

perthermia in Two Unrelated Families.<sup>1</sup> Although we are pleased that this article merited an editorial, Nonanesthetic Malignant Hyperthermia by Lehmann-Horn *et al.*,<sup>2</sup> we have several concerns about its content.

First, we question the editorial's statement, "The *in vitro* contracture test performed on a muscle biopsy of the boy reported in this article would be considered by Europeans as malignant hyperthermia (MH) equivocal."<sup>2</sup> As reported by Groom *et al.*, case 1 had a mean response of 8.5 g (9.3, 9.0, 7.1 g) contracture in the presence of 3% halothane (less than 0.7 g contracture is designated non-MH susceptible) and a mean 2.4 g (1.9, 2.9 g, insufficient muscle to permit testing in triplicate) contracture in the presence of 2 mM caffeine (less than 0.3 g is non-MH susceptible)<sup>1</sup> (Sheila M. Muldoon, M.D., Professor of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, written communication, December 6, 2011). This MH contracture test was conducted according to the standards of the North American Malignant Hyperthermia Group<sup>3</sup> with clearly positive responses in all five muscle strips to both the halothane and the caffeine portions of this test.<sup>4</sup>

The North American and European MH biopsy methods are similar but not identical. The most important differences are bolus *versus* incremental halothane exposure and the European designation of an equivocal research diagnostic category for subjects demonstrating positive contracture responses only to halothane or only to caffeine exposures.<sup>3,5</sup>

Islander and Twetman have studied the concordance of the North American and European biopsy protocols. Although Islander and Twetman's excellent study found an accordance in diagnostic outcome between the European and North American protocols of 87%, they noted a 100% accordance for individuals with contractures exceeding thresholds in at least five of six tested muscle strips. They observed diverging outcomes in subjects with less reproducible test results near the cutoff limits of their respective protocols.<sup>6</sup> Because case 1's results markedly exceeded North American diagnostic thresholds by an order of magnitude in five of five tested muscle strips to both halothane and caffeine exposures, we contend that this patient should be designated by both North Americans and Europeans to be MH susceptible and not equivocal and thus, a suitable genetic research subject.

Second, although we are aware of individual case reports, there have been no large-scale human studies that support the statement of Lehmann-Horn *et al.* that MH-susceptible individuals presenting with ophthalmoplegia and muscle hypotonia, hypertrophy, or spasms will be at risk for nonanesthetic MH. We believe that the authors should have clearly noted that this was only their opinion.

Finally, despite diligent parental care and aggressive medical interventions, children such as the one described in case 1 are at risk of death from this poorly understood condition. In such situations, blaming the parents helps no one.

**Marilyn Green Larach, M.D., F.A.A.P.,\* Gregory C. Allen, M.D., F.R.C.P.C., Henry Rosenberg, M.D.** \*The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States, Pittsburgh, Pennsylvania. mlarach@gmail.com

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## In Reply:

We are happy to see that our editorial<sup>1</sup> prompts discussion, even though the points raised by Larach *et al.* result mainly from the removal of the designated statement of the global context of the editorial. Three points of criticism were made: (1) the interpretation of the *in vitro* contracture test result of the boy (Groom *et al.*<sup>2</sup>), (2) possible indicators for individuals at risk for nonanesthetic malignant hyperthermia (MH), and (3) the alleged blaming of the parents.

Regarding item 1: As Larach *et al.* correctly noted, the American and European protocols have been compared and found to be mostly concordant. However, Islander and Twetman differentiate between inclusion and exclusion of the MH equivocal results.<sup>3</sup> Simply put, 9 of 74 MH-susceptible results according to the North American protocol using 3% halothane were MH equivocal according to the European protocol using 2% halothane as trigger; that is 12%. Therefore, the *in vitro* contracture test of the boy could very well be considered MH equivocal by European standards. But more importantly, the message of the editorial was that the *in vitro* contracture test may not reliably identify persons at risk. This message becomes clear in the editorial by the statement: "In addition positive *In Vitro* Contracture Test results were found in only 24% of 45 individuals with exertional heat stroke,<sup>4</sup> and in 83% of 12 patients with exercise-induced rhabdomyolysis.<sup>5</sup> Therefore more appropriate test protocols

*in vitro* (heat, oxidative stress, and nitrogen species as triggers) or *in vivo* (using  $^{31}\text{P}$  MRI)<sup>6</sup> need to be developed.”

Regarding item 2: Again, the statement about possible indicators for individuals at risk for nonanesthetic MH was taken from the original context. It is very clear from the whole paragraph and the statements made immediately preceding the statement in question that we are stating our opinion—in accordance with the purpose of an editorial—and drawing our own conclusions from the cases reported by Groom *et al.*<sup>2</sup> “Alternatively only one RyR1 mutation (*i.e.*, in only 16% of the tetrameric RyR1 complexes, all four RyR1 subunits are impaired) might be sufficient if combined with a second mutation that is associated with a congenital myopathy. Therefore MH susceptible individuals presenting with ophthalmoplegia and muscle hypotonia, hypertrophy, or spasms will be at risk for nonanesthetic MH.” Therefore, it is evident that we are not citing a large-scale human study but rather identifying ophthalmoplegia, muscle hypotonia, hypertrophy, and spasms as possible indicators of an undetected, underlying myopathy.

Regarding item 3: Nowhere in the text do we assign any blame to the parents. We state, “As children have less developed compensation mechanisms for increased body heat and a higher incidence of MH events than adults (1:15,000 *vs.* 1:100,000),<sup>7</sup> their parents should be particularly careful.” Obviously, the parents must be more careful with any temperature elevation in children at risk than are parents of unaffected children. *A personal or family history of heat intolerance* should cause avoidance of hot environments, exhausting physical exertion, high fever, and all drugs that increase heat production and reduce heat dissipation. During an episode, cooling should be started immediately until dantrolene can be infused, as in a typical MH crisis. In the meantime, the recommendations given in our editorial have been supported by authorities in the field.<sup>8,9</sup> To avoid secondary organ damage, treatment in an intensive care unit is mandatory. The protection offered by various drugs against oxidative muscle damage should be tested as second-line therapy in MH animals, such as the naturally occurring MH-susceptible swine and transgenic mouse. The induction of MH by heat and the protection of MH by hypothermia have been described for these animals.<sup>10,11</sup>

**Frank Lehmann-Horn, M.D., Ph.D.,\* Werner Klingler, M.D., Ph.D., Karin Jurkat-Rott, M.D., Ph.D.** \*Ulm University, Ulm, Germany. frank.lehmann-horn@uni-ulm.de

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## Perioperative Role of Methadone in Adolescent Patients

*To the Editor:*

We congratulate Sharma *et al.* for their study of pharmacokinetics of methadone and its effect on postoperative pain scores and opioid consumption.<sup>1</sup>

We had a few questions and comments regarding their study. This study is primarily designed to evaluate the pharmacokinetics of methadone, and not its opioid-sparing effects. Lack of standardization of the intraoperative management and postoperative pain management may lead to multiple recognized and unrecognized confounding factors being unadjusted between the treatment groups. These confounding factors may be responsible for a lack of difference in the amount of postoperative opioid consumption between the controls and the three-methadone groups.<sup>2</sup>

A randomized prospective pediatric study<sup>3</sup> and another study on posterior spinal fusion surgery patients<sup>4</sup> found a beneficial effect of methadone administration on postoperative opioid consumption and pain scores. This observational study may not have the power and design to look at the clinical effects of methadone in the postoperative period.

The small sample size could lead to a Type II error, *i.e.*, acceptance of the null hypothesis when there exists a differ-