Greater than Normal Variability of Ca-induced Ca Release in Muscle Fibers of a Patient with a Positive Family History of Malignant Hyperthermia

Kazuo MARUYAMA, Mikikazu YAMAGIWA, Kazu NISHIMURA, Kunihiko KONISHI and Mannosuke MUNEYUKI

(Key words: malignant hyperthermia, Ca-induced Ca release)

Abnormality in calcium release from skeletal sarcoplasmic reticulum of malignant hyperthermia susceptible human and animal muscles is observed[1–3]. In the muscle fibers of patients with malignant hyperthermia (MH), the calcium (Ca)-induced Ca release from the sarcoplasmic reticulum (SR) is much greater than that in normal fibers[1]. According to this line of thought, preoperative demonstration of accelerated Ca-induced Ca release in muscle fibers can be used as a definitive test for the diagnosis of MH susceptibility. In the present study, we examined skinned fibers preoperatively prepared from the muscles of a patient whose family history was positive for MH.

Report of a Case

A 45-year-old oriental woman with a positive family history of MH was scheduled for surgery for chondrosarcoma of the epipharynx and thyroid cancer. In the past she had undergone appendectomy under spinal anesthesia and artificial abortion under intravenous anesthesia without complication. In the family history, her nephew had experienced an acute episode of MH, which had been successfully treated, under nitrous oxide, halothane, succinylcholine chloride anesthesia for surgical repositioning of bone fracture. The mother of the patient had suffered from tetanus. Results of preoperative physical examinations of the patient were normal, as were those of all routine preoperative laboratory tests. The serum creatinine phosphokinase (CPK) was 18 $u \cdot dl^{-1}$ (normal level, less than 80 $u \cdot dl^{-1}$). A piece of the quadriceps femoris, about 10 mm in width and 30 mm in length, was biopsied under spinal anesthesia with dibucaine 3 ml. The rate of Ca-induced Ca release mechanism in the SR of the skinned muscle fibers were measured by the method described by Endo et al.[1]. The results obtained were compared with the range of a normal subject previously examined and described by Endo et al.[1]. The rate of Ca-induced Ca release was determined in seven fibers in our patient. As shown in figure 1, the rate was apparently higher in three fibers. In the

Department of Anesthesiology and Otolaryngology, and the Intensive Care Unit Mie University School of Medicine, Tsu, Japan

Address reprint requests to Dr. Maruyama: Department of Anesthesiology, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie, 514 Japan

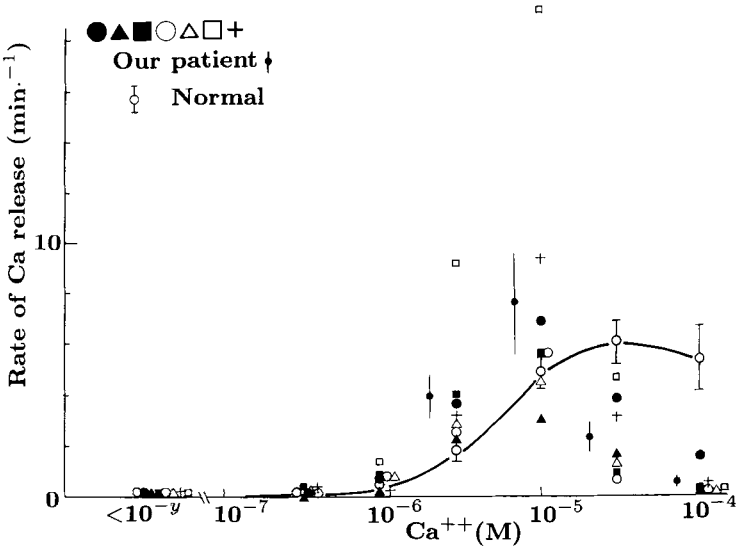

Fig. 1. The rates of Ca-induced Ca release were determined in seven fibers from our patient. The rates were apparently malignant hyperthermic in three fibers indicated by the symbols □, +, ●, at free Ca ion concentration of 10^{-5}.mol/l. A fiber indicated by a clear triangle (△) was within the normal range. In the other fibers the rates were slightly more accentuated (■, ○) or depressed (▲) than in normal fibers. The results showed greater than normal variability of Ca-induced Ca release in muscle fibers of the patient.

other fibers, the rates were within the normal range or slightly more accentuated or depressed than those in normal fibers. In our patient, Ca sensitivity (the Ca ion concentration at which the half-maximum rate of Ca release was obtained), as well as the maximum rate of Ca-induced Ca release, was greater than in normal fibers. These results showed our patient's muscle consists of a mixture of normal and malignant hyperthermic fibers.

The patient was premedicated with morphine hydrochloride 10 mg i.m. one hour before induction. Anesthesia was induced with fentanyl 0.4 mg, diazepam 5 mg, and droperidol 5 mg, followed by pancuronium 5 mg with 65% nitrous oxide in oxygen. The trachea was intubated orally and anesthesia was then maintained with 65% nitrous oxide in oxygen plus fentanyl 0.1–0.2 mg i.v. every 45–90 min after the start of surgery. When the patient's rectal temperature rose from 36.7°C to 37.1°C in 30 min, surface cooling was initiated with a cooling blanket, after which there was no further rise in the temperature. No other suspicious signs, including the results of arterial blood gas analysis, were noted. The total duration of anesthesia was 5 hour 30 min. The postoperative course was unevenful and the patient was discharged from hospital 27 days later. It was recommended that, for any other treatment, she should be assumed to be susceptible to MH, even if the sensitivity was of low grade.

Discussion

Malignant hyperthermia is thought to be a hereditary disorder[5,6]. Regarding the pattern of its inheritance, single autosomal recessive inheritance and multigenic inheritance have been sug-

gested, but no conclusive proof has emerged. However, a mosaic may exist because the MH trait does not exhibit uniform severity or the same features[5]. The results obtained from our patient showed that the sensitivity of the Ca-induced Ca release mechanism displayed greater than normal variability of Ca-induced Ca release in muscle fibers. Accordingly, we speculated that the muscle in our patient consisted of a spectrum of fibers from normal to MH type with a mosaic pattern.

From the clinical standpoint of view, a patient is diagnosed as having positive susceptibility to MH even if only one of the patient's muscle specimen shows an abnormal contracture response in caffeine halothane contracture test[4]. Perhaps the episode of patient's nephew was an occurrence of MH inherited from the patient's side of the family.

Depending upon the degree of susceptibility, the ease with which MH is initiated could fluctuate[6]. This possibility could explain those situations in which individuals known to be susceptible have shown no sign of MH during exposure to triggering anesthetic agents[6]. The various gradations of clinical MH are said to be related to a genetic spectrum of susceptibility[7,8]. We speculate that MH was not triggered in our patient, because her susceptibility to MH was of a low grade. It thus seems possible that upon carrying out the tests for measuring the Ca-induced Ca release mechanism in skinned fibers, the results showing a spectrum ranging from normal to malignant hyperthermic indicate a low grade, but positive susceptibility to clinical MH. We don't know if this variability is characteristic for all MH-susceptible patients. It is anticipated that with continued experience, the true worth and significance of the muscle biopsy test using skinned fibers will become more apparent.

In summary, the results showed greater than normal variability of Ca-induced Ca release in muscle fibers. However, assessment of such results is difficult and details cannot be ascertained in interpretation of the results in Ca-induced Ca release in muscle fibers. Clinically, a patient shall be considered to be MH susceptible even if only one of the patient's muscle specimen shows an abnormal contracture response in caffeine halothane contracture test[4]. In the present case, anesthesia was carried out safely by avoiding the use of any triggering agents.

Acknowledgements: The authors are grateful to Dr. M. Endo at the Department of Pharmacology, Tokyo University School of Medicine for the determination of Ca-induced Ca release.

(Received Oct. 3, 1991, accepted for publication Feb. 4, 1992)

References

1. Endo M, Yagi S, Ishizuka T, et al: Changes in the Ca-induced Ca release mechanism in the sarcoplasmic reticulum of the muscle from a patient with malignant hyperthermia. Biomed Res 4:83–92, 1983
2. Kim DH, Sreter FA, Ohnishi ST, et al: Kinetic studies of Ca release from sarcoplasmic reticulum of normal and malignant hyperthermia susceptible pig muscles. Biochem Biophys Acta 775:320–327, 1984
3. Nelson TE: Abnormality in calcium release from skeletal sarcoplasmic reticulum of pigs susceptible to malignant hyperthermia. J Clin Invest 72:862–870, 1983
4. North American Malignant Hyperthermia Group: Recommendations for standardization of the caffeine halothane contracture test. Lake Bluff, Illinois, November 4–6, 1987
5. Britt BA: Malignant hyperthermia. Can Anaesth Soc J 32:666–677, 1985
6. Gronert GA: Malignant hyperthermia. Anesthesiology 53:395–423, 1980

7. Britt BA, Endrenyi L, Scott E: Effect of temperature, time and fascicle size on the caffeine contracture test. Can Anaesth Soc J 27:1–11, 1980
8. Kalow W, Britt BA, Chan FY: Epidemiology and inheritance of malignant hyperthermia. Malignant Hyperthermia. Edited by Britt BA. Int Anesthesiol Clin 17:119-139, 1979