Chapter 36
Mitochondrial Cardiomyopathy and Usage of L-Arginine

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Key Points

- Cardiomyopathy is present in 17–40 % of patients with mitochondrial disease and is one of the major causes of death in such patients.
- MELAS is a syndrome caused by an A-to-G transition at nucleotide position 3243 in tRNA-Leu of mtDNA and is the most common type of mitochondrial disease.
- In vivo functional imaging makes it possible to evaluate aspects of energy metabolism such as membrane potential and TCA cycle kinetics in MELAS patients noninvasively.
- L-Arg therapy is a promising approach for controlling the stroke-like episode of MELAS because of its vasodilative effect.
- L-Arg also has the potential to accelerate TCA cycle activity, irrespective of its vasodilative effect, and this can be used for treatment of mitochondrial cardiomyopathy.

Keywords Cardiomyopathy • MELAS • SPECT • PET • L-Arginine • TCA cycle

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Abbreviations

MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
mtDNA	Mitochondrial DNA
ATP	Adenosine triphosphate
LVH	Left ventricular hypertrophy
Arg	L-Arginine
NOx	Nitric oxide
SPECT	Single-photon emission computed tomography
^{99m}Tc-MIBI	Technetium 99 m methoxyisobutylisonitrile
^{123}I-BMIPP	Iodine-123-labeled 15-4-iodophenyl-3-(*R*,*S*)-methyl-pentadecanoic acid
PET	Positron emission tomography
TCA	Tricarboxylic acid
MBF	Myocardial blood flow

Introduction

It is well known that the most common morphology of cardiomyopathy is hypertrophy of the left ventricle. Practically, it is diagnosed as idiopathic hypertrophic cardiomyopathy, although occasionally it occurs secondary to systemic disease. The etiology of hypertrophic cardiomyopathy varies and can include ischemia, valve disease, inflammation, muscle dystrophy, toxemia, collagen disease, and metabolic diseases such as amyloidosis, Fabry's disease, and mitochondrial disease [1]. Accordingly, the treatment and prognosis of each individual disease differ, making a correct diagnosis important.

A recent epidemiological study has revealed that the prevalence or risk of developing mitochondrial DNA (mtDNA) disease is 12.48 per 100,000 individuals in the general population [2]. Moreover, pathogenic mtDNA mutations that can potentially cause disease are detected in at least one in 200 live births, indicating that mtDNA is not as rare a disease as once thought previously [3].

The human mitochondrial genome disorders discovered up to the present are cited in MITOMAP (URL: http://www.mitomap.org/), and more than 40 mutations of mtDNA or nuclear DNA associated with structural mitochondrial cardiomyopathy have been reported (Tables 36.1, 36.2, and 36.3). Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is the most common type of mitochondrial disease and is also related to familial cardiomyopathy, which is caused by an A-to-G transition at position 3243 (A3243G) in tRNA-Leu of the mtDNA [4, 5]. This mutation reduces the activity of NADH–ubiquinone oxidoreductase (complex I), leading to impairment of respiratory chain function with consequent reduction of adenosine triphosphate (ATP) production [6]. Furthermore, this mutant and wild-type mtDNA coexist in each individual cell (heteroplasmy), and the proportion of mutant mtDNA must exceed a certain fixed level in order to result

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Table 36.1 mtDNA mutations in rRNA/tRNA regions causing cardiomyopathy

Position	Locus	Disease	Allele	RNA	Homoplasmy	Heteroplasmy
1391	MT-RNR1	HCM	T1391C	12S rRNA	+	–
1556	MT-RNR1	HCM	C1556T	12S rRNA	+	–
1644	MT-TV	HCM + MELAS	G1644A	tRNA Val	–	+
3242	MT-TL1	MM/HCM + renal tubular dysfunction	G3242A	tRNA-Leu (UUR)	+	+
3243	MT-TL1	DMDF/MIDD/SNHL/FSGS/ cardiac + multiorgan dysfunction	A3243G	tRNA-Leu (UUR)	–	+
3260	MT-TL1	MMC/MELAS	A3260G	tRNA-Leu (UUR)	–	+
3303	MT-TL1	MMC	C3303T	tRNA-Leu (UUR)	+	+
4269	MT-TI	FICP	A4269G	tRNA Ile	–	+
4295	MT-TI	MHCM/maternally inherited hypertension	A4295G	tRNA Ile	+	+
4316	MT-TI	HCM with hearing loss/poss. hypertension factor	A4316G	tRNA Ile	+	+
4317	MT-TI	FICP/poss. hypertension factor	A4317G	tRNA Ile	+	–
5545	MT-TW	HCM severe multisystem disorder	C5545T	tRNATrp	–	+
8296	MT-TK	DMDF/MERRF/HCM/epilepsy	A8296G	tRNA Lys	+	+
8348	MT-TK	Cardiomyopathy/SNHL/poss. hypertension factor	A8348G	tRNA Lys	+	+
8363	MT-TK	MICM+DEAF/MERRF/autism/ LS/ataxia + lipomas	G8363A	tRNA Lys	–	+
9997	MT-TG	MHCM	T9997C	tRNAGly	nd	+
12297	MT-TL2	Dilated cardiomyopathy/LS/ failure to thrive and LA	T12297C	tRNA-Leu (CUN)	+	+
12308	MT-TL2	CPEO/stroke/CM/breast and renal and prostate cancer risk/altered brain pH	A12308G	tRNA-Leu (CUN)	+	+
15923	MT-TT	Infantile CM	A15923G	tRNAThr	–	+
16032	MT-TP	Dilated cardiomyopathy	[a]	tRNA Pro	–	+

HCM hypertrophic cardiomyopathy, *MM* mitochondrial myopathy, *DMDF* diabetes mellitus + deafness, *MIDD* maternally inherited diabetes and deafness, *SNHL* sensorineural hearing loss, *FSGS* focal segmental glomerulosclerosis, *MMC* maternal myopathy and cardiomyopathy, *FICP* fatal infantile cardiomyopathy + a MELAS-associated cardiomyopathy, *MHCM* maternally inherited hypertrophic cardiomyopathy, *MERRF* myoclonic epilepsy and ragged-red muscle fibers, *MICM* maternally inherited cardiomyopathy, *DEAF* maternally inherited deafness or aminoglycoside-induced deafness, *LS* Leigh syndrome, *LA* lactic acidemia, *CPEO* chronic progressive external ophthalmoplegia, *CM* cardiomyopathy

[a]T16032TTCTCTGTTCTTTCAT (15 bp dup) (cited from MITOMAP and adapted to the text contents)

in clinically apparent respiratory chain failure [7, 8]. Thus, energy production differs from tissue to tissue and also among organs, markedly energy-dependent organs tending to be affected most significantly. The distinct clinical features of MELAS patients are systemic and include myopathy, lactic acidosis, stroke-like episodes, hearing loss, diabetes mellitus, gastrointestinal manifestations, renal failure, and cardiomyopathies [4, 7, 8].

Mitochondrial cardiomyopathy often results in concentric left ventricular hypertrophy (LVH), and the severity of the LVH correlates with the burden of mitochondrial disease (Fig. 36.1). The reasons for development of LVH have been investigated using knockout mice with a deficiency in the mitochondrial adenine nucleotide translocator [9]. Like MELAS patients, these experimental mice show

Table 36.2 mtDNA mutations in the coding/control genes causing cardiomyopathy

Position	Locus	Disease	Allele	Nucleotide change	Amino acid change	Homoplasmy	Heteroplasmy
3337	MT-ND1	Cardiomyopathy	G3337A	G-A	V-M	+	–
3395	MT-ND1	HCM with hearing loss	A3395G	A-G	Y-C	–	+
3397	MT-ND1	ADPD/possibly LVNC cardiomyopathy associated	A3397G	A-G	M-V	+	–
3407	MT-ND1	HCM/muscle involvement	G3407A	G-A	R-H	+	–
5001	MT-ND2	Developmental delay, seizure, cardiomyopathy, lactic acidosis	A5001AA	A-AA	Frameshift	–	+
8528	MT-ATP8/6	Infantile cardiomyopathy	T8528C	T-C	W-R (ATP); M(start)-T(ATP6)	+	+
8558	MT-ATP8/6	Possibly LVNC cardiomyopathy associated	C8558T	C-T	P-S(ATP8); A-V(ATP6)	+	–
9058	MT-ATP6	Possibly LVNC cardiomyopathy associated	A9058G	A-G	T-A	+	–
15498	MT-CYB	HCM/WPW, DEAF	G15498A	G-A	G-D	–	+
15693	MT-CYB	Possibly LVNC cardiomyopathy associated	T15693C	T-C	M-T	+	–

ADPD Alzheimer's disease and Parkinson's disease, *LVNC* left ventricular noncompaction, *WPW* Wolff–Parkinson–White syndrome (cited from MITOMAP and adapted to the text contents)

Table 36.3 Nuclear DNA mutations causing mitochondrial cardiomyopathy

Gene	Chromosome function	Chromosome	Inheritance	Clinical phenotype
Structural gene				
NDUFV2	FP fraction	18p11	AR	Cardiomyopathy, hypotonia, encephalopathy
Complex assembly				
NDUFAF1 (CIA30)	Assembly	15q13.3	AR	Cardioencephalopathy
SCO2	Copper transport	22q13	AR	Neonatal cardioencephalomyopathy
COX10	Heme A farnesyltransferase	17p12–p11.2	AR	Neonatal tubulopathy and encephalopathy, LS, cardiomyopathy
COX15	Heme A synthesis	10q24	AR	Early-onset hypertrophic cardiomyopathy
TMEM70	Assembly	8q21.11	AR	Neonatal encephalopathy, cardiomyopathy
Mitochondrial import				
DNAJC19	Protein import	3q26.3	AR	Cardiomyopathy, ataxia
Mt protein synthesis				
MRPS22	Mitochondrial translation	3q23	AR	Cardiomyopathy, tubulopathy
Iron homeostasis				
BOLA3	Iron–sulfur cluster biosynthesis	2p13.1	AR	Encephalomyopathy, cardiomyopathy
CoQ10 biosynthesis				
COQ9	CoQ10 deficiency	16q13	AR	Neonatal lactic acidosis, seizures, cardiomyopathy
Chaperon function				
G4.5 (tafazzin)	Cardiolipin defect	Xq28	X linked	Barth syndrome, X-linked dilated cardiomyopathy

FP flavin protein, *AR* autosomal recessive, *CoQ* coenzyme Q (cited from MITOMAP and adapted to the text contents)

Fig. 36.1 Representative photograph of hypertrophic cardiomyopathy of a patient with mitochondrial disease

ragged-red muscle fibers, lactic acidosis, and cardiac hypertrophy, suggesting that deficiency of ATP production plays an important role in these conditions. On the other hand, a rare form of dilated-type mitochondrial cardiomyopathy has also been reported [10, 11]. A subset of patients with LVH progress to the dilated phase, which resembles idiopathic hypertrophic cardiomyopathy [12], but in some cases dilated cardiomyopathy is already present in childhood [13]. This discrepancy has been explained using a transgenic mouse model of mtDNA mutations, in which increased production of mitochondrial reactive oxygen species during the aging process leads to initiation of apoptosis and plays a crucial role in the development of dilated cardiomyopathy [14].

The frequency of cardiomyopathy in patients with mitochondrial disease is reported to be 17–40 % and is one of the major causes of death in affected patients [15–17]. Unfortunately no effective therapies for cardiomyopathy have been found to date. Koga et al. reported that L-arginine (Arg) infusion during the acute phase of the stroke-like episodes in MELAS patients dramatically improved all of the stroke-like symptoms within 30 min [18]. Moreover, oral administration of L-Arg during the interictal phase significantly decreased the frequency and severity of stroke-like episodes in MELAS patients [19]. L-Arg therapy is therefore now a promising approach for controlling the stroke-like episode of MELAS. Here we further investigated the therapeutic effect of L-Arg infusion in patients with cardiomyopathy and the possible mechanisms responsible.

In Vivo Functional Imaging of Mitochondrial Cardiomyopathy

Although the histopathologic abnormalities of mitochondrial cardiomyopathy have been clearly revealed using autopsied and/or biopsied tissue samples, the pathogenesis of cardiomyopathy has been discussed largely on the basis of the experimental studies [9, 14, 20]. Here we evaluated energy states in the myocardium of patients with MELAS using in vivo functional imaging.

Evaluation of Mitochondrial Membrane Potential and the Anaerobic Pathway Using Single-Photon Emission Computed Tomography (SPECT)

Technetium 99 m methoxyisobutylisonitrile (^{99m}Tc-MIBI) is incorporated and retained in the mitochondria of myocardial cells, a process that depends on mitochondrial membrane potential [21]. This tracer is not retained in necrotic or irreversibly ischemic myocardium and therefore can be used for assessing myocardial perfusion and myocardial cell viability [22].

Iodine-123-labeled 15-4-iodophenyl-3-(*R*,*S*)-methyl-pentadecanoic acid (^{123}I-BMIPP) is converted to acyl-CoA, a common pathway of myocardial fatty acid metabolism, but is not metabolized via beta-oxidation, which reflects the enhanced triglyceride pool [23]. An increasing number of studies have reported that patients with idiopathic hypertrophic cardiomyopathy show reduced uptake of ^{123}I-BMIPP and that this is related to impairment of the plasma membrane of cardiac myocytes [24].

Using these two tracers, we recently reported that in MELAS patients, the ^{99m}Tc-MIBI washout rate (WOR) was increased, resulting in decreased uptake of ^{99m}Tc-MIBI (Fig. 36.2) [25]. In contrast, ^{123}I-BMIPP uptake increased according to the severity of left ventricular function (Fig. 36.2) [25]. These findings confirmed that respiratory chain failure leads to a continuous energy shift from the aerobic to the anaerobic (glycolytic) pathway, resulting in the lactic acidemia that is observed in MELAS patients. To ameliorate the over-reduction stress resulting from respiratory chain failure, reduction of dihydroxyacetone phosphate to glycerol-3-phosphate occurs in order to oxidize superfluous nicotinamide adenine dinucleotide [NADH] to [NAD$^+$], the excess glycerol-3-phosphate being utilized for synthesis of triglyceride. Accumulation of ^{123}I-BMIPP in MELAS patients was provoked by this enhanced triglyceride pool (Fig. 36.2) [25].

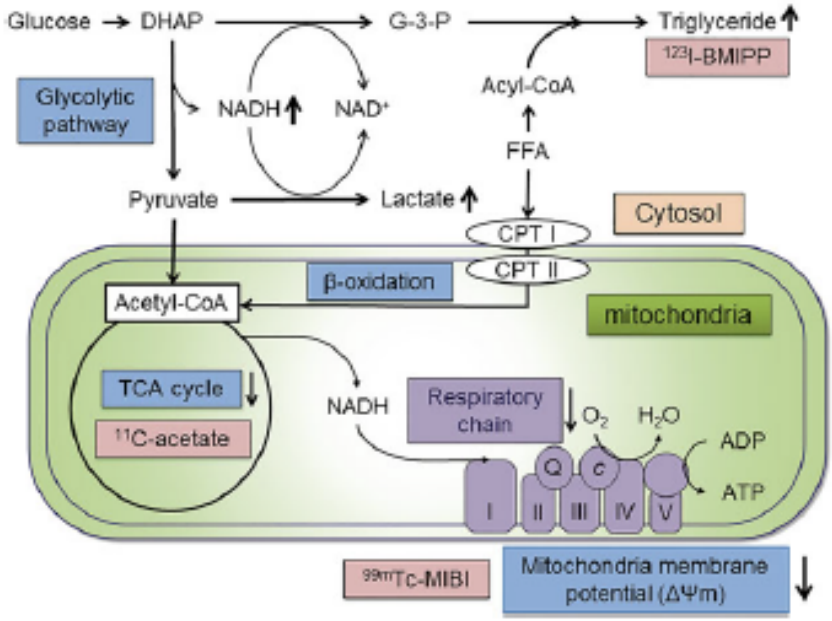

Fig. 36.2 Schematic illustration of energy production pathways in which functional imaging can be adapted. ^{99m}Tc-MIBI is incorporated and retained in the mitochondria depending on mitochondrial membrane potential created by the respiratory chain. ^{123}I-BMIPP is incorporated into the TG pool, associated with an excess of glycerol-3-phosphate (G-3-P), and is enhanced by increased glucose utilization. ^{11}C-acetate PET is responsible for the flux of TCA cycle. *CPT* carnitine palmitoyltransferase, *FFA* free fatty acid (cited from Ref. [25] with modifications)

Evaluation of TCA Cycle Kinetics Using Positron Emission Tomography (PET)

Radiolabeled ^{11}C-acetate kinetics demonstrated by PET are closely correlated with myocardial oxygen consumption [26, 27]. The acetate is known to be a substrate that can be utilized readily by the heart and is incorporated directly into the tricarboxylic acid (TCA) cycle after conversion to acetyl CoA. Therefore, ^{11}C-acetate can be used to measure the flux of the TCA cycle without being affected by conditions of energy production in the heart such as normoxemia, ischemia, and reperfusion, which advantages over other conventional tracers such as ^{18}F-deoxyglucose and ^{11}C-palmitate [28].

^{11}C-acetate PET also has the potential for detecting myocardial blood flow (MBF) using the early-phase (0–3 min after tracer injection) kinetics of ^{11}C-acetate [29]. Since the flux of the TCA cycle was measured using the delayed-phase (7–20 min after injection) kinetics of ^{11}C-acetate, these two parameters can be measured in exactly the same location in the heart.

Our SPECT study in MELAS patients with cardiomyopathy demonstrated a shift in energy production from the aerobic to the anaerobic pathway [25], although TCA cycle activity, which is of central importance in oxidative metabolism, was not fully evaluated. We therefore applied ^{11}C-acetate PET to MELAS patients and compared the findings with those in healthy controls [30]. The results revealed that TCA cycle activity tended to be lower in the patients than in the controls, thus confirming a shift of energy production to the anaerobic pathway according to impairment of electron transport and oxidative phosphorylation resulting from respiratory chain failure (Fig. 36.2) [25].

Effect of L-Arginine Administration on Mitochondrial Cardiomyopathy Evaluated by ^{11}C-Acetate PET

As described at the beginning of this chapter, L-Arg administration is now a promising therapy for the acute and interictal phase of the stroke-like episodes in MELAS patients [19]. One suggested mechanism is that L-Arg, which is a precursor of nitric oxide (NOx), may increase blood flow in the cerebral microcirculation and reduce ischemic damage to the brain. From the fact that the concentrations of L-Arg, citrulline, and NOx were low in the acute phase of the stroke-like episodes in MELAS patients, it seems plausible to supplement the amounts of these substances [19]. An improvement of endothelial function in MELAS patients was also observed after oral L-Arg supplementation, which would explain the long-term outcome [31]. As the impact of L-Arg administration on mitochondrial cardiomyopathy has not yet been reported, we recently evaluated the acute effect of L-Arg administration on cardiomyopathy using ^{11}C-acetate PET [30].

We performed ^{11}C-acetate PET before and after L-Arg infusion (0.5 g/kg, within 30 min) in six patients with clinically and genetically diagnosed MELAS. After L-Arg injection, TCA cycle activity (expressed as K_{mono}) of the entire heart did not increase significantly, although four of the six patients showed improvement after L-Arg administration. Due to heteroplasmy, mitochondrial dysfunction occurs in various tissues to varying degrees, a phenomenon known as "mosaicism of mitochondrial disease." Therefore, we further divided the heart into nine segments. TCA cycle activity was improved after L-Arg injection among six to eight segments in four responders, whereas it was five segments in two nonresponders. On the other hand, MBF increased in two patients, decreased in two patients, and remained the same in two patients after L-Arg infusion. To analyze the relationship between TCA cycle activity and MBF, we prepared a bull's-eye map of these two parameters before and after L-Arg injection. Figure 36.3 shows representative data for a MELAS patient who showed an increase of TCA cycle activity after L-Arg infusion. Surprisingly, the regions of improved TCA cycle activity did not correspond to the regions of increased MBF.

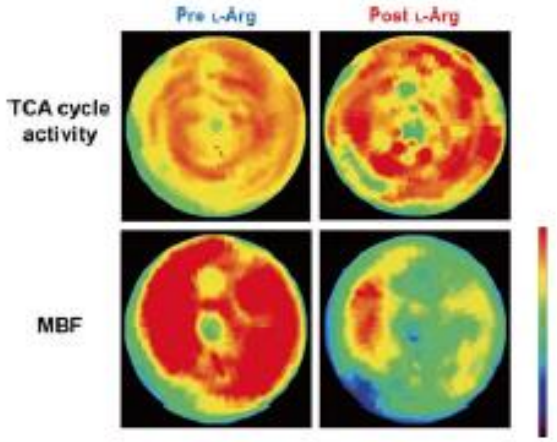

Fig. 36.3 Representative bull's-eye map of TCA cycle activity (*upper deck*) and myocardial blood flow (MBF; *lower deck*) before and after L-arginine administration in MELAS patients (cited from Ref. [30])

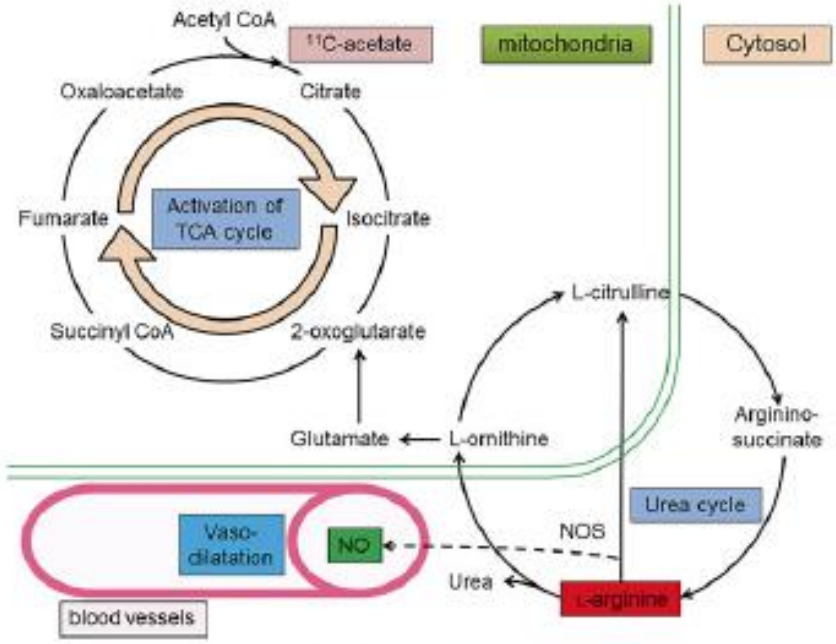

Fig. 36.4 Schematic illustration of L-Arg catabolism. Nitric oxide (NO) is synthesized from L-Arg catalyst of nitric oxide synthase (NOS). L-Arg has another potential to enter the TCA cycle by conversion to 2-oxoglutarate

L-Arg is a well-known precursor of NOx affected by endothelial nitric oxide synthase, a strong endogenous vasodilator [32, 33]. Accordingly, we expected that the regions of improved TCA cycle activity would match the regions of increased MBF, but no such relationship was observed. Although the reason for this remains obscure, Arg has a wide range of biological roles, such as a precursor for synthesis of urea, NOx, citrulline, ornithine, creatine, and agmatine. Furthermore, ornithine generates polyamine, proline, and particularly glutamate, which undergoes conversion to 2-oxoglutarate and enters the TCA cycle (Fig. 36.4). Therefore, an excess of 2-oxoglutarate in the TCA cycle induced by L-Arg injection could be responsible for acceleration of TCA cycle activity with little relevance to the coronary microcirculation.

The primary cause of the stroke-like episodes in MELAS patients remains uncertain but is thought to involve angiopathy, cytopathy, or both. Potential therapeutic effects of L-Arg for strokes are mainly thought to contribute to amelioration of angiopathy through its vasodilative effect and improvement of endothelial function. The logic of this approach is result from the loss of NOx in vascular endothelial and smooth muscle cells. However, the concentration of NOx was quite elevated in the interictal phase of stroke-like episodes [19]. Moreover, an in vitro experimental study has revealed that the synthesis of NOx was increased in cybrid cells carrying the A3243G mutation, which supports this condition [34]. Our study suggests that L-Arg enhances TCA cycle activity irrespective of vasodilation, which rescues the cytopathy (over-reduction stress) of MELAS patients. A recent study has also revealed that L-Arg improved the activity of complex I activity, a nonvascular system, in cybrid cells harboring A3243G mutation, thus strongly supporting our hypothesis regarding the metabolic effect of L-Arg [35].

Accordingly, our study has clearly demonstrated that L-Arg has dual pharmaceutical effects—vasodilatation (angiopathy) and acceleration of the TCA cycle (cytopathy)—which can be used as a treatment for patients with mitochondrial cardiomyopathy.

Conclusions

Mitochondrial cardiomyopathy is caused by respiratory chain failure due to mtDNA mutation, one of the key conditions that determine the prognosis of patients with mitochondrial disease. Functional imaging modalities such as SPECT and PET enable evaluation of in vivo energy production and the efficacy of treatment for patients with MELAS. It was clearly revealed that TCA cycle activity was markedly suppressed, resulting in a change in oxidative metabolism from an aerobic to an anaerobic state. L-Arg has the potential to enhance TCA cycle activity without being affected by any vasodilative effect, suggesting dual pharmaceutical effects that could be applied for treatment of mitochondrial cardiomyopathy.

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Conflict of Interest None.

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