Commentary

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Mitochondrial Dysfunction in Vascular Diseases: Recent Insights Into Arterial and Venous Pathologies

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Introduction

Mitochondrial dysfunction (MD) is characterized by impaired ATP production, elevated oxidative stress, loss of mitochondrial membrane potential (MMP), and systemic metabolic disturbances. Recently, the link between MD and vascular pathologies has gained significant research attention, particularly regarding its impact on endothelial cells, vascular smooth muscle cells, and circulating blood cells. In endothelial cells, MD can be triggered by various factors, including insulin resistance [1], hypoxia [2], particulate matter [3], as well as aging, chronic inflammation, physical inactivity, and antioxidant deficiency [4]. Given that cardiovascular diseases (CVD) remain a leading cause of global morbidity and mortality [5], MD has emerged as a promising target for therapeutic and preventive strategies [6]. This has spurred extensive research across population-based, molecular, bioinformatic, and biophysical fields. This commentary covers peer-reviewed studies published in English over the past five years (with the exception of an article [5] mentioned earlier), focusing on the mechanistic links between MD and both arterial and venous diseases.

Arterial Diseases

Arterial diseases represent a major global healthcare challenge due to their substantial morbidity and mortality. To elucidate the underlying pathophysiological mechanisms, researchers employ diverse methodologies, including animal models, human biopsy analysis, and *in silico* modeling. Highlighted below are studies focusing on mitochondrial function or incorporating MD as one of the research approaches.

Atherosclerotic lesions represent the most prevalent pathology in arterial diseases and are frequently studied using mouse models such as *ApoM-/-* mice combined with a high-fat diet (HFD). Utilizing this model, Shi *et al.* [7] demonstrated that a deficiency in Apolipoprotein M (ApoM)—a key protein component of high-density lipoproteins—induces mitochondrial impairment in aortic endothelial cells. Specifically, *ApoM-/-* mice exhibited mitochondrial swelling and reduced mitochondrial density compared to *ApoM+/+* controls, with these effects being further exacerbated by HFD. Furthermore, lipidomic analysis of HFD-fed *ApoM-/-* mice revealed elevated serum acylcarnitine levels—a marker of mitochondrial overload and incomplete fatty acid oxidation—alongside significant alterations in fatty acid metabolites in both liver tissue and serum. *In vitro* experiments using EA.hy926 cells showed that ApoM overexpression preserves mitochondrial integrity by enhancing autophagy. Conversely, exposing EA.hy926 cells to the supernatant of ApoM-deficient cells increased mitochondrial oxidative stress (assessed via MMP-sensitive dyes), an effect mitigated by autophagy agonists. Notably, oxygen consumption rate analysis yielded complex results: ApoM-overexpressing cells showed decreased basal respiration, substrate oxidation, and ATP production, while non-mitochondrial oxygen consumption increased—findings the authors attributed to specific cell-line characteristics. Collectively, these data suggest that ApoM exerts an atheroprotective effect by maintaining mitochondrial function through the autophagic pathway.

Beyond metabolic dysregulation, chronic hypertension is a critical driver of atherosclerotic progression. Recently, Li *et al.* [8] investigated mitophagy in vascular smooth muscle cells using the Spontaneously Hypertensive Rat (SHR) model. RNA-Seq analysis of the thoracic aorta in SHR versus Wistar-Kyoto controls revealed significant enrichment of differentially expressed genes within the autophagy-lysosome signaling pathway, suggesting that mitophagy plays a pivotal role in hypertensive pathology. The study focused on Pink1 and LC3, key proteins in mitochondrial quality control and autophagosome formation. Western blot analysis confirmed the upregulation of *Pink1*, *Parkin*, and *LC3* in SHRs, indicating activated mitophagy. Notably, mitophagy inhibitors exerted a vasodilatory effect, while *Pink1* knockdown via shRNA attenuated vasoconstriction and reduced reactive oxygen species (ROS) production. These findings underscore the involvement of the Pink1-mediated mitophagy pathway in the vascular remodeling and oxidative stress associated with hypertension.

Table 1. Distinctive metabolic features of patients categorized by CAD status and CVD risk (comparison of the top five identified metabolic pathways) (adapted from Deidda *et al*., 2021 [12]).

Metabolic pathway	Association with mitochondrial function	CAD/high-RF*	CAD/low-RF	No-CAD/high-RF	No-CAD/low-RF
Glutathione metabolism	Glutathione neutralizes free radicals, protecting mitochondrial membranes and DNA from oxidation, participates in the synthesis of iron-sulfur clusters necessary for the respiratory chain, prevents the permeability of mitochondrial membranes and, as a consequence, cell apoptosis		+		
Amino sugar metabolism	Amino sugars modulate mitophagy and signal the mitochondria about the cell's need for energy	+			
Glycerolipid metabolism	Beta-cleavage of fatty acids and the synthesis of cardiolipin, a glycolipid essential for the respiratory chain and the final stages of synthesis of some glycerolipids, occur in the mitochondria; MD leads to the accumulation of lipid droplets		+	+	+
Urea cycle	The first two reactions of the cycle occur within the mitochondria; mitochondria are capable of capturing and detoxifying ammonia			+	
Methionine metabolism	Mitochondria supply the one-carbon fragments needed to produce methionine from homocysteine (methionine is necessary for the assembly of respiratory chain enzymes and reduces free radical production in the mitochondria)	+	+		+
Glycine/serine metabolism	The major part of the conversion of serine to glycine and the first step in the synthesis of heme from glycine occur in the mitochondria; mitochondria prevent toxic accumulation of glycine				+
Alanine metabolism	Mitochondrial enzymes in muscle convert pyruvate to alanine for safe transport to the liver, while alanine transferase (an enzyme found in the cytosol and mitochondria) converts alanine to pyruvate, which is used by the mitochondria for energy production	+		+	
Ammonia recycling	The urea cycle is initiated in the mitochondria; mitochondrial enzymes control the ammonia content in the cell and form its transport forms (glutamine)	+	+		
Transfer of acetyl groups into mitochondria	Provides the tricarboxylic acid cycle with Acetyl-CoA			+	+

* Risk factor.

In humans, carotid atherosclerosis, peripheral arterial disease (PAD) and coronary artery disease (CAD) are the most common forms of atherosclerosis. In 2025, Fu and Zhang [9] conducted an *in silico* study to identify diagnostic genes associated with both MD and the progression of human carotid atherosclerotic plaques. Through bioinformatic analysis of early- and late-stage plaque samples, four key genes were identified: *ALDH1B1*, *CRY1*, *EFHD1*, and *NIPSNAP3B*. Notably, the expression of these genes was significantly downregulated in advanced-stage lesions compared to early-stage atherosclerosis. These findings suggest that the suppression of these mitochondrial-related genes may serve as a potential mechanism driving plaque development and destabilization.

A four-week pilot study by Szarvas *et al.* [10] explored the impact of nicotinamide riboside supplementation—a potent NAD^+ precursor—on elderly patients with PAD. Preliminary results indicated improvements in endothelial function, cerebrovascular reactivity, and cognitive performance. As a critical metabolic cofactor, NAD^+ facilitates ATP production by coupling the tricarboxylic acid cycle with oxidative phosphorylation. Furthermore, via sirtuin activation, NAD^+ regulates mitochondrial dynamics, antioxidant defense, and metabolic adaptation. The authors believe that the observed effect was a consequence of improved mitochondrial function and normalization of NO production. These preliminary findings provide a rationale for large-scale clinical trials investigating nicotinamide riboside's potential to restore vascular function in PAD patients.

Additionally, Schoenherr *et al.* [11] published a protocol for a randomized controlled trial comparing conservative and interventional management of PAD-induced gastrocnemius muscle ischemia resulting from superficial femoral artery atherosclerosis. The conservative arm focuses on supervised systematic physical training, while the interventional arm involves surgical revascularization (e.g., angioplasty or femoropopliteal bypass grafting). A control group will consist of non-ischemic patients undergoing varicose vein (VV) surgery. The study aims to evaluate the restoration of mitochondrial function using high-resolution respirometry and citrate synthase activity assays in ischemic muscle biopsies (*in vitro*), alongside assessments of endothelial function. By prioritizing mitochondrial bioenergetics in muscle biopsies as a key outcome measure, the authors underscore its role as a critical determinant of therapeutic success in PAD.

An observational study by Deidda *et al.* (2021) [12], involving 241 participants, aimed to characterize the metabolomic profiles of patients categorized by CAD status and CVD risk levels. The cohort was stratified into four groups: (1) CAD present/high CVD risk; (2) CAD present/low CVD risk; (3) CAD absent/high CVD risk; and (4) CAD absent/low CVD risk. Utilizing gas chromatography-mass spectrometry followed by enrichment analysis, the five most enriched metabolic pathways for each group were identified. These pathways are primarily associated with mitochondrial function (Table 1, Ref. [12]).

The findings suggest that patients with CAD exhibit a more pronounced activation of the ammonia utilization system, whereas those without CAD show enrichment in pathways related to mitochondrial energy consumption. In individuals at high CVD risk, significant enrichment of the alanine metabolism pathway was observed; in a mitochondrial context, this may stem from alterations in both the urea cycle and energy production processes. Notably, the group with both high CVD risk and confirmed CAD demonstrated a more marked enrichment of the amino sugar metabolism pathway, potentially indicating impaired carbohydrate metabolism. Consequently, these results provide indirect evidence of an association between MD and both CAD and CVD risk, as reflected in the divergent enrichment of key metabolic pathways.

The quantification and structural integrity analysis of mitochondrial DNA (mtDNA) represent robust methods for assessing mitochondrial impairment. In the context of CAD, Campolo *et al.* [13] demonstrated a significant association between early-onset CAD and mitochondrial damage in peripheral blood cells. The study involved a cohort of 118 patients with early-onset CAD and 150 healthy controls. Utilizing quantitative PCR, the *MT-ND1* gene (representing a stable, non-deleted region of the mitochondrial genome), the remaining fragment after mtDNA 4977 bp deletion ($mtDNA^{4977}$) (Fig. 1), and *HBB* (nuclear genome) were amplified. By comparing the amplicon yield of these stable and deletion-prone regions, the authors identified a reduction in mtDNA copy number (mtDNA-cn) and an increased frequency of $mtDNA^{4977}$ deletions in patients with early-onset CAD compared to the control group.

Beyond the endothelial dysfunction associated with disease progression, surgical interventions can also induce proinflammatory and thrombogenic phenotypes. Specifically, coronary artery bypass grafting (CABG) triggers a marked increase in platelet activation and oxidative stress, particularly when involving extracorporeal circulation. A randomized controlled trial by Gąsecka *et al.* [14] investigated the efficacy of various aspirin dosing regimens following CABG. The study evaluated several parameters, including platelet mitochondrial oxygen consumption and whole-blood DNA base damage. The analysis showed no significant alterations in oxidative stress parameters, with the exception of a temporary decrease in platelet mitochondrial oxygen consumption one month postoperatively in patients receiving 75 mg of aspirin twice daily, compared to levels at seven days and three months post-CABG. The authors attributed discrepancies between these findings and their previous data—which suggested aspirin's efficacy in mitigating oxidative stress—to variations in measurement methodologies and treatment protocols. Consequently, the

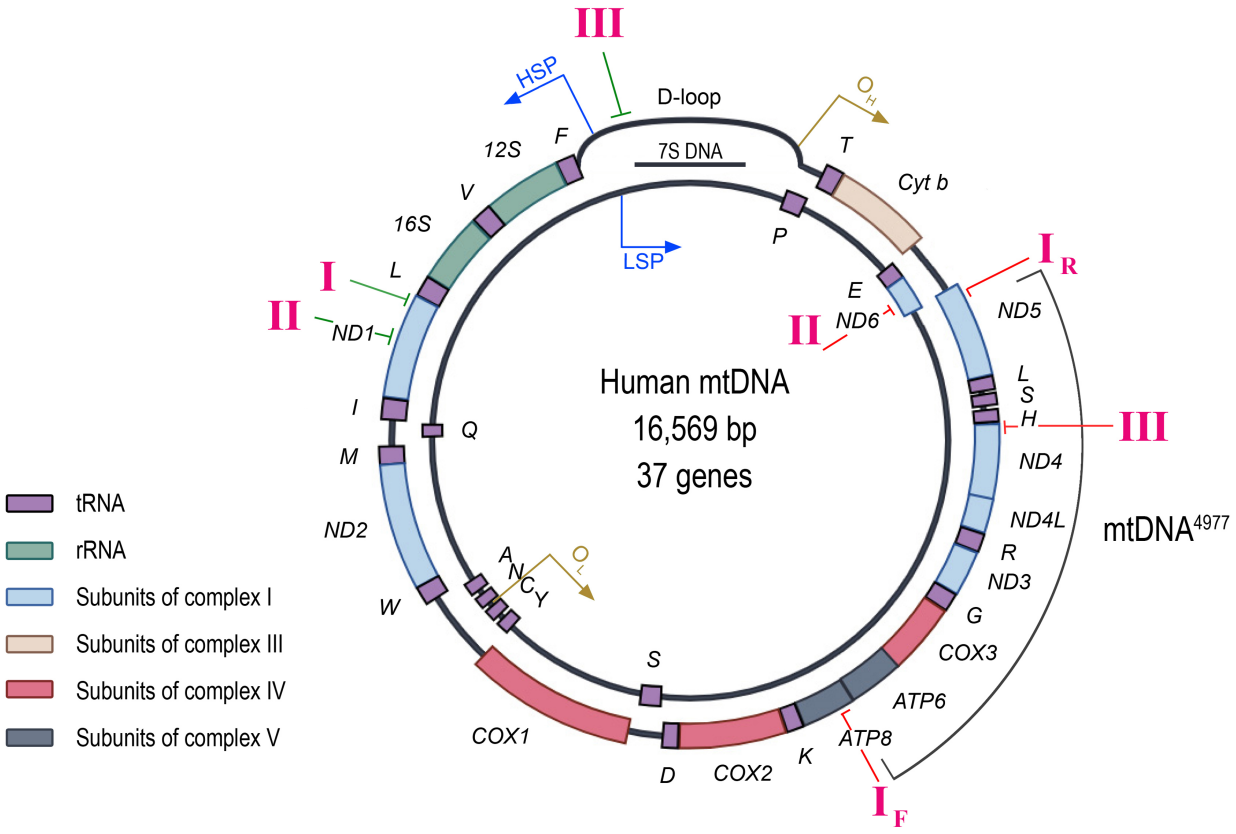

Fig. 1. Schematic representation of human mtDNA with indication of the primer systems used. The outer circle indicates the heavy (H-) strand, while the inner circle indicates the light (L-) strand. O_H, origin of H-strand synthesis; O_L, origin of L-strand synthesis; HSP, promoter for transcription of H-strand; LSP, promoter for transcription of L-strand; D-loop, displacement loop; 7S DNA, a short, single-stranded DNA molecule; rRNA, ribosomal RNA; ND, NADH dehydrogenase; COX, cytochrome C oxidase; ATP, ATP synthase; Cyt b, Cytochrome b; tRNAs (transfer RNA) for: F, Phenylalanine; V, Valine; L, Leucine; I, Isoleucine; Q, Glutamine; M, Methionine; W, Tryptophan; A, Alanine; N, Asparagine; C, Cysteine; Y, Tyrosine; S, Serine; D, Aspartic acid; K, Lysine; G, Glycine; R, Arginine; H, Histidine; E, Glutamic acid, T, Threonine; P, Proline; The primer systems used in the studies discussed in this commentary are marked with Roman numerals: I—Campolo *et al.* (2025) [13] (I_F/I_R—forward/reverse primers; the system detects a deletion), II—Nymberg *et al.* (2021) [15], III—Smetanina *et al.* (2022) [16] (to be discussed below in the text); mtDNA^{4977}—mtDNA 4977 bp deletion region; red indicators point to the location of the target site for integrity assessment, and green indicators point to the location of the target site for mtDNA copy number assessment. Visualization was prepared using Adobe Photoshop CS, version 8.0, Adobe Systems Inc., San Jose, CA, USA.

observed alterations in oxidative stress were deemed clinically insignificant.

Venous Pathologies

Venous pathologies are highly prevalent; however, mitochondrial dysfunction in this context remains less explored than in other cardiovascular disorders. Nevertheless, several significant studies have emerged over the past five years. The above-mentioned methodology for assessing mtDNA quantity and quality via PCR-based analysis has traction due to their cost-effectiveness, simplicity, and interpretability. In 2021, Nymberg *et al.* [15] reported a population-based cohort study designed to evaluate the association between whole-blood mtDNA-cn and the risk of venous thromboembolism (VTE). Following 2117 women (aged 50–60 years) from southern Sweden over five years, 87 VTE cases were identified. Using droplet digital PCR targeting mitochondrial genes (*MT-ND1*, *MT-ND6*) (Fig. 1) and nuclear reference genes (*EIF2C1*, *RPP30*), no significant correlation between mtDNA-cn and VTE risk (hazard ratio near unity) was found. Consequently, the authors concluded that while mtDNA-cn is relevant in other cardiovascular contexts, it does not serve as a viable marker for VTE.

A little later, Smetanina *et al.* [16] investigated content and integrity of mtDNA in VVs using an optimized droplet digital PCR approach. By targeting the D-loop

(a low-deletion region) and *MT-ND4* (a frequent deletion site) (Fig. 1) relative to the nuclear *LINE-1* sequence, they demonstrated reduced mtDNA content and impaired mtDNA integrity in VV segments compared to healthy paired segments. A decrease in mtDNA-cn was specifically shown in the medial layer of the vein wall. Beyond PCR analysis, intravital staining with membrane potential-sensitive dyes revealed diminished MMP in both endothelial and smooth muscle cells within varicose-transformed segments.

In 2025, Rațiu *et al.* [17] provided indirect evidence for the role of mitochondrial function in mitigating oxidative stress in VVs. Their *ex vivo* experiments showed that acute vitamin D treatment significantly reduced ROS in VV tissue from both obese and non-obese individuals. Given that vitamin D lacks direct H_2O_2-scavenging properties, the authors proposed that its antioxidative effect stems from improved mitochondrial efficiency, including enhanced oxidative phosphorylation, reduced electron leakage, and upregulated antioxidant defenses.

In the same year, Tan *et al.* [18] integrated DNA methylation, gene expression, and proteomic datasets to identify mitochondrial genes associated with reduced VV risk. Key candidates included *HADHA*, *BCL2L1*, and *PARK7*. *HADHA* encodes a subunit of the mitochondrial trifunctional protein involved in fatty acid β-oxidation; *BCL2L1* regulates mitochondrial membrane potential and channel opening; and *PARK7* acts as an oxidative stress sensor. Collectively, these findings indicate the contribution of mitochondrial functional alterations to the pathogenesis of venous disease.

Conclusions

In summary, recent works highlight MD as a pivotal factor in the pathogenesis of both arterial and venous disorders. Alterations in mtDNA integrity, copy number, mitochondrial biogenesis, and metabolic flux contribute significantly to vascular wall remodeling.

Venous mitochondrial biology remains critically understudied. While cutting-edge methodologies have provided substantial insights into the nature of these vascular pathologies, data obtained from arterial models cannot be directly extrapolated to the venous system due to distinct vessel morphologies, hemodynamics, and functional profiles. To further advance the field, a focus on characterizing mitochondrial dynamics—specifically fission/fusion, trafficking, and spatial distribution—appears warranted to better elucidate intracellular events driving disease initiation and progression. Furthermore, tissue-specific mtDNA methylation, which potentially regulates genome integrity and copy number, represents a critical knowledge gap within cardiovascular medicine.

Leveraging high-throughput data offers a powerful pathway forward. Extant bioinformatic datasets on differentially expressed genes may be utilized to model mitochondrial behavior across diverse physiological conditions. Additionally, while metabolomic analysis remains resource-intensive, it provides an indirect assessment of mitochondrial metabolic status. Ultimately, establishing precise cause-and-effect relationships and deciphering the compensatory mechanisms of mitochondria in CVD is essential. A discussion of literature data from the past five years underscores that considering these mitochondrial pathways offers promising avenues for the development of novel diagnostic biomarkers and targeted antioxidant therapies in vascular medicine.

Abbreviations

MD, mitochondrial dysfunction; MMP, mitochondrial membrane potential; CVD, cardiovascular diseases; HFD, high-fat diet; SHR, Spontaneously Hypertensive Rat; ROS, reactive oxygen species; PAD, peripheral arterial disease; CAD, coronary artery disease; VV(s), varicose vein(s); mtDNA, mitochondrial DNA; mtDNA-cn, mtDNA copy number; CABG, coronary artery bypass grafting; VTE, venous thromboembolism.

Availability of Data and Materials

All data analyzed during this study are included in this published article.

Author Contributions

Conceptualization, MAS, MLF, and VAK; original draft preparation and editing, VAK and MAS; visualization, VAK; supervision, MAS. Each author (VAK, MLF, and MAS) has participated sufficiently in this work of drafting the article or revising the article for the important rational content. All authors read and approved the final manuscript. All authors have also agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

The grammatical and stylistic editing of this manuscript was assisted by the Gemini large language model developed by Google LLC (Mountain View, California, USA, 2026). After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

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