

Prevention of an Acute Severe Exacerbation of Stiff-person Syndrome during Surgery

Albert J. Gros, Jr., M.D.,* Leslie C. Thomas, M.D.,† Kevin L. McKinley, M.D.,‡ Jay A. Van Gerpen, M.D.§

STIFF-PERSON syndrome (SPS) is a rare autoimmune central nervous system disorder characterized by fluctuating rigidity and paroxysmal painful spasms of axial and/or limb muscles, due to spinal cord hyperexcitability.¹ Exacerbations of SPS can be triggered by abrupt tactile or auditory stimulation, movement, and stress or surgery.^{2,3} We present a case of a woman with SPS who had an acute exacerbation during surgery, and we describe prophylactic measures taken that prevented an acute severe exacerbation of SPS during a subsequent procedure.

Case Report

A 30-yr-old woman with long-standing, severe SPS presented for insertion of a neurostimulator device for neurogenic bladder. Discussion with the patient revealed that she had experienced "seizure-like" activity and progressive rigidity during three previous surgeries, once with general anesthesia and twice with monitored anesthesia care (MAC). For all three surgeries, as with the current surgery, she had continued her routine treatment for SPS, consisting of 15 mg oral diazepam and 20 mg oral baclofen every 6 h, including the morning of surgery. She was also taking intravenous immunoglobulin (IVIg) every 5 weeks. Her last dose of IVIg was given approximately 3.5 weeks before this surgery.

There was a high suspicion that the seizure-like activity reported by the patient was an acute exacerbation of SPS. After further discussion with the patient, MAC was planned. Sedation was started in the preoperative area with 4 mg midazolam and 50 μ g fentanyl by intravenous injection. The patient was then brought to the operating room, monitors were applied, supplemental oxygen was administered, and the patient was positioned prone while still alert and cooperative. Over the next 30 min, she was given additional 8 mg midazolam and 50 mg diphenhydramine in divided doses. Further sedation was accomplished with a propofol infusion at 30 μ g \cdot kg⁻¹ \cdot min⁻¹, which was weaned over the subsequent 25 min after the start of the procedure. Throughout the surgery, the patient was sedated but cooperative, oriented, and able to respond to commands: a Ramsay Sedation Score of 2-3.⁴ The surgery (60 min) was uneventful until the very end. As the surgeons were making the final adjustments to the neurostimulator, the patient became anxious, then unresponsive, and experienced muscle spasms initially involving the face, which progressed to the neck and upper extremities. She concomitantly developed a transient mild tachycardia

(approximately 80 beats/min to approximately 105 beats/min) as well as hyperemia and hyperthermia isolated to the face and neck. Spontaneous ventilation was maintained throughout, with no major hemodynamic instability (arterial oxygen saturation 100%, +end-tidal carbon dioxide by capnograph, blood pressure approximately 130/80 mmHg). Based on her history, we suspected an exacerbation of SPS. The patient was turned supine, and 5 mg midazolam and 100 mg sodium thiopental were administered intravenously, with improvement of the tachycardia and transient resolution (5 min) of the facial and upper extremity spasms. The patient then progressively developed rigidity of her trunk and extremities. The spasms and rigidity continued postoperatively, and a lorazepam infusion was started in the postanesthesia care unit. Neurology became involved and confirmed by electroencephalography that the patient did not experience a seizure, but had in fact experienced an acute exacerbation of SPS. After several hours of the lorazepam infusion, the spasms subsided, but there was persistent rigidity of her entire body. The next morning, she was transferred to the intensive care unit, where she was given a course of IVIg (2 g/kg) over 4 days, with complete resolution of symptoms on the fourth day. She experienced no sequelae from the event and was discharged on the fifth postoperative day on her routine regimen of diazepam, baclofen, and IVIg.

Three months later, after a fall, the patient was scheduled for a replacement of her malfunctioning neurostimulator during MAC. In an attempt to prevent an SPS exacerbation during the subsequent surgery, she was admitted to the hospital 4 days before surgery for a preoperative course of IVIg. As with the previous surgery, we used 18 mg midazolam and 400 μ g fentanyl in divided doses as well as a propofol infusion. The patient remained sedated but cooperative, oriented, and able to respond to commands: a Ramsay Sedation Score of 2-3.⁴ Except for mild rigidity of her fingers and feet, the surgery was uneventful. She remained in the hospital overnight for an additional dose of IVIg and observation. The next day, she was discharged to her home after complete resolution of the rigidity.

Discussion

Stiff-person syndrome is a rare autoimmune disease characterized by muscle spasms and rigidity, which may be induced and/or exacerbated by tactile and auditory stimuli, as well as emotional stress or surgery.^{1,3} SPS is usually caused by an immune response against glutamic acid decarboxylase, which is the enzyme that transforms glutamate, a central nervous system excitatory amino acid, into γ -aminobutyric acid, an inhibitory neurotransmitter.² Blocking this pathway impairs γ -aminobutyric acid production, reducing the inhibitory activity of spinal interneurons. The latter may result in rigidity and spasm due to spinally mediated hyperexcitation.^{5,3} Although currently there is no cure for SPS, symptoms can be treated by augmenting spinal cord γ -aminobutyric acid-mediated activity with benzodiazepines and baclofen, both γ -aminobutyric acid type B agonists. Plasmapheresis and IVIg have been used to diminish the

* Resident, † Staff, Department of Anesthesiology, ‡ Chairman, § Staff, Department of Neurology.

Received from the Departments of Anesthesiology and Neurology, Ochsner Clinic Foundation, New Orleans, Louisiana. Submitted for publication August 29, 2005. Accepted for publication November 17, 2005. Support was provided solely from institutional and/or departmental sources. Presented in part at the Annual Meeting of the Gulf Atlantic Anesthesia Residents' Research Conference, Miami, Florida, March 4-6, 2005.

Address correspondence to Dr. Gros: Department of Anesthesiology, Ochsner Clinic Foundation, 1514 Jefferson Highway, Jefferson, Louisiana 70121. agros@ochsner.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

underlying autoimmune response causing SPS.³ The use of plasmapheresis and IVIg enhances the long-term management of SPS by improving quality of life and reducing exacerbations.⁶

Our patient's quality of life was relatively good, and her symptoms were well controlled on a routine regimen of diazepam, baclofen, and IVIg therapy. Nonetheless, maintenance therapy alone was not adequate to prevent acute exacerbations of SPS during previous surgeries, which were most likely related to stress-induced augmentation of the autoimmune response. The two procedures discussed in this report had to be performed during MAC because of the need for appropriate feedback from the patient during the case. Aya *et al.*⁷ suggested that regional anesthesia is acceptable in patients with SPS under adequate sedation. Stress is a well-accepted trigger of SPS,^{2,3} and acute exacerbations of SPS had occurred in our patient during previous surgeries, during both general anesthesia and MAC.

Benzodiazepines have been used successfully in the treatment of SPS,³ and for that reason, we chose midazolam for sedation. Diphenhydramine and propofol were used as intraoperative adjuvants to midazolam. Despite receiving 12 mg midazolam, 50 mg diphenhydramine, 50 μg fentanyl, and 30 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ propofol, our patient still experienced an exacerbation of SPS requiring an unintended hospital stay, an intensive care unit stay, and IVIg therapy. Because of chronic use of diazepam and baclofen, we anticipated that high doses of benzodiazepines would be required for sedation. However, we were cautious with the administration of sedatives because the surgery was performed with the patient in the prone position. Nonetheless, insufficient sedation may have been the reason for an exacerbation of SPS despite the relatively high doses of sedatives used. A larger dose of midazolam was administered during the second case, but with similar clinical effect, resulting in the patient being calm, cooperative, and able to respond to commands. Alternatively, general endotracheal anesthesia could have been administered but seemed less practical considering the need for patient cooperation and feedback during the procedure. A monitor of wakefulness may have been useful in titrating sedation in this patient.

There is little experience with SPS patients having anesthesia and surgery. Our decision to administer prophylactic IVIg before the subsequent surgery was extrapolated from experience in the perioperative management of myasthenia gravis.^{8,9} Although SPS and

myasthenia gravis are different diseases, they are both mediated by an autoimmune etiology, albeit affecting two distinct targets. Both diseases respond to immunosuppression, particularly IVIg and plasmapheresis therapy, and are exacerbated by similar factors, such as surgery and stress. Indeed, prophylactic administration of IVIg before surgery in patients with myasthenia gravis is comparable in efficacy to plasmapheresis, but with fewer adverse effects.⁹ Considering the success attained with plasmapheresis and IVIg in the perioperative treatment of myasthenia gravis, as well as with the chronic treatment of both SPS and myasthenia gravis, it seemed intuitive to decrease the circulating pathogen (antiglutamic acid decarboxylase antibody) rather than to try to suppress the end-organ effects (higher doses of receptor modulators, such as benzodiazepines).

Given the rarity of SPS, no prospective trials of preoperative IVIg therapy *versus* placebo have been performed. Nevertheless, given the severe exacerbations of SPS on four separate occasions during surgery in our patient, we believe that prophylactic administration of IVIg preoperatively in SPS patients who have a history of exacerbations during previous surgeries seems prudent.

In conclusion, we present a case of a woman with SPS who had severe acute exacerbations of SPS during multiple surgeries. Prophylactic preoperative administration of IVIg prevented an acute severe exacerbation of SPS from occurring during a subsequent surgery.

The authors thank Alan C. Santos, M.D. (Chairman, Department of Anesthesiology, Ochsner Clinic Foundation, Jefferson, Louisiana), for editorial assistance.

References

1. Moersch FP, Woltman HW: Progressive fluctuating muscular rigidity and spasm ("stiff-man syndrome"): Report of a case and some observations in 13 other cases. *Mayo Clin Proc* 1956; 31:421-7
2. Nikhilesh J, Sayeed ZA, Saravanan PK, Paul J: Stiff person syndrome. *J Assoc Physicians India* 2001; 49:568-70
3. Stayer C, Meinck H-M: Stiff-man syndrome: An overview. *Neurologia* 1998; 13:83-8
4. Ramsay MA, Savege TM, Simpson BR, Goodwin R: Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974; 2:656-9
5. Haslam N, Price K: Anaesthesia for stiff-person syndrome. *Anaesthesia* 2002; 57:298-9
6. Gerschlager W, Brown P: Effect of treatment with intravenous immunoglobulin on quality of life in patients with stiff-person syndrome. *Mov Disord* 2002; 17:590-3
7. Aya D, Fukuda T, Ohkoshi N, Furukawa H, Toyooka H: Regional anesthesia for a patient with stiff-person syndrome [in Japanese]. *Masui* 2004; 53:66-8
8. Abel M, Eisenkraft JB: Anesthetic implications of myasthenia gravis. *Mt Sinai J Med* 2002; 69:31-7
9. Perez NJ, Dominguez AM, Llorens-Figueroa JA, Ferrá-Betancourt A, Pardo A, Quiala M, Gali Z: A comparative study of intravenous immunoglobulin and plasmapheresis preoperatively in myasthenia gravis [in Spanish]. *Rev Neurol* 2001; 33:413-6

Hemoglobin M (Milwaukee) Affects Arterial Oxygen Saturation and Makes Pulse Oximetry Unreliable

Astrid G. Stucke, M.D.,* Matthias L. Riess, M.D., Ph.D.,* Lois A. Connolly, M.D.†

HEMOGLOBIN M (Milwaukee) is a rare dominant hereditary disorder where glutamate replaces valine in position 67 on the beta chain of the hemoglobin molecule.¹ This causes a permanently increased level of methemoglobin ranging between 15 and 30%. Patients are cyanotic but do not exhibit any other symptoms, and life expectancy is unaffected.² Animal studies have shown that high methemoglobin levels alter pulse oximetry readings.³ In addition, *in vitro* studies showed that hemoglobin M (Milwaukee) has reduced oxygen affinity.¹ These factors have not been methodically evaluated in a clinical setting for patients with hemoglobin M (Milwaukee). Therefore, we sought to investigate how to achieve optimal oxygenation during general anesthesia and to measure how reliable pulse oximetry was in a patient with this disorder. We present a unique set of arterial blood gas analyses with corresponding pulse oximetry readings at different inspiratory oxygen fractions (F_{IO_2}) and two different levels of arterial carbon dioxide tension (P_{aCO_2}).

Case Report

A 50 yr-old, 79-kg patient presented for pancreaticoduodenectomy. He had been diagnosed with hemoglobin M (Milwaukee) disease as an infant and developed cyanosis at the age of 3–4 months. His mother, brother, and son also live with the disease. He had not experienced any negative side effects of the disease throughout his life. Except for prominent cyanosis, the physical examination results were normal, as were his vital signs. Only pulse oximetry (Nellcor Oximet XL SpO₂; Marquette Medical Systems Inc., Milwaukee, WI) showed a baseline saturation of 92%. Baseline hematocrit was 41%, fractional methemoglobin concentration was 16.3%, and fractional oxygen saturation (S_{aO_2})‡ was 65.2% on room air. Before induction, two peripheral intravenous lines and a radial artery catheter were placed. Anesthetic management and surgery were uneventful. Total surgical blood loss amounted to 600 ml, which did not require transfusion. With approval by the Institutional Review Board of Froedert Memorial Lutheran Hospital (Milwaukee, Wisconsin), we obtained multiple arterial blood gas

samples at different F_{IO_2} and two different levels of P_{aCO_2} . Hemoglobin and hematocrit values were compared between the blood gas analyzer in the operating room (Radiometer Copenhagen ABL 700; Radiometer Medical A/S, Brønshøj, Denmark) and that in the central hospital laboratory (Advia 2120; Bayer, Tarrytown, NY).

We made the following observations: (1) Pulse oximetry showed 100% saturation when the available reduced hemoglobin was fully saturated ($S_{aO_2} = 85\%$); for lower S_{aO_2} levels, pulse oximetry increasingly overestimated saturation, *i.e.*, at an S_{aO_2} of 65%, pulse oximetry still showed a saturation of 92% (fig. 1). (2) Hemoglobin M (Milwaukee) showed a decreased Hill coefficient of the oxygen-hemoglobin dissociation curve, *i.e.*, it has a decreased affinity for oxygen (fig. 2). Full saturation of the available reduced hemoglobin was only reached at a high arterial oxygen tension (P_{aO_2}) of 420 mmHg, which equaled an F_{IO_2} of 0.9. (3) A change in P_{aCO_2} within the clinically used range of 32–42 mmHg did not cause a shift in the oxygen-hemoglobin dissociation curve. (4) For the hematocrit values that were measured in our patient, the cooximeter blood gas analyzer showed values that were on average 10% below that of the laboratory analyzer.

Discussion

Hemoglobin M (Milwaukee) is a cyanotic condition in which methemoglobinemia is persistent as a fixed percentage of non-oxygen-binding ferric hemoglobin. In our patient, methemoglobin was constantly 15–16%. This condition is different from inherited or acquired methemoglobin reductase deficiency and will therefore not respond to reducing agents such as methylene blue or ascorbic acid. In fact, these patients have normal methemoglobin reductase and can reduce artificially increased methemoglobin back to baseline levels.^{2,4} Abnormality exists in the structure of hemoglobin itself. The biochemical characteristics of hemoglobin M (Milwaukee) have been extensively investigated *in vitro*; however, the clinical implications have never been evaluated in a systematic fashion. Kinetic studies show that the cooperative binding properties of normal hemoglobin are impaired by increased methemoglobin levels.^{5,6} We created an oxygen-hemoglobin dissociation curve for our patient from multiple blood gas analyses. Assuming that methemoglobin interferes with the cooperativity of the hemoglobin subunits and considering that changes in cooperativity do not influence the P_{50} of the curve, we used a $P_{aO_{250}}$ of 27 mmHg for the curve fit. Our results match *in vitro* findings that the Hill coefficient of the oxygen-hemoglobin dissociation curve is decreased in hemoglobin M (Milwaukee) (1.1–1.3)^{1,5} compared with normal hemoglobin (approximately 2).⁷ That is, oxygen affinity was greatly reduced in hemoglobin M (Milwaukee), and an F_{IO_2} of greater than 0.8 was

* Resident, Department of Anesthesiology, † Associate Professor of Anesthesiology.

Received from the Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin. Submitted for publication September 16, 2005. Accepted for publication December 19, 2005. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Stucke: Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226. astucke@mcw.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

‡ The fractional oxygen saturation as determined by laboratory cooximetry is defined as $S_{aO_2} = O_2Hb / (O_2Hb + Hb + COHb + MetHb)$ with O_2Hb (oxyhemoglobin), Hb (reduced hemoglobin), $COHb$ (carboxyhemoglobin), and $MetHb$ (methemoglobin).

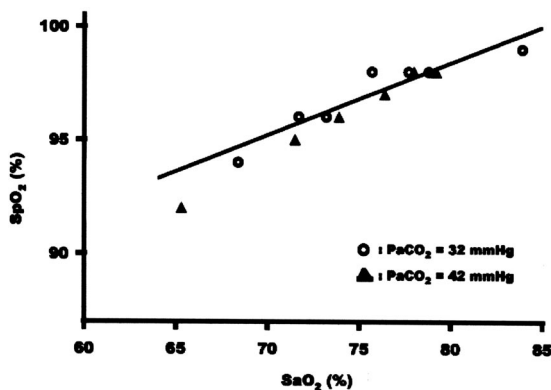


Fig. 1. Relation of fractional oxygen saturation (SaO_2) and saturation according to pulse oximetry (SpO_2). Pulse oximetry systematically overestimates the actual oxygen saturation with an increased discrepancy at lower SaO_2 values. There is no difference between lower and higher arterial carbon dioxide tension ($Paco_2$).

necessary to achieve near-full saturation of the available reduced hemoglobin.

Because a prominent Bohr effect had been described in the literature for a pH range between 6.75 and 7.85,¹ we examined whether mild hyperventilation ($Paco_2 = 32$ mmHg, pH 7.45) increased oxygen affinity compared with a normal $Paco_2$ (42 mmHg, pH 7.34). However, there seemed to be no difference within this clinically used range.

An important factor for patient care is the discrepancy between oxygen saturation as displayed by pulse oximetry and the actual SaO_2 as can be determined by blood gas analysis (fig. 1). The effects of methemoglobinemia on pulse oximetry have been delineated.⁸ In traditional pulse oximetry, light absorbance is measured at two wavelengths: 660 and 940 nm. The pulse oximeter then

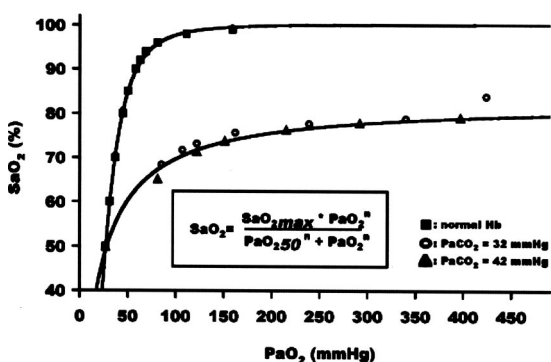


Fig. 2. Oxygen-hemoglobin dissociation curve for standard hemoglobin (Hb) at pH of 7.4 and base excess of 0, and hemoglobin M (Milwaukee) at arterial carbon dioxide tension ($Paco_2$) of 42 mmHg, pH of 7.34, and base excess of -2.8 in our patient. The equation for the curve fit is given. The Hill coefficient (n) and thus oxygen affinity are reduced in hemoglobin M (Milwaukee) but appear similar for higher and lower $Paco_2$. Note that dependent on the patient's methemoglobin level of approximately 15% maximal saturation of the available reduced hemoglobin is reached at a fractional oxygen saturation (SaO_2) of approximately 85%. $PaO_{2.50}$ = oxygen tension at $SaO_2 = 50\%$; PaO_2 : arterial oxygen tension; SaO_{2max} = maximal $SaO_2 = 100\%$.

calculates the ratio of absorbance at both wavelengths, compares this number with historic data from healthy volunteers, and thus generates a value for the arterial oxygen saturation.⁸ An absorption ratio of 1:1 represents an SaO_2 of 85% when only oxyhemoglobin and reduced hemoglobin are present.⁸ Incidentally, methemoglobin shows an absorption ratio of approximately 1:1 at these wavelengths, so that high levels of methemoglobin ($> 35\%$) produce a value for pulse oximetry of approximately 85%, which is nearly independent of the actual SaO_2 .⁸ In our patient with a methemoglobin level of approximately 15%, pulse oximetry yielded values that overestimated the true SaO_2 with increasing discrepancy at lower SaO_2 . The same tendency has also been shown in an animal model.³ Coximetry measures the light absorbance at four or more discrete wavelengths and can thus distinguish between oxyhemoglobin, reduced hemoglobin, carboxyhemoglobin, and methemoglobin fractions. In patients with significant methemoglobinemia, it is essential to obtain true values for SaO_2 with coximetry. Once a ratio is established between pulse oximetry and coximetry, pulse oximetry is valuable for trending oxygenation.

Last, in our patient, coximetry underestimated the hematocrit by approximately 10–15%. Because hemoglobin M patients are mildly anemic, a nominal transfusion threshold may be reached earlier, and a control hematocrit value should be obtained from the laboratory before the decision for transfusion is made.

In conclusion, hemoglobin M (Milwaukee) shows greatly decreased oxygen affinity compared with normal hemoglobin. High F_{IO_2} may be necessary to achieve optimal saturation of the available reduced hemoglobin. Mild hyperventilation does not influence oxygen affinity. Pulse oximetry values are falsely high, and oxygen saturation should be verified with blood gas analysis.

The authors thank Edward J. Zuperku, Ph.D. (Professor, Department of Anesthesiology, Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin), for his support with the statistical analysis.

References

1. Udem L, Ranney H, Bunn H: Some observation on the properties of hemoglobin M Milwaukee-1. *J Mol Biol* 1970; 48:489-98
2. Pisciotto AV, Ebbe SN, Hinz JE: Clinical and laboratory features of two variants of methemoglobin M disease. *J Lab Clin Med* 1959; 54:73-87
3. Barker SJ, Tremper KK, Hyatt J: Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. *ANESTHESIOLOGY* 1989; 70:112-7
4. Nagai M, Yoneyama Y: Reduction of methemoglobins M Hyde Park, M Saskatoon, and M Milwaukee by ferredoxin and ferredoxin-nicotinamide adenine dinucleotide phosphate reductase system. *J Biol Chem* 1983; 258:14379-84
5. Makino N, Sugita Y, Nakamura T: Kinetic studies on the cooperative ligand binding by hemoglobin M Milwaukee. *J Biol Chem* 1979; 254:2353-7
6. Fung LW, Minton AP, Ho C: Nuclear magnetic resonance study of heme-heme interaction in hemoglobin M Milwaukee: Implications concerning the mechanism of cooperative ligand binding in normal hemoglobin. *Proc Natl Acad Sci U S A* 1976; 73:1581-5
7. Roughton FJ, Severinghaus JW: Accurate determination of O₂ dissociation curve of human blood above 98.7 percent saturation with data on O₂ solubility in unmodified human blood from 0 degrees to 37 degrees C. *J Appl Physiol* 1973; 35:861-9
8. Tremper KK, Barker SJ: Pulse oximetry. *ANESTHESIOLOGY* 1989; 70:98-108