ISSN 2616-5791 Vol.5, Issue 8: 33-39, DOI: 10.25236/AJMHS.2024.050806

Diagnostic Role of Metabolomics in Acute Aortic Dissection: Overview

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Abstract: *Acute aortic dissection (AAD) is a severe and often fatal cardiovascular emergency with a high mortality rate. Nevertheless, the specific mechanisms underlying AAD occurrence and development remain unclear, resulting in delayed diagnosis and the absence of a definitive biomarker for the disease. In recent years, the rapid advancement of high-throughput omics detection technologies has opened up new avenues for investigating the mechanism behind AAD from various aspects. Metabolomics, which has emerged after genomics, transcriptomics, and proteomics, has been applied to elucidate the pathogenesis and identify biomarkers for AAD. Metabolomics studies have revealed significant associations between AAD occurrence and succinate metabolism, lipid metabolism, and levels of trimethylamine oxidation (TMAO). This article aims to review the diagnostic potential of metabolomics in preventing and managing AAD, highlighting its role in precision diagnosis and treatment.*

Keywords: *Acute aortic dissection, Metabolomics, Metabolites, Mechanism, Biomarker*

1. Introduction

Acute aortic dissection (AAD) occurs when the aortic intima ruptures, causing separation of the true and false lumen of the aortic wall due to blood rushing into the media, resulting in distalization of the aortic wall with the circulating blood pressure[1]. Within 48 hours of onset, AAD patients face a 1% increase in the risk of death per hour without intervention [2], and the mortality rate reaches 30% within 3 years of diagnosis[3]. Despite being a severe and often fatal cardiovascular disease, AAD lacks specific biomarkers for early diagnosis, and its early clinical symptoms are atypical. As a result, patients often miss the optimal treatment window and may experience aortic rupture or other severe complications. Shockingly, up to 39% of AAD cases are only diagnosed during autopsy[4, 5]. Currently, the diagnosis of AAD primarily relies on a single imaging modality. However, these methods have limitations. Computed tomography angiography (CTA) is restricted by ionizing radiation and the potential nephrotoxicity of contrast agents[6]. Transesophageal echocardiography (TEE) is relatively invasive and has limited imaging capabilities[7]. Therefore, there is a need to identify a safe, effective, highly sensitive, and specific non-invasive detection method for the prevention and treatment of AAD. Recent studies have demonstrated altered levels of metabolites, such as total cholesterol, high-density lipoprotein cholesterol[8, 9], and homocysteine[10], in patients with AAD. The rapid advancement of metabolomics research provides an opportunity to detect metabolism-related biomarkers and offers new insights into the diagnosis and treatment of AAD[11]. This article aims to review the diagnostic potential of metabolomics in AAD and further explore the relationship between metabolomics and aortic dissection.

2. Methods or methodology to apply metabolomics in AAD

Human diseases are often the result of complex interactions between multiple genes and environmental factors. These pathological conditions typically coincide with changes in metabolites within the body. In recent years, there has been a surge in high-throughput molecular biotechnology, leading to an increase in omics research. Among these omics disciplines, metabolomics is particularly

ISSN 2616-5791 Vol.5, Issue 8: 33-39, DOI: 10.25236/AJMHS.2024.050806

sensitive to environmental influences and can provide real-time insights into the pathophysiological processes of diseases[12, 13]. It uncovers potential pathogenic targets and biomarkers for early disease detection and development, which may go unnoticed through conventional methods. Metabolomics can be categorized into untargeted metabolomics and targeted metabolomics. Untargeted metabolomics investigates all metabolite components in biological samples to explore clinical hypotheses. On the other hand, targeted metabolomics focuses on detecting specific metabolic substances, primarily used for metabolic pathway analysis and result verification. There are three commonly employed mass spectrometry-based techniques in metabolomics(Table 1): Gas Chromatography-Mass Spectrometry (GC-MS), Liquid Chromatography-Mass Spectrometry (LC-MS), and Mass spectrometry imaging (MSI). Additionally, Nuclear Magnetic Resonance spectroscopy (NMR spectroscopy) is another widely used detection technique for metabolomics. These techniques enable the detection of various metabolites in the body, while subsequent bioinformatics analysis provides a comprehensive and systematic understanding of their changes.

3. Sample selection in AAD metabolomics

Adequate and rational experimental design plays a pivotal role in metabolomics research. Various factors such as sample selection, sample pretreatment, utilization of MS and NMR detection methods, enrollment conditions, and adherence to standard operating procedures significantly influence the outcomes of metabolomics experiments.

Metabolomics research involves the analysis of various biological samples, including biological fluids (such as serum, urine, bronchoalveolar lavage fluid, cerebrospinal fluid, and saliva), as well as tissues or cells obtained from biopsies. Blood and urine are the most commonly used biological samples in metabolomics research due to their ease of collection and less invasive nature, allowing for the assessment of overall metabolic profiles in a biological system[14]. In AAD metabolomics research, blood samples are predominantly utilized due to their convenient and standardized collection methods[15-19]. It mainly involves related factors such as inflammation, cell signaling transduction, coagulation, and fibrinolysis. Blood samples encompass two main forms, serum and plasma, which are widely employed in metabolomics studies. The choice between the two remains a topic of ongoing debate.Plasma has the advantage of shorter processing time than serum because it does not have to wait for blood to agglutinate. In addition, coagulation time, room temperature during operation, and production and release of compounds such as peptides during agglutination are additional variables that affect the accuracy of the experiment, so plasma is preferred for metabolite analysis[20]. At the same time, however, some researchers[21] proposed that the preservation of plasma samples involves heparin, citric acid and Ethylene Diamine Tetraacetic Acid (EDTA), because some co-eluted polar metabolites will cause interference and serious matrix effects. Compared with serum samples, the application of serum samples in the metabolomics study of AAD is more advantageous. Urine samples and aortic tissue samples are less commonly employed in metabolomics research for AAD. However, urine samples can be valuable for studying AAD complicated with acute kidney injury and renal artery involvement. On the other hand, aortic tissue samples are mainly used to investigate the differences and distinctions between aortic aneurysm and aortic dissection[22].

Currently, thousands of metabolites have been identified or predicted. Due to the diverse characteristics of metabolites, such as molecular weight, polarity, and concentration, no single detection technology can comprehensively determine all metabolites in a sample. Nuclear Magnetic Resonance (NMR) is a low-cost method for metabolite analysis. It allows for quantitative analysis and provides precise structural information. Moreover, NMR is non-invasive and can be repeated with biological samples. However, its disadvantage lies in its lower sensitivity compared to mass spectrometry (MS). NMR is limited to detecting metabolites with high abundance[23], which poses challenges in leveraging it for biomarker discovery in AAD metabolomics research. Conversely, the combination of MS technology and GC/LC enables higher sensitivity and better detection of low-abundance metabolites. Both GC-MS and LC-MS have their advantages and disadvantages. GC-MS provides excellent separation and high detection sensitivity. It also includes a searchable metabolite database, which makes qualitative analysis relatively easy. But most of the sample processing in the early stage requires derivatization. LC-MS offers a wider detection range and higher sensitivity without the need for derivatization. At present, both GC-MS and LC-MS are widely used in metabolomics research on cardiovascular diseases[24, 25].

ISSN 2616-5791 Vol.5, Issue 8: 33-39, DOI: 10.25236/AJMHS.2024.050806

4. Application of metabolomics in AAD

4.1 Other biomarkers of omics

There are many kinds of markers in human blood, but there is no clear laboratory index that can be used as the prediction and diagnosis of AAD. C-reactive protein, matrix metalloproteinase 9(MMP9) and monocyte chemotactic protein 1 (MCP-1) are all common clinical inflammatory markers. Research conducted by Liu Jian demonstrated that the combined use of these three markers showed promising results in high sensitivity and specificity for diagnosing AAD and its complication of acute lung injury[26]. Nevertheless, further validation is required to establish their diagnostic value. In recent years, multi-omics studies have also investigated potential diagnostic markers for AAD, focusing on genes, non-coding RNA, and other factors. For instance, Tugce et al. examined the expression profiles of hsa-miRNA-143-3p and hsa-miRNA-22-3p in patients with type AAD, aortic aneurysm, and healthy individuals. They analyzed 28 serum samples from 9 AAD patients, 9 aortic aneurysm patients, and 10 healthy individuals. Differential targets were identified using bioinformatics tools and then validated through qPCR. The results revealed that the expression levels of hsa-miRNA-143-3p and hsa-miRNA-22-3p were significantly higher in the aortic aneurysm group compared to the control group. However, no significant difference in expression was observed between the aortic dissection group and the control group. Additionally, the study found that the expression of KRAS, MAPK7, and MAPK14 was lower in the dissection group than in the control group, while the expression of the anticoagulant protein TAGLN was higher in the dissection group compared to the control group[27]. Some researchers analyzed the protein profiles in blood samples from patients with aortic dissection. They discovered that osteopontin (OPN) exhibited significantly higher expression in the plasma of dissection patients, while the levels of monocyte chemoattractant protein-1 (MCP-1) and MCP-2 were decreased. The ROC curve analysis indicated that OPN could serve as a diagnostic biomarker for aortic dissection, with a sensitivity of 92% and specificity of 99%. These findings suggest that these differentially expressed molecules may play a crucial role in the development of aortic dissection and hold promise as potential biomarkers[28].

4.2 Application of metabolomics

Metabolomics, as a post-genomics field, employs high-throughput analysis techniques and bioinformatics to study small molecular metabolites (with a molecular weight below 1500). Its goal is to characterize the metabolic changes occurring in organisms under non-physiological conditions, both qualitatively and quantitatively. An ideal biomarker for AAD should possess sensitivity, predictive ability, and cost-effectiveness and be easily accessible in biological samples. Such a biomarker can provide important information on disease severity, temporal patterns, progression, and clinical outcomes through reasonable experimental design and research methods.

Cui et al.[18] conducted a study using non-targeted metabolomics and MS analysis and discovered that the plasma level of succinic acid was significantly elevated in patients with AAD. This finding was further validated using targeted metabolomics in independent groups of AAD patients and healthy controls. Furthermore, the inhibition of the p38α-CREB-OGDH axis in macrophages, as well as knockdown of p38α, resulted in reduced phosphorylation of CREB, decreased expression of OGDH, lower succinate levels, and reduced expression of inflammatory cytokines in macrophages. By conducting a myeloid-specific knockout of p38α in mice, it was observed that the incidence of AAD was reduced, vascular dilation was alleviated, and vascular inflammation was reduced. Furthermore, intervention with succinate in the p38α myeloid-specific knockout mice reversed the reduction of AAD induced by p38α knockout. These findings suggest that succinic acid could serve as a supplementary indicator for the pre-hospital diagnosis of AAD patients, distinguishing them from acute myocardial infarction and pulmonary embolism. Additionally, targeting succinate-related pathways, such as reducing plasma succinate levels or inhibiting succinate-induced mitochondrial dysfunction, may hold potential as therapeutic strategies for AAD. In another study conducted by Yang et al.[19], non-targeted metabolomics analysis revealed a significant increase in the plasma level of C18 ceramide among patients with Thoracic Aortic Dissection (TAD). This finding was further validated through quantitative analysis in an independent cohort. The results indicate that disruptions in ceramide metabolism could contribute to aortic inflammation and play a crucial role in the development of TAD. These findings hold the potential to identify new targets for drug therapy and serve as a potential biomarker for TAD. In their investigation of serum metabolomic profiles, Zhou et al.[16] identified notable changes in lysophosphatidylcholine and sphingomyelin levels among patients with AAD. Specifically, several sphingomyelins, including sphinganine, phytosphinganine, and ceramide, were

ISSN 2616-5791 Vol.5, Issue 8: 33-39, DOI: 10.25236/AJMHS.2024.050806

significantly decreased in patients with Stanford type A AAD. These findings suggest that a combination of these two metabolite families may serve as potential biomarkers for diagnosing AAD and distinguishing between Stanford type A and Stanford type B AAD. In a study conducted by Zeng et al.[17], notable changes in metabolite levels were observed among AAD patients, particularly in the phosphatidylcholine metabolic pathway. Trimethylamine oxide (TMAO) levels were significantly elevated in AAD patients and were found to be associated with the severity of AAD. Conversely, the levels of carnitine, choline, and betaine were decreased. Studies[29] indicate that TMAO can directly activate inflammatory pathways, including the NF-κB signaling pathway, in human aortic endothelial cells and smooth muscle cells. Therefore, TMAO holds potential as a biomarker for AAD diagnosis and evaluation. On the other hand, betaine has been shown to possess anti-inflammatory properties in various diseases. It regulates the body's oxidative stress response through sulfur-containing amino acids, inhibits the NF-κB signaling pathway, and suppresses the activation of the NLRP3 inflammasome. Betaine regulates energy metabolism, reduces endoplasmic reticulum stress, and diminishes apoptosis[30]. These findings suggest that betaine may play a negative regulatory role in the development of AAD. Ren et al.[15] employed High-Performance Liquid Chromatography (HPLC-MS) to measure the levels of N1-acetyl-N2-formyl-5-methoxykynurenine (AFMK), glycerophosphocholine, and ergothionine in the peripheral blood of AD patients. The levels of these metabolites were more than 50 times higher in AD patients compared to normal individuals, indicating their potential as specific and sensitive markers for early AD diagnosis. Furthermore, AFMK, an oxidation product of melatonin, demonstrated the ability to inhibit the production of proinflammatory cytokines[31]. The finding suggests that AFMK may play a protective regulatory role in mitigating dysregulated inflammatory responses associated with AAD[32].

Marfan syndrome (MFS), a hereditary connective tissue disorder, increases the risk of aortic dissection in affected patients. Bartenbach et al. [33]conducted a targeted metabolomics study to analyze the amino acid and lipid metabolic pathways in MFS patients. They discovered low levels of serum taurine and histidine, with taurine levels being correlated with disease severity. These differential metabolites can potentially serve as early markers for diagnosing MFS and preventing aortic dissection. Recent studies[34] have identified that elevated levels of interleukin 6 (IL-6) (>108 pg/ml) and D-dimer (>14.0 μg/ml) are highly indicative of early poor prognosis in acute Stanford type A aortic dissection. Furthermore, a D-dimer level of ≥5.9 mg/L is associated with in-hospital mortality in these patients[35]. However, at present, D-dimer is only used for the risk assessment of patients with aortic dissection and cannot be used as the gold standard for diagnosis. As is shown in Table 1.

Table 1: Three mass spectrometry-based metabolomics techniques

Detection technique	Advantages	Disadvantages
GC-MS[36-38]	1. Mature technology 2. The price is relatively cheap 3. Good analytical reproducibility 4. Suitable for the detection of volatile metabolites 5. Public databases are helpful for metabolite identification	1. Sample pretreatment requires derivatization 2. Sample analysis takes a long time 3. Difficulty in detecting unknown compounds
LC-MS[39, 40]	1. High sensitivity 2. Sample pretreatment process is simple 3. Wide coverage of metabolite detection 4. Short sample analysis time	The price is relatively expensive
MSI[41, 42]	1. High throughput separation of isomeric and allogenic substances 2. In situ imaging can be performed with the help of ionization technology 3. The location information of metabolites can be provided	1. Sample analysis takes a long time 2. The imaging quality is affected by the resolution
NMR spectroscopy [43-45]	1.There is no need for complex pre-treatment procedures such as sample preparation or fractional separation. 2. The required detection time is short. 3. It can be used to elucidate the dynamics and mechanisms of metabolite transformation and to explore metabolic pathways.	1.Low sensitivity. 2. The price is relatively expensive.

In summary, there are significant differences in metabolites between patients with aortic dissection and the normal group, which can be identified through metabolomics research methods. Metabolomics

ISSN 2616-5791 Vol.5, Issue 8: 33-39, DOI: 10.25236/AJMHS.2024.050806

studies have further revealed the involvement of succinic acid metabolism, abnormal lipid metabolism, and D-dimer in the occurrence and progression of aortic dissection. These findings show promising applications in early diagnosis, understanding disease development, identifying therapeutic targets, and unveiling the underlying mechanisms.

5. Conclusion and prospect

The diagnosis of AAD relies solely on imaging evidence and lacks specific and sensitive biomarkers. Metabolomics is a rapidly developing research technology that focuses on identifying differential metabolites and exploring changes in metabolic pathways. By analyzing the changes in endogenous metabolites in AAD patients compared to a control group using MS or NMR technology, it is possible to screen for differential metabolites that can provide valuable insights for the diagnosis and treatment of AAD.

Metabolomics-based AAD research is still in the early stages, with limited studies available for reference. The application of biomarkers for aortic dissection in clinical practice is hindered by cost, diagnostic interval, and testing conditions. The clinical utility and reliability of biomarkers such as succinate, lipid metabolites, and TMAO still require further validation in future studies. Early screening and diagnosis based on metabolomics for AAD pose significant challenges. It may be necessary to integrate multiple omics technologies, including metabolomics, to explore the pathogenesis and metabolic processes of AAD and identify potential therapeutic targets.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

FL and KL involved in study design and drafting of the manuscript. YL revised the manuscript. YC and LD reviewed and approved the manuscript. All authors contributed to the article and approved the submitted version. These authors contributed equally to this work and share first authorship.

Acknowledgement

Maoming City 2021 Science and Technology Innovation Strategy Special Fund Project of Guangdong Province (No.2021S0033) ;China Postdoctoral Science Foundation (No.2021M702780); This study was supported by grants from Guangdong Province major heart disease diagnosis and treatment engineering technology research center Program (2017).

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