 9 responders and 13 nonresponders to cardiac resynchronization therapy (CRT). A, Distinction of basal plasma metabolomic profiles of responders and nonresponders to CRT by orthogonal partial least squares discriminant analysis (OPLS-DA). B, An integral panel of the most important metabolites permitting prediction of responders by variable importance in the projection (VIP). C, A panel of the most important metabolite differences between responders and nonresponders (* $P<.05$).

Table 1

Baseline Characteristics of the HF and Control Patients[*]

Variable	HF Patients (N=24)	Control Patients (N=10)	*P Value*
Age, y	65.3±15.0	65.4±13.0	.79
Male sex,	20 (83)	6 (60)	.19
CAD	11 (46)	1 (10)	.06
Ischemic cardiomyopathy	10 (42)	0	.02
Hypertension	11 (46)	3 (30)	.46
Diabetes	9 (38)	1 (10)	.21
QRS duration, ms	172±24	103±23	<.001
LVEF, %	23.5±6.3	62.9±3.3	<.001
LVEDD, mm	66.6 ±9.9	48.6±2.7	<.001
ACEI/ARB	16 (67)	0	<.001
β-Blocker	18 (75)	5 (50)	.23
Digoxin	7 (29)	0	.08
Statin	14 (58)	0	.002

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CAD, coronary artery disease; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction.

[*] Values are number (percentage) or mean±standard error of the mean unless indicated otherwise.

Table 2

Comparison of Clinical Parameters Before and After CRT[*]

Variable	Control N=10	Pre-CRT N=24	Post-CRT N=24	*P Value* Pre vs. Post
NYHA class, grade	1.0±0	2.7±0.4	2.1±0.6	<.03
LVEF, %	62.9±3.3	23.5±6.3	32.0±8.6	<.001
LVEDD, mm	48.6±2.7	66.6±9.9	64.9±10.6	.15
Mitral regurgitation, grade	1.7±0.6	2.3±0.6	2.0±0.6	<.01
Pulmonary artery systolic pressure, mm Hg	30.6±4.7	43.02±12.6	38.2±11.6	<.01

Abbreviations: LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[*] Values are mean±standard error of the mean unless indicated otherwise.