Hypertension remains an important modifiable risk factor for cardiovascular disease, associated with increased morbidity and mortality. Deciphering the mechanisms involved in the pathogenesis of hypertension is critical, as its prevalence continues increasing worldwide. Mitochondria, the primary cellular energy producers, are numerous in parenchymal cells of the heart, kidney, and brain, major target organs in hypertension. These membrane-bound organelles not only maintain cellular respiration but also modulate several functions of the cell including proliferation, apoptosis, generation of reactive oxygen species, and intracellular calcium homeostasis. Therefore, mitochondrial damage and dysfunction compromise overall cell functioning. In recent years, significant advances increased our understanding of mitochondrial morphology, bioenergetics, and homeostasis, and in turn of their role in several diseases, so that mitochondrial abnormalities and dysfunction have been identified in experimental models of hypertension. In this review, we summarize current knowledge of the contribution of dysfunctional mitochondria to the pathophysiology of hypertension-induced cardiac damage, as well as available evidence of mitochondrial injury-induced damage in other organs. Finally, we discuss the capability of antihypertensive therapy to ameliorate hypertensive mitochondrial injury, and the potential position of mitochondria as therapeutic targets in patients with hypertension.

**Keywords**
Mitochondria • Hypertension • Blood pressure

**Introduction**
Hypertension is a chronic medical condition that affects ~1 billion people worldwide, and is estimated to continue increasing. Elevated blood pressure inflicts long-term damage in the heart and other organs, which might be associated with potentially life-threatening complications, and often starts at the cellular and subcellular levels.

In order to satisfy its high-energy demands, the cardiac cells have high numbers of mitochondria, intracellular organelles present in almost all eukaryotic cells. Unlike other organelles, two distinct (outer and inner) membranes divide the mitochondria into two compartments, the intermembrane space and the matrix (Figure 1A). While the outer bilayer lipid membrane is freely permeable to small molecules, the inner membrane is permeable only to oxygen, carbon dioxide, and water. The inner membrane houses the complexes of the electron transport chain (ETC) system and carriers for anions, and is formed as folds (cristae) that increase its total surface area. The intermembrane space is involved in oxidative phosphorylation, while the matrix contains mitochondrial DNA (mtDNA) and enzymes catalyzing the citric acid cycle.2

The primary function of the mitochondria is production of energy in the form of adenosine triphosphate (ATP). Furthermore, mitochondria mediate cell survival and death (apoptosis), regulate generation of reactive oxygen species (ROS) for cellular signalling, modulate intracellular calcium homeostasis, and participate in thermogenesis.3 Therefore, mitochondrial damage and dysfunction can have a profound impact on overall cellular functioning.

Myocardial mitochondria are vulnerable to the effects of hypertension, which most commonly impairs mitochondrial structure, bioenergetics, or homeostasis. Although antihypertensive drugs have the capacity to attenuate mitochondrial injury secondary to hypertension, drugs that specifically target the mitochondria may prove more efficacious in ameliorating hypertensive mitochondrial dysfunction or end-organ damage. This review aims to summarize the current available evidence of myocardial mitochondrial injury in hypertension, and the potential role of mitochondria as therapeutic targets in hypertensive subjects.
Characteristics and mechanisms of mitochondrial abnormalities and dysfunction

Structural mitochondrial alterations secondary to hypertension may include decreased mass and density, swelling, as well as cristae remodelling, fragmentation, or loss. Decreased mitochondrial mass and density has ramifications for mitochondrial function, as fewer and smaller-sized mitochondria compromise their oxidative capacity and energy production. Osmotic swelling of the matrix space is frequently secondary to ultrastructural changes in the inner mitochondrial membrane, which loses its tubular invaginations. As swelling progresses, cristae are retracted and eventually disappear, jeopardizing the stability of the ETC complexes.

Hypertension has been prominently associated with damage and loss of cardiolipin, a phospholipid uniquely found in the inner mitochondrial membrane and necessary for proper cristae formation. Staining cardiac cross-sections with nonyl-acridine-orange reveals decreased cardiolipin content in hypertensive animals (Figure 1B). Importantly, cardiolipin interacts with complexes I, III, and IV, favouring...
their assembly in high-order structures (supercomplexes), and sustaining the activity of the ETC. Its unique structure (non-bilayer forming phospholipids) creates a high mitochondrial membrane potential increasing ATPase synthase activity. Furthermore, cardiolipin regulates mitochondrial dynamics and prevents the formation and opening of the mitochondrial permeability transition pore (mPTP), and release of cytochrome c from mitochondria to the cytosol where it triggers apoptosis.7

Hypertension-induced mitochondrial structural abnormalities are often accompanied by alterations in mitochondrial metabolic and bioenergetic functions, including decreased respiration and ATP production and increased production of ROS. Decreased ETC activity and ATP production diminishes vital cellular functions and increases mitochondrial ROS production. Importantly, mtDNA is particularly sensitive to oxidative damage, due to the lack of histone, telomeres, and defence mechanisms.8 Likewise, cardiolipin is susceptible to oxidative damage due to its proximity to sites of ROS generation.6 Thus, ROS-induced mtDNA mutations and cardiolipin peroxidation constitute important causes of mitochondrial dysfunction and decreased ETC activity.9,10 Oxidized cardiolipin also sensitizes mitochondria to calcium, which triggers mPTP opening and apoptosis. Furthermore, increased ROS decreases mitochondrial membrane fluidity and energy production, creating a vicious cycle of oxidative damage. Under normal circumstances, mitochondrial ROS are scavenged by superoxide dismutase (SOD)-1 and -2, located between the mitochondrial membranes and in the mitochondrial matrix, respectively.11 Therefore, mitochondrial damage may result from an imbalance between ROS generation and antioxidant defences.

Alterations of mitochondrial homeostasis, which have been observed in experimental models of hypertension, affect three major cellular processes: biogenesis, dynamics, and mitophagy. Biogenesis, the process by which new mitochondria are formed, comprises a network of transcription factors that regulate the expression of mitochondrial proteins, modulating their function.12 Furthermore, mitochondrial biogenesis increases cellular aerobic metabolic capacity and attenuates inflammation and oxidative stress by upregulating antioxidant and anti-inflammatory mediators.13 Mitochondrial dynamics encompasses two major pathways that remain in equilibrium under normal circumstances: fusion that promotes formation of long filamentous mitochondria, and fission (fragmentation) that generates small spherical mitochondria.14 Importantly, mitochondrial dynamics regulate key cellular processes including generation of ATP and ROS, apoptosis, and calcium homeostasis.15 Finally, mitophagy, autophagic degradation of mitochondria, acts as a quality-control program.16 Therefore, downregulation of mitochondrial biogenesis, a shift towards fission, and upregulation of mitophagy in hypertension may severely compromise cell energy production.

Cardiac mitochondrial damage in experimental hypertension

Intriguing insights into the contribution of mitochondria to the development of hypertension may be gleaned from studies assessing cardiac mitochondria in experimental models of hypertension and heart failure (Table 1). These studies provide evidence of hypertension-induced mitochondrial structural and functional abnormalities, including alterations of biogenesis and dynamics, renin angiotensin aldosterone system (RAAS)-induced mitochondrial damage, ROS overproduction, apoptosis, and mtDNA mutations (Figure 2A).

For example, despite similar volume, cardiac mitochondria from hypertensive rats are disorganized and show reduced number of cristae.17 Cardiac mitochondria are normally in continuous interaction with the sarcoplasmic reticulum and sarcromeric structures forming ‘intracellular energetic units’ to allow optimal energy transfer, thus alterations in mitochondrial arrangement may impair muscle power and contractile function.18 Mitochondrial structural changes are also accompanied by reduced mitochondrial respiration, disclosed by decreased complex-I activity. The notion that mitochondrial damage compromises cardiomyocyte contractility suggests a possible role of mitochondria in the development of hypertension-induced cardiac dysfunction. Conversely, extracellular matrix expansion and fibrosis secondary to hypertension may directly contribute to structural mitochondrial abnormalities and contractile dysfunction.19 Therefore, despite the link between damaged mitochondria and hypertensive heart disease, a cause–effect relationship remains to be established.

Alterations in myocardial mitochondrial biogenesis and dynamics have been frequently reported in hypertensive animals. Both peroxisome proliferator-activated receptor (PPAR)-α and -γ co-activator

Table 1  Evidence of myocardial myocyte mitochondrial damage in hypertension

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(PGC)-1α are expressed in the myocardium and provide transcriptional regulation of cardiac metabolism and function. Likewise, mitochondrial fusion is essential for normal cardiac respiratory and contractile function. In Dahl salt-sensitive rats, decreased myocardial mitochondrial mass and fatty acid oxidation are accompanied by downregulation of genes involved in mitochondrial biogenesis like PPAR-α and estrogen-related receptor-α pathways. Moreover, mRNA levels of the fusion proteins mitofusin-1 and -2, and optic atrophy-1 were decreased in hypertensive rats, suggesting a shift towards increased mitochondrial fragmentation. Defects in mitochondrial biogenesis and dynamics might thus impair intracellular organization, interfering with energetic coupling between mitochondria and the sarcoplasmic reticulum-ATPase.

In line with these observations, we have shown in pigs that renovascular hypertension leads to cardiac diastolic dysfunction and myocardial hypoxia, inflammation, oxidative stress, and apoptosis. These
observations were associated with decreased mitochondrial biogenesis, evidenced by downregulation of PPAR-α, as well as PGC-1α and its receptor guanine adenine-binding protein. Decreased expression of PGC-1α and disparities in mitochondrial dynamics have also been reported in cardiac left ventricular (LV) mitochondria from spontaneously hypertensive rats (SHRs) accompanied by decreased expression of sirtuin-1 and 5′ AMP-activated protein kinase,24 which protect from myocardial hypertrophy and hypertension. Furthermore, hypertensive rats exhibited reduced enzyme activities and expression of ETC subunits, indicating that mitochondrial function and remodelling are compromised in hypertension-induced myocardial hypertrophy. However, whether mitochondrial alterations are the primary cause or downstream consequence of hypertensive myocardial injury remains obscure.

Increasing evidence supports the notion that cardiac mitochondrial abnormalities in hypertension might be mediated by RAAS activation. Renin-induced cardiac dysfunction in rats is accompanied by impaired mitochondrial density and structure, disclosed by degenerative, swollen mitochondria, and cardiomyocytes that manifest typical features of apoptosis (membrane blebbing, nuclear changes, and dense chromatin areas).25 Furthermore, complex-III, ATP synthase, and creatine kinase activity are reduced in hypertensive heart mitochondria, while cytochrome c release and caspase-3 expression are upregulated, implying stimulated apoptosis. These observations may implicate the RAAS in regulation of mitochondrial function in hypertension.

Generation of mitochondrial ROS has been also implicated in the pathogenesis of hypertensive heart disease. Hypertension induced by unilateral nephrectomy in mice increases cell and cytosolic nicotinamide-adenine-dinucleotide phosphate (NADPH)-oxidase level and mitochondrial ROS overproduction, associated with systolic heart dysfunction, suggesting that hypertension leads to mitochondrial damage.26 Conversely, NADPH oxidase is involved in aortic superoxide production in deoxycorticosterone acetate (DOCA)-salt hypertensive rats, and its inhibition attenuates systolic blood pressure, suggesting that mitochondrial ROS also contribute to the development of hypertension.27 Importantly, in a model of pressure overload, increased generation of mitochondrial ROS in the rat LV leads to cardiac fibrosis and dysfunction.28

An additional observation linking mitochondrial dysfunction with hypertension is mitochondria-dependent apoptosis. Apoptosis is an important contributor to progressive LV dysfunction, as opening of the mPTP eventuates in induction of caspase-3 and -9. In agreement, apoptotic signals and myocardial expression of bcl-2-associated-X-protein, cytochrome c, and activated caspase-8 and -9, are all increased in SHR.29 In neonatal rat cardiomyocytes, mechanical stretch induces mitochondria-dependent apoptosis via proapoptotic molecules of Bcl-2 family proteins, which can be prevented by mPTP blockade.30

Cardiomyocyte apoptosis is considered an essential process in the progression to heart failure, commonly found in human myocardial infarcts.31 Transgenic mice expressing a conditionally active myocardial caspase exclusively show lower myocyte apoptosis and heart failure, implicating apoptosis as a causal mechanism of heart failure.32 Apoptosis may alternatively be a consequence of heart disease, as myocardial oxidative stress activates the intrinsic apoptotic pathway by promoting mitochondrial outer membrane permeabilization.33 However, although commonly considered pathological, apoptosis also prevents necrotic cell death and inflammation, offering a better controlled form of cell death.34 Therefore, inhibition of mitochondria-dependent apoptosis might be a two edge sword.

Hypertension-induced inflammatory mediators may also compromise mitochondrial integrity and function. Progressive increase in interleukin (IL)-1 levels in diabetic rats is associated with decreased activity of the cardiac mitochondrial aldehyde dehydrogenase-2.35 Similarly, tumour necrosis factor (TNF)-α treatment in vitro magnifies morphological changes in mitochondria and decreases membrane potential and ATP production in adipocytes,36 implicating mitochondria as targets of systemic inflammation.

In turn, injured mitochondria possess inflammatory properties, including damage-associated molecular patterns (DAMPs), which might produce cardiomyocyte injury.37 Cellular injury releases mitochondrial DAMPs into the circulation eliciting a sepsis-like neutrophil-mediated organ injury.38 Furthermore, mitochondrial DAMPs activate the inflammasome, a group of intracellular multiprotein complexes that activate caspase-1 and proinflammatory cytokines.39 Alternative, mtDNA that escapes from autophagy leads to inflammatory responses in cardiomyocytes, inducing myocarditis and dilated cardiomyopathy.40 Importantly, inflammatory factors like interferon-γ increase sensitivity to vascular cell apoptosis, which is prevented by suppression of the mitochondrial apoptosis pathway, establishing a link between mitochondria-dependent inflammation and vascular apoptosis.41 Taken together, these observations implicate mitochondria in the genesis of chronic inflammation in failing hearts.

Although the number of mitochondria in endothelial cells is relatively low, they are critically involved in endothelial dysfunction, a hallmark of hypertension. Increased oxidative stress leads to both mitochondrial abnormalities and impaired endothelial function.42 In agreement, lipid peroxidation causes mitochondrial structural damage in arterial endothelial cells, which may lead to their dysfunction (Figure 1C, unpublished data). Recently, arginase-II, a mitochondrial enzyme expressed in endothelial cells, has been implicated in the pathogenesis of endothelial dysfunction, as its activation reduces nitric oxide availability and increases oxidative stress.43 Arginase-II-mediated endothelial dysfunction has been reported in several conditions including atherosclerosis, hypertension, and diabetes mellitus.44–46 Mitochondrial dysfunction and increased superoxide production are directly associated with the development and maintenance of endothelial dysfunction in patients with Type-2 diabetes.47 Furthermore, coexistence of diabetes mellitus and pressure overload decreases mitochondrial biogenesis and impairs contractile function, underscoring the role of mitochondria in the pathogenesis of heart failure.48 Importantly, attenuating mitochondrial hydrogen peroxide emission using mitochondrial-targeted-peptides preserves insulin sensitivity despite a high-fat diet, linking mitochondrial bioenergetics to insulin resistance.49

Mitochondrial dysfunction also alters intracellular calcium homeostasis, which in smooth muscle cells regulates peripheral vascular resistance, influencing the risk of hypertension. Mitochondrial calcium additionally promotes biogenesis by upregulating PGC-1α expression.50 In addition, increased myocardial expression of mitophagy markers is associated with changes in calcium cycling proteins, contributing to LV interstitial fibrosis and diastolic dysfunction.51 Hence, mitochondrial abnormalities might provoke myocardial remodelling and dysfunction through alterations in intracellular calcium signalling.
Mitochondria and hypertension

Mitochondrial dysfunction and hypertensive heart disease.

Mitochondrial abnormalities and dysfunction are likely central pathogenic mechanisms in other major target organs in hypertension (Figure 2B). Several studies in experimental hypertension have reported renal mitochondrial injury. We have demonstrated that mitochondrial biogenesis is impaired in the post-stenotic kidney of renovascular hypertensive pigs, associated with augmented apoptosis, oxidative stress, tubular injury, and fibrosis. Likewise, progressive atrophy and fibrosis in the clipped-kidney of 2K1C mice can be inhibited by activation of the mitochondrial biogenesis marker PPAR-α. In the brain, respiratory function and coenzyme-Q content in mitochondria are significantly decreased in SHR, associated with decreased ATP synthesis. In addition, mass spectrometry revealed ETC assembly defects in hypertensive rats, accompanied by complex-I dysfunction, elevated ROS production, decreased ATP synthesis, and impaired respiration. Interestingly, these changes were found in the brain stem, a region involved in blood pressure regulation, suggesting a role of mitochondrial injury in the development and progression of hypertension. Taken together, these studies link renal and brain mitochondrial injury and dysfunction to experimental hypertension, although the cause-and-effect relationship requires further investigation.

Mitochondrial injury-induced damage in other organs

Mitochondrial-targeted therapies

Mitochondria-targeted antioxidants are novel cell-permeable compounds that may attenuate hypertensive injury by protecting mitochondria from oxidative damage. MitoQ is a ubiquinone derivative that prevents lipid peroxidation and mitochondrial damage in several experimental models. In vitro studies demonstrated that MitoQ protected mammalian cells from apoptosis induced by hydrogen peroxide, but not by TNF-α, suggesting that it specifically targets mitochondrial oxidative damage. MitoQ also blunts hypertension, improves endothelial function, and reduces cardiac hypertrophy in SHR. Furthermore, its combination with low-dose losartan provides additive therapeutic benefit, by attenuating hypertension and reducing LV hypertrophy in SHR in vivo, and by a direct antihypertrophic effect on rat cardiomyocytes in vitro. Hence, MitoQ provides both hemodynamic and mitochondria-specific beneficial effects. However, the dependence on mitochondrial membrane potential to drive the uptake and concentration of MitoQ limits its efficacy in conditions that abolish membrane potential, including severe mitochondrial injury.

Drugs that block the mPTP may also attenuate hypertension-induced mitochondrial damage and dysfunction. In rat kidneys, cyclosporine-A improves the functional and histological parameters and attenuates oxidative stress induced by renal ischaemia/reperfusion. However, a plethora of adverse effects including LV hypertrophy, limits its use in hypertensive patients. Bendavia, also known as SS-31, selectively binds to cardioplin, preventing its peroxidation and loss. We have shown that Bendavia infusion during renal revascularization improved myocardial mitochondrial biogenesis, cardiac function, and oxygenation, and attenuated myocardial remodelling 4 weeks later. In agreement, Bendavia prevents cardiac remodelling and diastolic dysfunction in a mouse model of Ang-II-induced cardiomyopathy. These studies demonstrated a unique potential for this compound in attenuating hypertensive myocardial injury and facilitating cardiac recovery. Bendavia also

mtDNA alterations have been also implicated in the development of hypertensive heart disease. A point mutation in the mitochondrial cyt b gene, a component of the ETC complex-III, has been reported in severe hypertrophic cardiomyopathy, while mitochondrial tRNA mutations induce loss of mitochondrial function and hypertension. Similarly, mutations of the mitochondrial ATPase gene in hypertensive patients and SHR have been linked to the initiation and development of myocardial hypertrophy. These observations motivated the development of knockout and transgenic mouse models of mitochondrial function components. It is important to acknowledge that mitochondrial dysfunction is a common feature of ageing which, in turn, is associated to a higher risk of hypertension. Age-related increase in oxidative stress produces mtDNA mutations that aggravate mitochondrial ROS production, creating a vicious cycle that may exacerbate hypertension-induced mitochondrial injury.

Increased mitochondrial biogenesis. These observations again underscore a potential role of RAAS blockers in preserving the damaged mitochondria turnover in renovascular hypertension-induced heart disease.

Finally, losartan and the calcium channel blocker amlodipine equally reduced blood pressure in SHR, but only losartan prevented mitochondrial dysfunction, decreased tissue injury and improved renal function. Similarly, uncoupling protein-2 content increases, while mitochondria hydrogen peroxide production rate decreases, in kidney mitochondria isolated from enalapril-treated rats. Collectively, these observations suggest a specific role of RAAS inhibitors to prevent hypertensive mitochondrial injury.

The mechanisms by which RAAS blockade preserves mitochondria may include direct effects on Ang-II type 2 receptors located in the inner mitochondrial membrane of cardiac myocytes. Activation of these receptors modulates mitochondrial bioenergetics, improving ETC efficiency and ATP production. Ang-II also promotes mitochondrial superoxide generation via NADPH oxidase, thus, its blockade might counteract oxidative damage. Furthermore, ACEI increase antioxidant defences by augmenting the activity of both cytosolic and mitochondrial SOD. This in turn protects mitochondria from oxidative damage, preserving their structure and function.

Treatment strategies to attenuate hypertensive mitochondrial injury

Anti-hypertensive drugs

Importantly, blocking the RAAS confers cardio- and renoprotective benefits beyond blood pressure reduction, some of which may include mitochondrial protection.

In rats, long-term RAAS inhibition with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) increases myocardial expression of mitochondrial nitric oxide synthase, a variant of neuronal nitric oxide synthase present in cardiomyocytes. Furthermore, a non-antihypertensive dose of enalapril in SHR protects cardiac tissue and mitochondria function, suggesting a direct effect of the RAAS on mitochondria. In swine renovascular hypertension, treatment with valsartan and conventional triple therapy similarly decreased blood pressure, yet only valsartan attenuated LV hypertrophy, myocardial autophagy and mitophagy, and increased mitochondrial biogenesis. These observations again underscore a potential role of RAAS blockers in preserving the damaged mitochondria turnover in renovascular hypertension-induced heart disease.

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preserves renal mitochondrial biogenesis and attenuates tissue injury in the post-stenotic swine kidney during revascularization, underscoring its potential to limit renal ischaemia-reperfusion injury.\textsuperscript{82} Furthermore, chronic mitochondrial protection with Bendavia also decreases tissue damage in the swine stenotic kidney without revascularizing, improving renal function, endothelial function, and oxygenation.\textsuperscript{82} Taken together, these results uncover the potential of mitochondrial protection for restoring renal function in chronic experimental renovascular disease.

The feasibility of mitochondria-targeted therapies to ameliorate cardiac and renal injury in human subjects has been evaluated in few clinical trials. The efficacy of mitoQ has only been tested in patients with Parkinson’s disease and hepatitis C,\textsuperscript{83} but administration of cyclosporine (a potent mPTP inhibitor) before the onset of coronary reperfusion decreased infarct sizes in patients with acute myocardial infarction.\textsuperscript{84} Finally, the efficacy of Bendavia as an adjunct to reperfusion is currently being evaluated in patients with acute coronary events (NCT01572909)\textsuperscript{85} and renovascular disease (NCT01755858).

Conclusions

Accumulating data from experimental models of hypertension implicate mitochondrial injury in the development and progression of hypertension and target organ injury. Nevertheless, a cause–effect relationship and the clinical importance of mitochondrial injury in the development and progression of hypertension remain to be confirmed. RAAS blockade seems to confer direct benefits by attenuating mitochondrial alterations in hypertensive models. Novel strategies that target the mitochondria and preserve their morphology and function have shown intriguing benefit in experimental hypertension. Their ability to alleviate symptoms and complications of hypertension warrants further experimental and clinical research.

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Conflict of interest: Dr. A.L. and L.O.L. serve on the Advisory Board for Stealth Biotherapeutics, Inc.

References


Fulminant variant of Loeffler disease mimicking arrhythmic right ventricular cardiomyopathy in the course of enterobiasis

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A 37-year-old male farmer initially presented with recurrent palpitations and fatigue following recent influenza-like infection. Laboratory tests showed mild eosinophilia (828/μL), C-reactive protein elevation and troponin release, and Enterobius vermicularis infestation, which triggered treatment with pyrantel. Rest electrocardiogram revealed left-axis deviation, right bundle branch block, and epsilon-like wave in V1–V3. Resting 12-leads ECG showed late-gadolium enhancement. Transthoracic echocardiography revealed impaired left ventricular function (LVEF 24%), dilatation and dysfunction of right ventricle (RV) with apical RV trabeculations, endocardial hyperechogenicity, local a- and dyskinetic, which altogether met Task Force criteria of arrhythmic right ventricular cardiomyopathy (ARVC). Contrast-enhanced computed tomography confirmed right lung congestion.

Coronary angiography revealed multivessel disease: right coronary artery (80% stenosis), left circumflex artery (90% stenosis), and left anterior descending artery (60% stenosis), with prolonged QRS complex and atrial flutter. Anticoagulation was initiated, and the patient was referred for primary angioplasty and stenting of left anterior descending artery.

Subsequent coronary angiography revealed residual stenosis of left anterior descending artery (30% stenosis) and left circumflex artery (40% stenosis), with prolonged QRS complex and atrial flutter. Anticoagulation was initiated, and the patient was referred for primary angioplasty and stenting of left anterior descending artery.

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