

# Anesthetic Approach for Mitral Valve Repair in a Patient with Mitochondrial Myopathy: Case Report

## Mitral Kapak Onarımı Yapılan Mitokondriyal Miyopatili Bir Hastada Anestezi Yaklaşımı

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**ABSTRACT** A thirty nine-year-old female patient with mitochondrial myopathy had a muscle biopsy that revealed an appearance of ragged-red fiber in the histochemical analysis and had muscle incompetence, phytosis and ophthalmoplegia findings was diagnosed as progressive external ophthalmoplegia and she was scheduled for the surgery of mitral valve prolapsus and a third degree mitral insufficiency. The patient had left bundle branch block in the preoperative electrocardiogram and creatine phosphokinase and lactate dehydrogenase levels were high in blood biochemistry. Lactic acid levels couldn't be tested. Considering the risk of malign hyperthermia, intravenous general anesthesia was applied using fentanyl, propofol, midazolam, and vecuronium. The patient was cooled up to 28°C during cardiopulmonary bypass and ring annuloplasty was applied to mitral valve. Cardiopulmonary bypass procedure was completed without any problems. There was no abnormality in the electrolytes and acid-base levels as well as hemodynamic findings in the intra and postoperative periods. The patient was extubated on the postoperative 14th hour. In this case report, we discussed the anesthetic approach applied in a patient with mitochondrial myopathy undergone cardiopulmonary bypass for mitral valve repair.

**Key Words:** Mitochondrial myopathies; anesthesia, general; mitral valve; cardiopulmonary bypass

**ÖZET** Kas güçsüzlüğü, pitozis, oftalmopleji bulguları ve kas biyopsisinin histokimyasal incelemesinde ragged-red fiber görünümüyle bir mitokondriyal miyopati olan progresiv eksternal oftalmopleji tanısı konmuş olan 39 yaşında kadın hastaya mitral valv prolapsusu ve üçüncü derecede mitral yetmezliği nedeniyle ameliyat kararı alındı. Hastanın preoperatif elektrokardiyografisinde sol dal bloğu vardı, kan biyokimyasında CPK, LDH düzeyleri yüksekti. Laktik asit düzeyi bakılmadı. Malign hipertermi riski göz önüne alınarak fentanil, propofol, midazolam ve vekuronyum kullanılarak intravenöz genel anestezi uygulandı. Kardiyopulmoner baypas sırasında 28 dereceye soğutuldu, mitral kapağa ring annuloplasti uygulandı. Kardiyopulmoner baypas sorunsuz olarak sonlandırıldı. İntraoperatif ve postoperatif hemodinamik bulgulara, elektrolit ve asid-baz dengesinde anormallik olmadı. Hasta postoperatif 14. saatte ekstübe edildi. Bu olgu sunumunda, mitral valv onarımı için kardiyopulmoner baypas yapılan mitokondriyal miyopatili bir hastada uygulanan anestezi yaklaşımımızı tartıştık.

**Anahtar Kelimeler:** Mitokondriyal miyopatiler; anestezi, genel; mitral kapak; kardiyopulmoner baypas

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**M**itochondrial myopathy is a common definition of disease groups in which biochemical disorders in the muscle energy metabolism due to mitochondrial dysfunction can occur, particularly not only in muscles but also the organs that especially need more energy are affected

and present with different clinical pictures.<sup>1</sup> Kearns-Sayre Syndrome, MERRF Syndrome (Myoclonous Epilepsy Associated with Ragged-Red Fibers), MELAS Syndrome (Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, Stroke-Like Episodes), Chronical Progressive External Ophthalmoplegia and Leigh's Disease may be listed as mitochondrial myopathies.<sup>2</sup>

Lots of mitochondrial DNA (mtDNA) or nuclear DNA defects resulting in metabolic defects at the level of mitochondrial respiratory chain have been defined.<sup>1,2</sup> The most serious hereditary mitochondrial diseases develop in infancy and generally result in mortality while the prognosis may vary in those initiating in adulthood. The changes in normal and mutant mtDNA ratio (heteroplasm) existing in target organ during embriogenesis are indicated as the cause of differences in symptoms and findings observed in mitochondrial myopathies clinically.<sup>2</sup> Ptosis, ophthalmoplegia, cerebral, hepatic, and renal insufficiencies with muscle weakness, cardiomyopathy, cardiac transmission defects, endocrinopathy, and lactic acidosis may develop in patients.<sup>2</sup>

Although there are articles about non-problematic general anesthesia applications in this group of patients, increased sensitivity against general anesthetics (intravenous, inhalation), opioids, and muscle relaxants have been reported.<sup>2,3</sup> Tendency towards malign hyperthermia is the frequent issue that anesthetists considered in all myopathies.

In this case report, we discussed the anesthetic approach applied in a patient with mitochondrial myopathy undergone open heart surgery for mitral valve repair.

## CASE REPORT

A thirty-nine-year-old female patient (40 kg) with the complaints of extreme fatigue, exhaustion, lessening in effort capacity, asthma, giddiness and fainting had been followed for about 10 years with the diagnosis of mitral valve prolapsus and mitral insufficiency. On the increase of her complaints,

surgical operation was decided as a result of the examinations by cardiology and cardiovascular departments.

The patient's history revealed that she had been diagnosed as progressive external ophthalmoplegia and mitochondrial myopathy and she was followed up by neurologists for the last 15 years. The patient referred a doctor for the first time at the age of 12 due to ptosis on both eyelids and underwent an operation under local anesthesia. In the following years, her complaints of fatigue, dysphagia and ptosis persisted increasingly. In histochemical examination of her muscle biopsy taken at the age of 25, it was reported that the diameters of muscle fibers were not equal to each other; that there were hypertrophic muscle fibers accompanying atrophic ones; there was no central nucleus in some muscle fibers; there was a mitochondrial accumulation of type 1 fibers in subsarcolemmal region and there was mitochondrial myopathy due to diffuse ragged-red fibres (RRF) appearance. She was diagnosed as Progressive External Ophthalmoplegia by the neurology department and was taken to be followed up and carnitine treatment was begun. At the same period, she was diagnosed as minimal mitral valve insufficiency. She had a term pregnancy once but the baby has died of respiratory insufficiency 11 hours after birth.

On the preoperative neurologic examination, it was reported that there was bilateral asimetric ptosis and restriction in her eye movements towards four directions, the retching reflex decayed and she had dysphagia and both her legs fell early in Mingazzini test.

The respiratory system and abdominal examination was normal. Arterial tension was 100/85 mmHg and there was 3/6 systolic murmur especially at the mesocardiac and mitral focus. The ejection fraction on preoperative transthoracic echocardiography was 50%, left atrium diameter was 45 mm, pulmonary arterial pressure was measured as 40 mmHg. Mitral anterior leaflet in left ventricle was slightly thickened and prolapsed, there was a third degree mitral insufficiency and

first-second degree tricuspid insufficiency. On ECG, there was left bundle branch block.

Biochemical analysis was as follows: SGOT 43 U/L (5-34 U/L), SGPT 39U/L (0-55 U/L), CPK: 688U/L (29-168 U/L), LDH: 345U/L (125-243 U/L) and BUN and creatinine were in normal limits. Lactic acid level was not analyzed.

Increased sensitivity to muscle relaxants and the possibility of malign hyperthermia were taken into account when anesthesia was planned. Dantrolene was made available preoperatively and flashing was performed by high oxygen receiving to anesthesia machine. Premedication was done by 5 mg of diazepam given orally at the preceding night and in the morning before operation. In the operation room, five derivation electrocardiography, invasive arterial blood pressure, SpO<sub>2</sub> were used and in the anesthesia induction after bispectral index monitorization, 250 µg fentanyl, 60 mg lidocain, 15 mg etomidate and 8 mg vecuronium were intravenously administered. Following endotracheal intubation, central venous pressure was monitorized by applying double catheter into the right internal jugular vein and nasopharyngeal temperature probe was inserted. Anesthesia was maintained by fentanyl (3-8 µg/kg/hour) and propofol (3-5 µg/kg/hour) infusion with a bispectral index value between 40-50 and by 2 mg midazolam at intervals intravenously. Arterial blood gas analyses were performed every hour (every 15 min on cardiopulmonary bypass) and his core temperature was monitored continuously. When cardiopulmonary bypass procedure began, the infusion dosages of fentanyl and propofol were decreased. Routine cardiopulmonary bypass protocol was applied: The operation was performed under moderate hypothermia (28°C) with cold cardioplegia crystalloid. Cardiopulmonary bypass was conducted with a roller pump and a membrane oxygenator. The pump was primed with 1500 mL lactated Ringer's solution to which 100 mmol/L of sodium bicarbonate and 5000 IU of heparin were added. After systemic anticoagulation with heparin 400 IU/kg (activated clotting time 400 [performed on a kaolin-based test]), cardiopulmonary bypass was instituted at a flow rate of 2.4 L/min/m<sup>2</sup>. Since

there was no calcification and degeneration at mitral valve, the tissue loss at anterior leaflet was repaired and ring annuloplasty was applied. When cardiopulmonary bypass was completed, protamine was administered and 5 µg/kg/min. dopamine infusion was started. Total duration of bypass procedure was 100 minutes, cross clamp time was 73 minutes and anesthesia duration was 260 minutes. Totally 700 µg fentanyl, 720 mg propofol, 6 mg midazolam and 18 mg vecuronium were administered intraoperatively. Neuromuscular monitorization was not performed. No acidosis was found in peroperative blood gas samples and blood glucose level was found to be maximum 186 mg/dl.

Only 0.9% isotonic serum was used as infusion liquid. The patient was taken to intensive care room without extubation receiving 5 µg/kg/min dopamine infusion. She was awoken on the eighth hour after the operation and was extubated on the fourteenth hour. In intensive care unit on the second postoperative day, she received coumadine (2.5 mg) orally and she was taken to service room on the third day. During the intensive care unit, she had no fever, biochemical or electrolysis values were normal and no metabolic acidosis was observed.

## DISCUSSION

Progressive external ophthalmoplegia is a mitochondrial myopathy resulting from sporadic mtDNA deletions. It was reported that the most common symptoms were ptosis and ophthalmoplegia and that it was accompanied by diabetes mellitus, hypothyroidism, hyperparathyroidism and short stature and might begin with the complaints of weakness, muscle fatigue and intolerance to exercise at any age.<sup>4</sup> It was reported that ophthalmoplegia could sometimes be seen as the early symptoms of Kearns-Sayre and MELAS Syndromes and in the following years also symptoms related with other organ dysfunctions might also begin.<sup>5</sup> In such cases with the increase of anaerobic metabolism due to defects in mitochondrias of muscle cells, serum lactate levels may rise. It was shown that high serum lactate levels were specific, but they are not sensitive, the sensitivity of lactat/piruvat ratio is higher.<sup>2</sup> On

the other side, it was reported that serum creatine phosphokinase level may be high or at normal levels in patients with progressive external ophthalmoplegia.<sup>4,6</sup> The most important diagnostic criteria for mitochondrial myopathy was emphasized to be the "Ragged-Red Fibres" appearance in the histochemical examination of muscle biopsy.<sup>2</sup>

Mitral valve prolapsus is not a frequent finding accompanying with progressive external ophthalmoplegia; indeed, it is mostly reported in Kearns-Sayre Syndrome.<sup>1,3</sup> However, it was demonstrated that cardiac conduction disorders and cardiomyopathy occurred in most mitochondrial diseases.<sup>1,3,7</sup> It was found that mtDNA deletion in the skeleton and myocard muscles of these patients are the same.<sup>7</sup> In addition to the authors emphasizing that normothermic cardiopulmonary bypass was more secure than hypothermic cardiopulmonary bypass, there are also authors indicating that hypothermic cardiopulmonary bypass can be used in mitochondrial myopathy patients undergoing open heart surgery.<sup>8</sup>

Although different general anesthesia methods have been used in patients with mitochondrial myopathy without any problems, it is not very clear which type of anesthetic medication and method is more confident.<sup>8</sup> It was indicated that increased sensitivity to general anesthetics, opioids and muscle relaxants occurs and the duration of their effect prolongs and thus postoperative complication risks increased.<sup>3,9</sup> In clinical reports, it is indicated that regional anesthesia is safer but postoperative complication risks are higher in general anesthesia applications compared with normal population.<sup>3</sup> A number of authors noted that such cases should be evaluated in detail preoperatively when planning anesthetic approach.<sup>1,3,5,9,10</sup> Also it was suggested that in addition to the clinical findings of myopathy, there could also be subclinical hepatic and renal deficiency, cerebral and cardiac dysfunction and these could only be detected by taking detailed medical history and performing physical examination.<sup>1</sup> It is also emphasized in some studies that preoperative starvation period duration should last for eight hours due to prolonged stomach

emptying time; blood sugar should be closely followed up due to tendency to hypoglycemia; a fluid solution containing glucose should be administered intravenously in the preoperative period; in order to avoid lactic acid level increase, ringer lactat should be avoided and oxygenation should be monitored.<sup>8</sup> In addition, it is reported that the elimination period of muscle relaxants prolongs and respiratory depression develops in late postoperative period in mitochondrial myopathy patients to whom rocuronium, atracurium, vecuronium, and mivacurium are applied.<sup>3,11,12</sup> However, there are reports conflicting these data. For example, it was indicated that the effect time of vecuronium did not prolong in mitochondrial myopathy case presentations where vecuronium was used during general anesthesia.<sup>13,14</sup>

A definite increased sensitivity to volatile and intravenous anesthetics was reported.<sup>1</sup> It is thought that although a certain encephalopathy hasn't developed in these patients, the need of anesthetic for neuronal bioenergy decreases. On the other hand, it is indicated that subclinical lessening of hepatorenal reserve may lead to prolonged effects of medication and effects of anesthetics, muscle relaxants and opioids may persist.<sup>1</sup> Also it is noted that the cardiovascular depression effects of anesthetics may increase and sudden cardiac arrest may develop due to anomalies in intrinsic muscle hypotonia, endocrinopathy, cardiomyopathy, and cardiac conduction disorders.<sup>15</sup> Since the respiratory response to hypoxia (hypoxemia) and hypercarbia may have been depressed, it is suggested that sedatives and opioids should be titrated.<sup>15</sup>

It is controversial whether there is a risk of malignant hyperthermia or not in the anesthesia applications in cases with mitochondrial myopathy.<sup>16</sup> Indeed, mitochondrial myopathies with a "minicore" and "multicore" histology are rarely seen and have been reported to have a tendency to malignant hyperthermia.<sup>17</sup> Because of the publications correlating mitochondrial myopathies with malignant hyperthermia, a number of authors suggest using general anesthetics without the risk of malignant hyperthermia while applying general

anesthesia to these cases.<sup>5,11,16,18,19</sup> Nevertheless, there are surveys indicating that they use volatile anesthetics without any problems.<sup>20,21</sup>

In our case, we have chosen to use propofol, fentanyl, and midazolam considering the risk of malign hyperthermia. It is known that propofol, fentanyl, and midazolam are secure agents for the patients susceptible to malign hyperthermia.<sup>22</sup> However, it is noted that propofol and midazolam inhibited the relation of mitochondrial respiration and oxidative phosphorylation.<sup>23,24</sup> While midazolam affects the respiratory chain over the mitochondrial benzodiazepin receptors, propofol modifies the mitochondrial enzyme conformation.<sup>23,24</sup> However, the results of these effects on patients with mitochondrial myopathy having respiratory chain defects are not clear and the superiority of any kind of anesthetics to others hasn't been made clear.

One of the drawbacks towards the use of propofol in patients with mitochondrial myopathy is that propofol itself cause high dosage of metabolic acidosis. "Propofol infusion syndrome" is mostly reported for patients in intensive care unit who received high dose and long time propofol for sedation.<sup>25</sup> On reviewing the anesthesia applications to patients with mitochondrial myopathy, there are case reports indicating non-problematic usage of propofol and midazolam taking the possible risks into account. These authors suggest close follow-up for acid-base conditions in such cases.<sup>15,26,27</sup>

In our case, intravenous propofol, fentanyl, and midazolam were used for anesthesia and

vecuronium was used as muscle relaxant. Intraoperative neuromuscular monitorization could not be done, but totally 18 mg. of vecuronium was used in the 260 minutes anesthesia time. Since the patients are transferred to intensive care room without extubation after cardiopulmonary bypass, it is difficult to comment on whether the effects of anesthetics and vecuronium have persisted for long time or not in postoperative period. In fact, we did not observe any delay in extubation time when compared with other cardiopulmonary bypass patients. Due to the restricted laboratory facilities, serum lactic acid level of the patient was followed through blood gas analysis and no metabolic acidosis was detected both intra and postoperative periods.

As a result, mitral annuloplasty operation was accomplished without any problems under medium hypothermic cardiopulmonary bypass by using propofol, fentanyl, midazolam and vecuronium in a patient with progressive external ophthalmoplegia which was one of the mitochondrial myopathy group diseases. In the general anesthesia approach for mitochondrial myopathy, it is important to take the detailed medical history and to evaluate the physical and laboratory findings carefully. In addition to the ptosis, ophthalmoplegia and muscle deficiency, there may be cerebral, cardiac, hepatic, renal, and pulmonary function deficiencies at different levels. While planning the anesthetic approach, it is necessary to be ready for possible complications and the patient and his/her should be informed in detail.

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